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LEARNING PHYSIOLOGY FROM INHERITED KIDNEY DISORDERS

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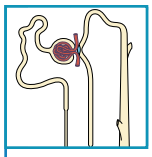


van der Wijst J, Belge H, Bindels RJM, Devuyst O. Learning Physiology From Inherited Kidney Disorders. *Physiol Rev* 99: 1575–1653, 2019. Published June 19, 2019; doi:10.1152/physrev.00008.2018.—The identification of genes causing inherited kidney diseases yielded crucial insights in the molecular basis of disease and improved our understanding of physiological processes that operate in the kidney. Monogenic kidney disorders are caused by mutations in genes coding for a large variety of proteins including receptors, channels and transporters, enzymes, transcription factors, and structural components, operating in specialized cell types that perform highly regulated homeostatic functions. Common variants in some of these genes are also associated with complex traits, as evidenced by genome-wide association studies in the general population. In this review, we discuss how the molecular genetics of inherited disorders affecting different tubular segments of the nephron improved our understanding of various transport processes and of their involvement in homeostasis, while providing novel therapeutic targets. These include inherited disorders causing a dysfunction of the proximal tubule (renal Fanconi syndrome), with emphasis on epithelial differentiation and receptor-mediated endocytosis, or affecting the reabsorption of glucose, the handling of uric acid, and the reabsorption of sodium, calcium, and magnesium along the kidney tubule.

I. INTRODUCTION: GENETICS OF KIDNEY DISORDERS

Over the past 25 yr, identification of the genetic variants causing inherited kidney diseases has tremendously enhanced our understanding of the molecular basis of disease, allowing to identify new therapeutic targets susceptible to alleviate disease onset or progression (159, 779). At the same time, these genetic discoveries have been a dominant force in the field of renal physiology, providing clues for a number of essential functions that were previously unknown or only postulated on the basis of classical experimental approaches (see BOX 1).

The clustering of kidney disease in families has long been recognized (184). From the 1980s, the technique of linkage analysis allowed to map a number of major disorders, including autosomal dominant polycystic kidney disease (ADPKD) to chromosome 16 in 1985 (595). This was followed by positional cloning, which allowed to identify disease-causing mutations in genes involved in "monogenic" or "Mendelian" diseases affecting various segments of the nephron, such as Alport syndrome (32), nephrogenic diabetes insipidus (624), ADPKD type 1 (739a), Liddle syndrome (686), Dent disease (439), Bartter and Gitelman syndromes (691, 694), cystinosis (748), and steroid-resistant nephrotic syndrome (72). With the emergence of next-generation sequencing (NGS) technologies (i.e., whole exome and whole genome sequencing), the identification of gene defects causing inherited kidney disorders is expected to increase rapidly. To date, more than 160 rare kidney diseases have been defined, with an overall prevalence of ~60–80 cases per 100,000 total population in Europe and the United States (US) (159). Classically, a disease is defined as "rare" if it affects <200,000 persons in the US, or <1 in 2,000 people in Europe (654). At least 10% of adults and nearly all children who progress to renal replacement therapy have an inherited kidney disease; collectively, the latter represent the fifth most common cause of end-stage renal disease (ESRD) after diabetes, hypertension, glomerulonephritis, and pyelonephritis (159).

The monogenic disorders of the kidney are caused by mutations in genes coding for a large variety of proteins including receptors, channels and transporters, enzymes, transcription factors, and structural components. Since the kidney is a complex organ involving numerous specialized cell types performing highly regulated homeostatic functions (184), these disorders often affect vital processes including water and electrolyte balance, blood pressure regulation, acid-base homeostasis, tis-

sue oxygen supply, hormone and vitamin metabolism, growth and puberty, innate and adaptive immunity, metabolic clearance and secretion of drug metabolites, and central nervous and cognitive functions. Thanks to the progress in renal replacement therapy (i.e., dialysis and transplantation), patients with inherited kidney disorders rarely die when their disease progresses. However, this apparent advantage is counterbalanced by compromised health with poor quality of life. For instance, children born with severe congenital nephropathies, who can be dialyzed from neonatal age onwards, face many decades of life with ESRD and high likelihood of altered physical, cognitive, and psychosocial development. Inherited kidney disorders have multi-systemic complications (27, 159).

BOX 1.

- The review discusses how identification of genes causing inherited tubulopathies yielded crucial insights in physiological processes that operate in the kidney tubule.
- The genes involved code for receptors, channels and transporters, enzymes, transcription factors, and structural components.
- This article specifically addresses genetic disorders causing proximal tubule dysfunction (renal Fanconi syndrome) or affecting the reabsorption of glucose, the handling of uric acid, and the reabsorption of sodium, calcium, and magnesium.
- Each section summarizes the physiology process, the clinical manifestations and genetics of the disease, the mechanistic insights, and the therapeutic perspectives.

In addition to monogenic renal diseases, there is strong evidence for a genetic (heritable) component to various aspects of renal function ranging from the glomerular filtration rate (GFR) to the tubular handling of ions and the susceptibility to chronic kidney disease (CKD) or hypertension. Classic twin studies demonstrated heritabilities between 40 and 50% for the tubular handling of major ions, and up to 63% for calculated creatinine clearance (327). A recent, population-based approach evidenced significant heritability values for the 24-h fractional excretions of common electrolytes, ranging from 16% for potassium (K^+) to 51% for calcium (Ca^{2+}) in the general adult population (500). The identification of the genetic component of such complex multi-factorial traits requires unbiased genome-wide mapping approaches such as genome-wide association studies (GWAS), which have emerged since the mid 2000s (828). These studies have been very successful at identifying genomic regions associated with estimated GFR (eGFR) (102, 407) and albuminuria (75) as well as CKD in the general population (553). As for other complex diseases, the identified genetic risk variants only confer relatively small increases in disease risk, with identification requiring large study populations (163). It should be pointed out, however, that the border between monogenic and complex genetic disorders is evolving, as an increasing number of GWAS based on defined traits and large populations is evidencing loci that contain genes involved in monogenic disorders (828). These findings, which are verified for traits related to eGFR, albumin excretion, and tubular handling of electrolytes (74, 133, 134, 553) support the existence of a continuum of risk variants in important genes that are associated with physiological variation in the general population (frequent variants, small effect size) and also involved in Mendelian disorders (rare variants, large effect size) (116, 456) **(FIGURE 1)**.

II. FOCUS OF THE REVIEW

The advent of genetic technologies and the rapid increase in the identification of genes causing inherited kidney disorders or associated with complex renal traits provided unprecedented insights into basic principles operating in different nephron segments. In turn, these insights improved our understanding of important transport mechanisms, their regulation, and their involvement in homeostatic processes, and they provided novel therapeutic targets. These discoveries were facilitated by large-scale international research consortia focusing on rare genetic disorders and were amplified by large collaborative studies for GWAS and subsequent mechanistic investigations (159, 161, 406, 441, 553, 812).

In this review, we discuss inherited disorders affecting different tubular segments **(TABLE 1; FIGURE 2)**, with emphasis on those that yielded critical insights for the understanding of epithelial transport processes. The review focuses on inherited disorders causing a dysfunction of the proximal tubule (renal Fanconi syndrome) which evidenced the role of epithelial differentiation and receptor-mediated endocytosis in multi-systemic complications and progression of renal disease; affecting glucose transport and uric acid handling; disturbing the renal handling of Na^+, with direct relevance for blood pressure regulation and mechanisms of action of diuretics; and affecting the handling of Ca^{2+} and Mg^{2+}. Disorders affecting acid-base balance, phosphate handling and its hormonal regulation (7, 43, 52, 321, 460, 549, 714, 783, 788, 802) and water handling (31, 61, 126, 403, 543, 637, 807) have been discussed in recent reviews and will not be addressed here. In each section, we summarize the specific physiology process, discuss the clinical manifestations and genetics of the associated inherited disorders, and detail the mechanistic insights and therapeutic perspectives provided by these studies.

III. RARE INHERITED DISORDERS HIGHLIGHTING TUBULAR FUNCTIONS

A. Proximal Tubule Dysfunction: Renal Fanconi Syndrome

1. Receptor-mediated endocytosis and endolysosomal compartment

The proximal tubule (PT) plays an essential role in the reabsorption and processing of a large amount of filtered ions

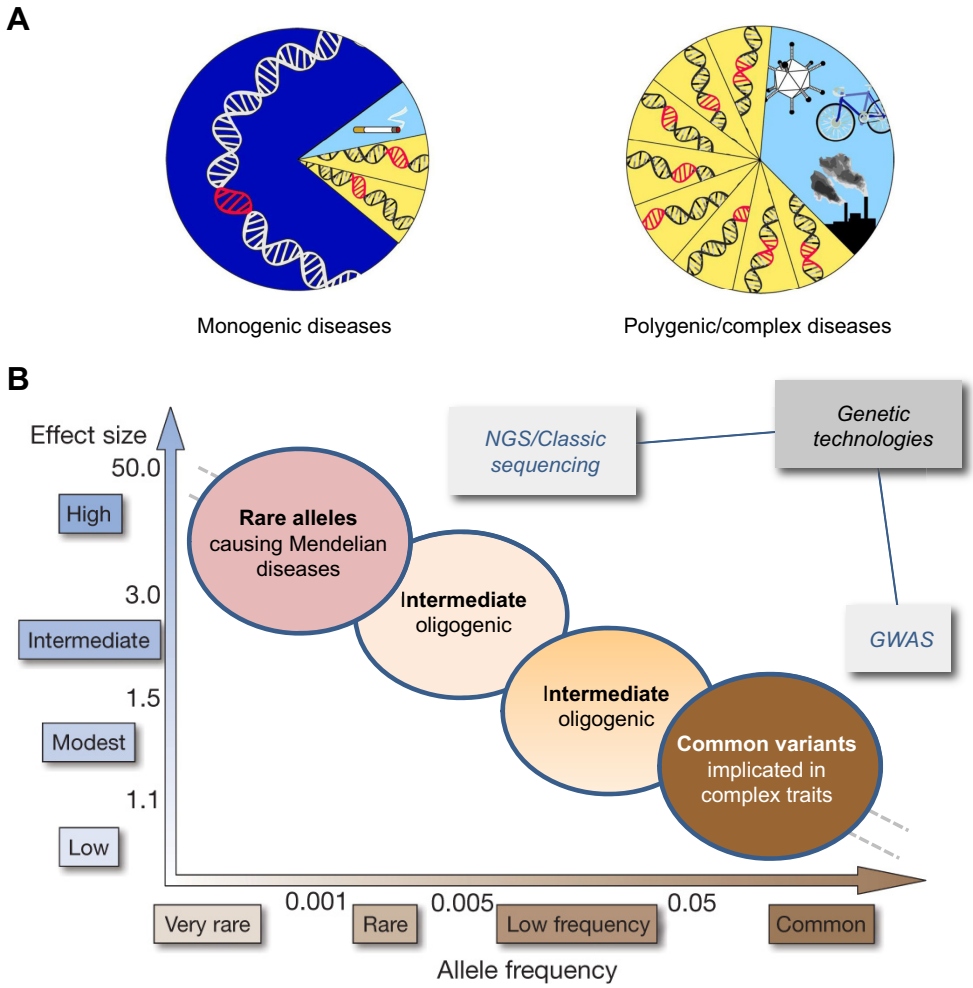


FIGURE 1. Genetic influence on disease. *A*: disorders with a genetic component are classically divided between monogenic diseases, in which a rare variant in a single gene is the main cause of the disease (dark blue sector), with possible additional, minor contributions of modifier genes (yellow sectors) and environment (light blue sector); and polygenic/complex diseases, where many variants each exerting a very small effect (yellow sectors), combined with a strong set of environmental factors (blue sector) contribute to disease. Oligogenic disorders are caused by, or modulated by, a few genes. *B*: the spectrum of genetic influence on disease can be represented by an inverse relationship between the strength of genetic effect (effect size) and the allele frequency in the population. Rare disease-associated allelic variants (typically, <1:2,000 individuals) are involved in Mendelian disorders, whereas common variants (typically >5% in the population) with small effect size contribute to complex traits. Genetic variants of intermediate effect-size contribute to polygenic disorders. Genetic technologies, including next-generation sequencing (NGS) and genome-wide association studies (GWAS), cover the spectrum. [Adapted from Manolio et al. (455) and Manolio et al. (456).]

and solutes. Approximately two-thirds of the filtered water, NaCl, Ca^{2+} as well as the totality of glucose, phosphate, amino acids are reabsorbed by a whole orchestra of specialized transport systems that operate on the apical (brush border) and basolateral area of the cells lining the various segments of the PT, driven by the electrochemical gradient generated by the basolateral Na^+-K^+-ATPase. These transport processes impose a high energy demand, which is sustained by numerous, elongated mitochondria typically identified in PT cells (408). In addition, PT cells also reabsorb a significant amount of albumin (66.5 kDa) and low-molecular-weight (LMW) plasma proteins that are filtered through the glomerular basement membrane. These LMW proteins include hormones [e.g., parathyroid hormone (PTH), insulin, epidermal growth factor, leptin, thyroglobulin], vitamin carrier proteins (transcobalamin-vitamin B_{12}, vitamin D-binding protein (DBP), retinol-binding protein, folate-binding protein), enzymes (e.g., cathepsin B, α-amylase, plasminogen, urokinase, lysozyme), lipoproteins, cell surface antigen components (β_2-microglobulin), immunoglobulin light chains, as well as drugs and toxins (e.g., aminoglycosides, gentamicin). As the majority of the LMW proteins are reabsorbed and metabolized by the PT cells, the human urine is virtually devoid of plasma proteins under physiological conditions (120, 194, 519).

The uptake of albumin and LMW proteins by PT cells principally involves receptor-mediated, clathrin-dependent en-

Table 1. *Rare inherited tubular disorders highlighting tubular functions*

	Transmission	MIM Number	Gene (Location)	Defective Protein	Protein Function
Proximal tubule dysfunction: renal Fanconi syndrome					
Donnai-Barrow syndrome (Faciooculoacousticorenal syndrome)	AR	222448	*LRP2 (2q31.1)*	Megalin	Low-density lipoprotein receptor-related protein 2, multiligand receptor
Imerslund-Gräsberck syndrome megaloblastic anemia 1, Finnish type	AR	261100	*CUBN (10p13)*	Cubilin	Multiligand receptor (including intrinsic factor-vitamin B_{12})
Imerslund-Gräsberck syndrome megaloblastic anemia 1, Norwegian type	AR	261100	*AMN (14q32.32)*	Amnionless	Partner of cubilin, directs subcellular localization of cubilin
Dent disease 1 (nephrolithiasis, hypercalciuric, *X*-linked)	XL	300009	*CLCN5 (Xq11.23)*	ClC-5	$2Cl^-/H^+$ exchanger
Dent disease 2	XL	300555	*OCRL (Xq26.1)*	OCRL	Inositol polyphosphate 5-phosphatase
Lowe oculocerebrorenal syndrome	XL	309000	*OCRL*	OCRL	Inositol polyphosphate 5-phosphatase
Cystinosis, nephropathic	AR	219800	*CTNS (17p13.2)*	Cystinosin	Lysosomal cystine-H^+ cotransporter
Cystic fibrosis	AR	219700	*CFTR (7q31.2)*	CFTR	ATP-binding cassette (ABC) transporter, Cl^- channel
Maturity-onset diabetes of the young, type 3 (MODY3)	AD	600496	*HNF1A (12q24.31)*	HNF1α	Transcription factor
Disorders of uric acid handling					
Renal hypouricemia type 1	AR	220150	*SLC22A12 (11q13.1)*	URAT1	Urate/anion exchanger
Renal hypouricemia type 2	AR	612076	*SLC2A9 (4p16.1)*	GLUT9	Facilitated glucose transporter, urate transporter
Disorders of glucose transport					
Familial renal glycosuria	AR/AD	233100	*SLC5A2 (16p11.2)*	SGLT2	Sodium/glucose cotransporter
Glucose/galactose malabsorption	AR	606824	*SLC5A1 (22q12.3)*	SGLT1	Sodium/glucose cotransporter
Fanconi-Bickel syndrome (hepatorenal glycogenosis)	AR	227810	*SLC2A2 (3q26.2)*	GLUT2	Facilitated glucose transporter
Disorders of sodium chloride transport					
Bartter syndrome type 1 (hypokalemic alkalosis with hypercalciuria 1, antenatal)	AR	601678	*SLC12A1 (15q21.1)*	NKCC2	Na^+-K^+-$2Cl^-$ cotransporter
Bartter syndrome type 2 (hypokalemic alkalosis with hypercalciuria 2, antenatal)	AR	241200	*KCNJ1 (11q24.3)*	ROMK	K^+ channel (renal outer-medullary K^+ channel)
Bartter syndrome type 3 (with hypocalciuria)	AR	607364	*CLCNKB (1p36.13)*	ClC-Kb	Cl^- channel
Bartter syndrome type 4 (neonatal, with sensorineural deafness)	AR	602522	*BSND (1p32.3)*	Barttin	Subunit of the ClC-Ka and ClC-Kb channels
Bartter syndrome type 4b, digenic (neonatal, with sensorineural deafness)	AR	613090	*CLCNKA (1p36.13), CLCNKB*	ClC-Ka; ClC-Kb	Cl^- channel; Cl^- channel
Gitelman syndrome (hypomagnesemia-hypokalemia, primary renotubular, with hypocalciuria)	AR	263800	*SLC12A3 (16q13)*	NCC	Thiazide-sensitive Na^+-Cl^- cotransporter
Pseudohypoaldosteronism type IIC (Gordon syndrome)	AD	614492	*WNK1 (12p13.33)*	WNK1	Ser/Thr kinase modulating Na^+- and K^+-coupled Cl^- transporters
Pseudohypoaldosteronism type IIB	AD	614491	*WNK4 (17q21.2)*	WNK4	Ser/Thr kinase modulating Na^+- and K^+-coupled Cl^- transporters
Pseudohypoaldosteronism type IID	AD	614495	*KLHL3 (5q31.2)*	KLHL3	Substrate adaptor for cullin-3
Pseudohypoaldosteronism type IIE	AD	614496	*CUL3 (2q36.2)*	Cullin-3	Component of ubiquitin E3 ligase complex
Liddle syndrome (pseudohyperaldosteronism)	AD	177200	*SCNN1G (16p12.2), SCNN1B (16p12.2)*	ENaC	γ-Subunit of amiloride-sensitive Na^+ channel; β-subunit of amiloride-sensitive Na^+ channel
Pseudohypoaldosteronism type I	AD	177735	*NR3C2 (4q31.23)*	MR	Mineralocorticoid receptor
	AR	264350	*SCNN1A (12p13.31), SCNN1G, SCNN1B*	ENaC	α-Subunit of amiloride-sensitive Na^+ channel; γ-subunit of amiloride-sensitive Na^+ channel; β-subunit of amiloride-sensitive Na^+ channel

Continued

Table 1.—*Continued*

	Transmission	MIM Number	Gene (Location)	Defective Protein	Protein Function
Disorders of calcium transport					
Familial hypocalciuric hypercalcemia, type 1	AD	145980	*CASR (3q13.3-q21.1)*	CaSR	Calcium-sensing receptor
Familial hypocalciuric hypercalcemia, type 2	AD	145981	*GNA11 (19p13.3)*	$G\alpha_{11}$	Guanine nucleotide-binding protein, G protein subunit α11
Familial hypocalciuric hypercalcemia, type 3	AD	600740	*AP2S1 (19q13.32)*	AP2S1	Adaptor-related protein complex 2, sigma-1 subunit
Neonatal severe hyperparathyroidism	AR	239200	*CASR*	CaSR	Calcium-sensing receptor
Autosomal dominant hypocalcemia 1 (with Bartter syndrome)	AD	601198	*CASR*	CaSR	Calcium-sensing receptor
Autosomal dominant hypocalcemia 2	AD	615361	*GNA11*	$G\alpha_{11}$	Guanine nucleotide-binding protein, G protein subunit α11
Disorders of magnesium transport					
Hypomagnesemia (intestinal, type 1)	AR	602014	*TRPM6 (9q21.13)*	TRPM6	Mg^{2+} channel
Hypomagnesemia (renal, type 2)	AD	154020	*FXYD2 (11q23.3)*	FXYD2	γ-Subunit of Na^{+}-K^{+}-ATPase
Hypomagnesemia (renal, type 3)	AR	248250	*CLDN16 (3q28)*	Claudin-16	Paracellular protein, component of tight junctions
Hypomagnesemia (renal, type 4)	AR	611718	*EGF (4q25)*	EGF	Epidermal growth factor
Hypomagnesemia (renal, type 5) with ocular involvement	AR	248190	*CLDN19 (1p34.2)*	Claudin-19	Paracellular protein, component of tight junctions
Hypomagnesemia (renal, type 6)	AD	613882	*CNNM2 (10q24.32)*	Cyclin M2	Membrane protein of unknown function
Hypomagnesemia, seizures, and mental retardation	AR, AD	616418	*CNNM2*	Cyclin M2	Membrane protein of unknown function
HELIX syndrome (hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia)	AR	617671	*CLDN10 (13q32.1)*	Claudin-10	Paracellular protein, component of tight junctions
SeSAME (or EAST) syndrome (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance)	AR	612780	*KCNJ10 (1q23.2)*	Kir4.1	K^{+} channel
Renal cysts and diabetes syndrome	AD	137920	*HNF1B (17q12)*	HNF1β	Transcription factor

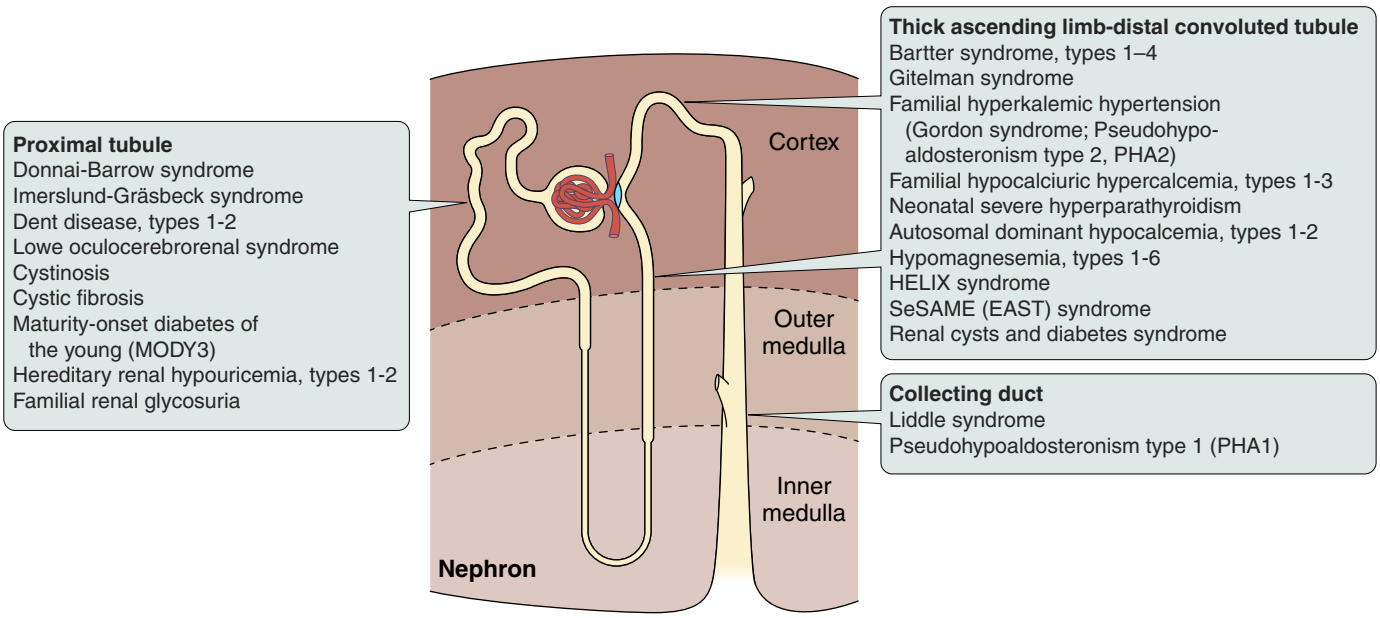


FIGURE 2. Segmental distribution of rare inherited kidney disorders. See text for details on the individual disorders.

docytosis **(FIGURE 3)**, which requires two multiligand receptors, megalin and cubilin, and the cooperating protein amnionless (AMN). These proteins are expressed at the brush border of the PT cells, with megalin showing a maximal expression level in the S1 versus S2 and S3 segments (194, 520). Megalin is a member of the low-density lipoprotein receptor (LDLR) family, whereas cubilin (also known as the intestinal intrinsic factor-vitamin B_{12} receptor) is a highly conserved membrane-associated protein with little structural homology to known endocytic receptors and is characterized by the absence of a transmembrane domain. Megalin seems to be involved in the endocytosis and intracellular trafficking of cubilin as suggested by the high-affinity binding of purified megalin to cubilin amino (NH_2)-terminal region in vitro (120). AMN is required for the apical sorting of cubilin and its participation in receptor-mediated endocytosis (136). Cubilin contributes ligand-binding regions of the receptor complex, whereas AMN ensures the membrane anchorage, biosynthetic processing, and recycling of the complexes at the plasma membrane (224). In addition to the proximal tubule, cubilin and amnionless are both expressed in the small intestine. Ligand binding and interactions between both receptors induce their internalization into coated vesicles and their subsequent delivery to endosomes and lysosomes for ligand processing and receptor degradation or recycling.

Through its binding capacity of hedgehog morphogens, megalin modulates sonic hedgehog activities crucial for developmental processes in a number of tissues, including the brain, the eye, and the heart (117). The biological importance of the apical receptor complex is evidenced by the severe and multi-sytemic manifestations of rare disorders targeting megalin and cubilin/amnionless **(FIGURE 4)**. Recessive mutations in the *LRP2* gene that encodes megalin cause Donnai-Barrow or facio-oculo-acoustico-renal (DB/FOAR) syndrome (MIM no. 222448) that is characterized by typical craniofacial anomalies (major hypertelorism with bulging eyes), high-grade myopia, deafness and LMW proteinuria (369, 712). Mutations in the *CUBN* and *AMN* genes that encode cubilin and amnionless, respectively, are associated with Imerslund-Gräsbeck syndrome (MIM no. 261100), a rare autosomal recessive disorder characterized by selective vitamin B_{12} (cobalamin) malabsorption causing megaloblastic anemia. Increased urinary excretion of cubilin ligands (e.g., transferrin, DBP, and albumin) is detected in patients harbouring mutations impairing the plasma membrane expression of cubilin (713). Recent studies have demonstrated that the apical expression of megalin, and thus the endocytic uptake capacity, reflects the differentiation state of PT cells. For instance, comparison of proliferation and differentiation markers revealed that primary human PT cells are less proliferative and more differentiated than HK-2 cells, reflected by a threefold increase in their endocytic uptake (578). These results are in line with studies demonstrating that primary cultured cells isolated from PT segments of mouse kidney preserve their differentiation and polarized transport processes (738). Furthermore, acquired PT dysfunction (e.g., by exposing PT cells to low dose of toxic κ-light chains) is inducing a phenotype switch of PT cells, with increased cell proliferation, decreased apical expression of endocytic receptors, and defective endocytosis and albumin uptake capacity (449).

The progression along the endolysosomal compartment depends on the continuous vesicular acidification from early endosomes to lysosomes (199). The decrease in pH

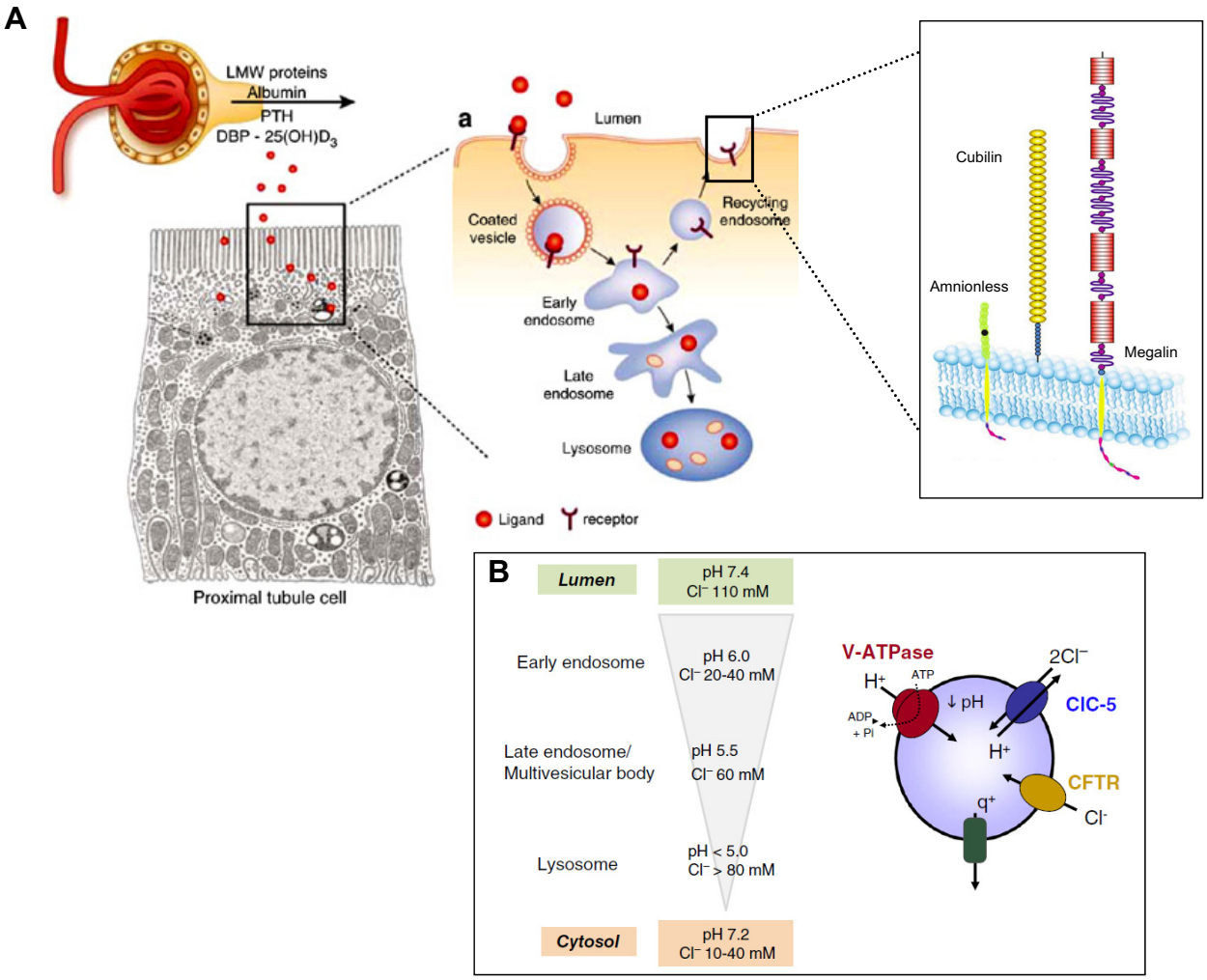


FIGURE 3. Receptor-mediated endocytosis in the proximal tubule of the kidney. *A*: albumin and low-molecular-weight (LMW) proteins, in red, are continuously filtered across the glomerular filtration barrier, to be reabsorbed and processed by the epithelial cells lining the proximal tubule (PT). The LMW ligands first interact with the nonselective megalin/cubilin/amnionless receptor complex at the apical membrane. After internalization, the receptor-ligand complexes progress along the clathrin-dependent endocytic pathway. The endosomes undergo a progressive acidification that results in the dissociation of the receptor-ligand complexes, with the receptors (*inset*) being recycled to the apical membrane, whereas the ligand is directed to acidic lysosomes for degradation. Other possible pathways for albumin handling by proximal tubule cells, including fluid-phase endocytosis and transcytosis back into the circulation, are not detailed. *B*: vesicular acidification and chloride concentration along the endolysosomal pathway. The endocytic pathway in PT cells involves coated pits and coated vesicles, followed by early endosomes that form recycling endosomes or mature to late endosomes and lysosomes. The luminal pH drops from 7.4 in the tubule lumen to 6.0 in early endosomes, 5.5 in late endosomes, and below 5.0 in lysosomes. Such vesicular acidification is necessary for dissociation of the ligand-receptor complex, recycling of receptors to the apical membrane, and progression of ligands into lysosomes. In parallel, the Cl^- concentrations drop from 110 mM in the extracellular space to 20–40 mM in early endosomes, 60 mM in late endosomes, and >80 mM in lysosomes, i.e., much higher than the 10–40 mM in the cytosol. *Right panel*: endosomal acidification that is achieved by ATP-driven transport of cytosolic H^+ through V-ATPase, also known as the proton pump. ClC-5 operates as a Cl^-/H^+ exchanger that facilitates acidification (countercurrent through the $2Cl^-/1H^+$ stoichiometry). The Cl^- channel CFTR is also enriched in the endosomal fraction containing ClC-5, and it participates, together with cation leakage ($q+$), in the electrical shunt necessary for sustained vesicular acidification. CFTR, cystic fibrosis transmembrane conductance regulator; ClC-5, chloride channel 5; V-ATPase, vacuolar H^+-ATPase; q^+, cation. [Adapted from Devuyst and Luciani (160), with permission from John Wiley and Sons; and Jentsch (349).]

in the successive endocytic compartments induces receptor-ligand dissociation and modulates vesicle trafficking, endosomal fusion events, and coat formation (328). In PT cells, endosomal acidification is driven by the electrogenic vacuolar H^+-ATPase (V-ATPase) **(FIGURE 3)**. The translocation of protons from the cytoplasm into the endosomes generates a transmembrane electrical potential ($\Delta\Psi$) with rapid inhibition of V-ATPase activity. The

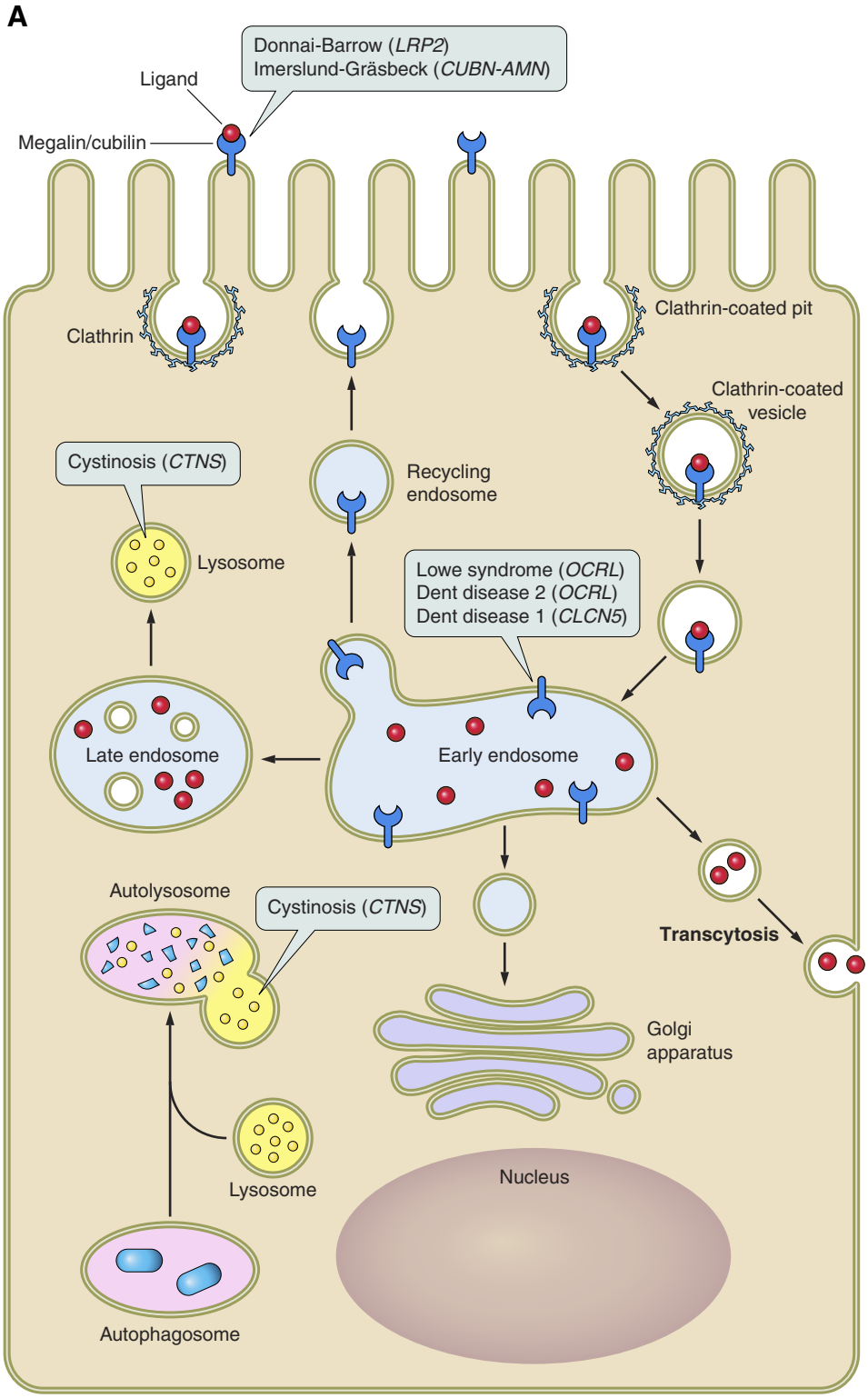


FIGURE 4. Rare disorders targeting the endolysosomal system in the proximal tubule, resulting in renal Fanconi syndrome. *A*: the main endocytic receptor for the clearance of filtered proteins is megalin (encoded by the *LRP2* gene), a member of the low-density lipoprotein receptor gene family. Cubilin (encoded by the *CUBN* gene) is another apical cell surface receptor in proximal tubule (PT) cells, associated with megalin and the amnionless subunit (not represented, encoded by *AMN*) to form a receptor complex for the trafficking of cargo through the early endosomes, late endosomes, and lysosomes of the cell. Endocytic activity in these cells critically requires the actions of *CLCN5* and *OCRL*. *CLCN5* encodes ClC-5, a Cl^-/H^+ exchanger that facilitates acidification and trafficking of endosomal vesicles. *OCRL* encodes inositol polyphosphate-5-phosphatase, which is required for proper vesicular trafficking between intracellular compartments and the plasma membrane. The lysosomal activity, important for cargo processing and autophagy, requires a functional cystinosin, a H^+-cystine cotransporter encoded by the *CTNS* gene. Several disorders are caused by mutations of genes coding for components of the endo-lysosomal system in the PT, including *LRP2* (Donnai-Barrow syndrome), *CUBN* and *AMN* (Imerslund-Gräsbeck syndrome), *CLCN5* (Dent disease 1), *OCRL* (Lowe syndrome and Dent disease type 2), and *CTNS* (nephropathic cystinosis). Typically, these disorders cause PT dysfunction and lead to inappropriate urinary loss of solutes and, often, to renal failure. *B*: phenotype of PT dysfunction in the ClC-5 knockout (KO) ($Clcn5^{Y/-}$) mouse model of Dent disease 1. *i*) Compared with wild-type ($Clcn5^{Y/+}$) littermates, $Clcn5^{Y/-}$ mice show polyuria, with inappropriate glucosuria, calciuria, phosphaturia, and proteinuria. *ii*) Immunoblot analysis confirms the urinary loss of low-molecular-weight proteins in $Clcn5^{Y/-}$ mice, including Clara cell protein of 16 kDa (CC16), transferrin, vitamin D-binding protein (DBP), and cathepsin B. *iii*) The molecular basis of the defective endocytosis is the loss of apical receptors megalin and cubilin in PT cells, as shown by decreased apical signal on immunofluorescence; and *iv*) by the redistribution of cubilin from the brush border to intracellular compartments in subcellular fractions (Percoll gradient) of the kidneys. [Modified from De Matteis et al. (148) and Willnow (813).]

maintenance of V-ATPase activity depends on the dissipation of $\Delta\Psi$, either by cation leakage or by chloride transport (571). Vesicular acidification requires in most cases a chloride (Cl^-) conductance. The intravesicular Cl^- concentration progressively increases from early endosomes (20–40 mM) to lysosomes (>80 mM) (705). It can directly affect the V-ATPase activity (497) as well as other ionic movements and vesicle recycling independently of its effect on pH (199, 705).

Impairment of PT transport processes leads to the loss of LMW proteins and solutes (e.g., phosphate, glucose, amino acids, urate) in the urine. The clinical entity of generalized PT dysfunction is referred to as renal Fanconi syndrome (or

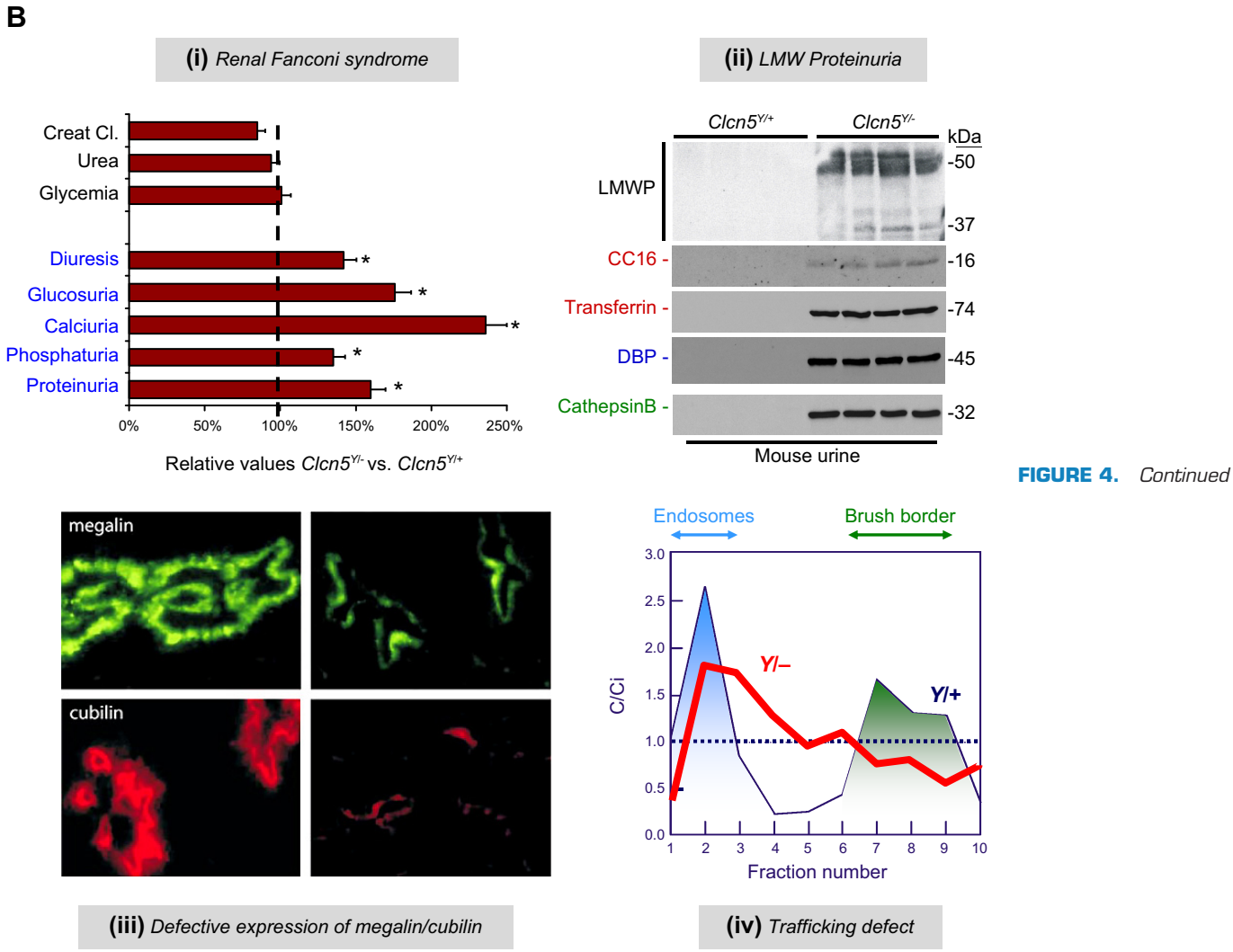


FIGURE 4. *Continued*

de Toni-Debré-Fanconi syndrome) to acknowledge the first description of such a case by Guido Fanconi at the Kinderspital Zurich in 1931 (197). The renal Fanconi syndrome (RFS) is characterized by the urinary loss of the above solutes and LMW proteins, causing dehydration and electrolyte imbalance, rickets, muscular weakness, growth retardation, and progressive renal failure (77, 389). The syndrome can be isolated or associated with multi-systemic disorders; it is variable in terms of severity, duration, extent of tubular dysfunction, and progression towards CKD. These variable clinical presentations reflect at least in part the causal disorder. The RFS can be acquired, for instance induced by exogenous susbstances (toxins, drugs) or associated with autoimmune disorders, or result from inherited disorders **(TABLE 2)** including endolysosomal diseases (e.g., Dent disease, cystinosis), metabolic disorders (e.g., Fanconi-Bickel syndrome, Wilson disease, tyrosinemia, galactosemia, congenital fructose intolerance) (165, 389, 695), or various types of mitochondrial dysfunctions (189, 596). Besides generalized PT dysfunction, isolated defects of proximal transport systems, such as disorders of glucose, urate, or phosphate transport, may also occur and will be discussed separately. In this section we discuss Dent disease and cystinosis **(FIGURE 4)**, two inherited disorders of the endolysosomal pathway that are invariably associated with variable forms of PT dysfunction (57, 515).

2. Dent disease

A) BRIEF CLINICAL DESCRIPTION. Dent disease (also named *X*-linked hypercalciuric nephrolithiasis, *X*-linked recessive hypophosphatemic rickets, *X*-linked recessive nephrolithiasis, or idiopathic LMW proteinuria) is a rare *X*-linked renal tubulopathy that was first reported by Dent and Friedman in two unrelated English boys with rickets associated with renal tubular damage characterized by hypercalciuria, hyperphosphaturia, LMW proteinuria, and aminoaciduria (156). Dent disease is characterized by LMW proteinuria associated with hypercalciuria, which may lead to nephrolithiasis, nephrocalcinosis, and renal failure. The disease may also be associated with PT dysfunction as evidenced by aminoaciduria, phosphaturia, glycosuria, uricosuria, kaliuresis, and impaired urinary acidification and is frequently complicated by rickets or osteomalacia. Usually these fea-

Table 2. *Causes of proximal tubule dysfunction (renal Fanconi syndrome)*

Idiopathic
Autosomal recessive or dominant
X-linked
Hereditary*
Arthrogryposis, renal dysfunction and cholestasis 1; ARCS1 (*VPS33B*)
Arthrogryposis, renal dysfunction and cholestasis 2; ARCS2 (*VIPAS39*)
Cystinosis (*CTNS*)
Cystinuria (*SLC3A1*, *SLC7A9*)
Dent disease 1 (*CLCN5*)
Dent disease 2 (*OCRL*)
Donnai–Barrow syndrome (*LRP2*)
Fabry disease (*GLA*)
Fanconi renotubular syndrome 1; FRTS1 (-)
Fanconi renotubular syndrome 2; FRTS2 (*SLC34A1*)
Fanconi renotubular syndrome 3; FRTS3 (*EHHADH*)
Fanconi renotubular syndrome 4; FRTS4 (*HNF4A*)
Fanconi–Bickel syndrome (*SLC2A2*)
Galactosemia (*GALT*)
Glycogen storage disease type I (von Gierke disease) (*G6PC*)
Hereditary fructose intolerance (*ALDOB*)
Imerslund–Gräsbeck syndrome (megaloblastic anemia 1; *CUBN, AMN*)
Iminoglycinuria (*SLC6A20, SLC6A19, SLC36A2*)
Lowe oculocerebrorenal syndrome (*OCRL*)
Maturity-onset diabetes of the young type 3 (*HNF1A*)
Renal tubular acidosis proximal, autosomal recessive (*SLC4A4*)
Tyrosinemia type I (*FAH*)
Wilson disease (*ATP7B*)
Renal Fanconi syndrome, autosomal dominant, with kidney failure (*GATM*)
Mitochondriopathies
Acquired
Myeloma
Sjögren syndrome
Renal transplantation
Acute tubulointersitial nephritis with uveitis (TINU) syndrome
Autoimmune interstitial nephritis and membranous nephropathy
Primary biliary cirrhosis
Renal hemosiderosis
Exogenous substances
Drugs: aminoglycosides, salicylate, valproic acid, Chinese herbs, ifosfamide, cisplatin, imatinib, mesylate, adefovir, cidofovir, tenofovir, zoledronic acid, deferasirox
Chemical compounds: paraquat, bismus, methyl-3-chromone, 6-mercaptopurine, toluene
Heavy metals: lead, cadmium, mercury, chromium, platinum
Honeybee stings: melittin

*Causative genes are in italics.

tures are present in males only, who may develop bone pain, rickets, failure to thrive, or even renal stones from early childhood. LMW proteinuria is the most consistent manifestation of Dent disease and is identified in almost all affected males and obligate female carriers (57, 165). Of note, proteinuria worsens with age and may reach the nephrotic range (>2 g/day), with evidence of glomerular lesions on renal biopsy (57, 220).

Generalized PT dysfunction (complete RFS) is rare in Dent disease (~10% of patients), whereas the presence of partial RFS (including LMW proteinuria and hypercalciuria with at least one manifestation of PT dysfunction) is detected in 70% of patients (57). Vitamin A deficiency and impaired night vision may be present and are due to the urinary loss of retinol binding protein (37). Hypercalciuria and nephrocalcinosis are also highly prevalent, although there is inter- and intrafamilial variability in the occurrence of nephrolithiasis which occurs in approximately half of the affected males (57, 164). Pseudo-Bartter syndrome, with renal losses of salt and K^+ and secondrary hyperaldosteronism, has been reported, increasing in frequency with age (57). A cumulative analysis of the clinical data from 377 male patients confirmed the main manifestations of the disease, and the occurence of micro- or macrohematuria, proteinuria in the nephrotic range, urinary concentration defect, Bartter-like phenotype, hypomagnesemia, and defects in urinary acidification (458).

Progression to end-stage renal failure occurs between the third and the fifth decades of life in 30–80% of affected males (57, 653). The link between nephrocalcinosis and renal failure has not been established in patients. The occurrence of these predominantly renal manifestations and their association with mutations in the *CLCN5* gene is referred to as Dent disease 1. A minority of patients with Dent disease present extra-renal manifestations such as mental developmental delay, hypotonia, and cataract, in association with mutations of the oculo-cerebrorenal syndrome of Lowe (*OCRL*) gene (306). The occurrence of these extra-renal manifestations associated with *OCRL* mutations is referred to as Dent disease 2.

B) GENETICS. Dent disease 1 (MIM no. 300009) is caused by inactivating mutations in the *CLCN5* gene (Xp11.22), which encodes the 746-amino acid electrogenic $2Cl^-/H^+$ exchanger ClC-5 (439, 567, 652). ClC-5 is a member of the CLC family of Cl^- channels/transporters and belongs to a cluster of three isoforms (ClC-3, ClC-4, ClC-5) that are mainly located in intracellular vesicles. ClC-5 is characterized by 18 α-helices, with two phosphorylation sites and one *N*-glycosylation site. Crystal structures of bacterial and eukaryotic CLCs showed that the protein forms diamond-shaped homodimers composed of two repeated halves that span the membrane in opposite orientations. Each subunit

has its own pore responsible for the selective coupling of the Cl^- flux to H^+ countertransport (183, 201, 349).

The described *CLCN5* mutations include large deletions (4%) as well as nonsense (17%) and frameshift (28%) mutations that produce premature stop codons, splice-site mutations (11%) predicted to interfere with correct splicing, and missense (37%) and small in-frame deletions (2.6%) affecting conserved residues (458). The mutations are scattered through the coding region, with no evidence for mutational hot spots (458, 823). Most of the *CLCN5* mutations (missense and nonsense) are predicted to result in a truncated or absent ClC-5 protein, which would lead to a complete loss of its antiporter function. Heterologous expression in *Xenopus laevis* oocytes or HEK293 cells has shown that most *CLCN5* mutations lead to a loss of Cl^- conductance (439). Further detailed studies of the *CLCN5* missense mutations revealed that these may lead to impaired processing and folding, with endoplasmic reticulum (ER) retention and degradation by quality control mechanisms (class 1); delay in processing and reduced stability (class 2); and normal trafficking but altered electrical activity (class 3) (446). Some mutations of *CLCN5* cluster at the dimer interface, which could impair dimerization and lead to rapid degradation of the mutant protein within the cell (446, 458, 824). Examination of a large cohort of 109 male patients with *CLCN5* mutations (Dent disease 1) could not establish a correlation between severe and moderate mutations (classified according to the types of mutations) and the phenotype at diagnosis, the decrease in eGFR, and tubular manifestations (57). A considerable intra-familial variability in disease severity has been reported, including for the extent of PT dysfunction and urinary wasting of bicarbonate and ions associated with a given *CLCN5* mutation (458).

There is genetic heterogeneity for Dent disease, with ~50–60% of patients harboring *CLCN5* mutations, ~15% with *OCRL* mutations, and the remaining 25–35% of patients having neither *CLCN5* nor *OCRL* mutations. Dent disease 2 (MIM no. 300555) defines patients with Dent disease who have extrarenal manifestations and share mutations in the *OCRL* gene with the oculo-cerebrorenal syndrome of Lowe (306, 688). There is a wide overlap between the manifestations of PT dysfunction in patients with Dent disease type 1 (*CLCN5* mutations) and Dent disease 2 (*OCRL* mutations), with all patients manifesting LMW proteinuria and ~90% hypercalciuria (76). The mild extrarenal manifestations of patients with Dent disease 2 include elevated levels of creatine phosphokinase (CPK) and/or lactate dehydrogenase (LDH), indicating muscle involvement, mild intellectual disability, mild developmental delay, and cataract; these manifestations are much less severe than in Lowe syndrome. Similarly, patients with Dent disease 2 are less likely to have nephrocalcinosis and urinary wasting of phosphate, amino acids, bicarbonate, and K^+, and a slower decrease in eGFR compared with patients with Lowe syndrome (76, 148, 848).

The *OCRL* gene encodes the inositol polyphosphate 5-phosphatase OCRL, which preferentially hydrolyzes the 5-phosphate of phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$]. Disease-causing mutations in *OCRL* result in the loss of 5-phosphatase activity and accumulation of $PI(4,5)P_2$ in PT cells of patients with Lowe syndrome (852). The vast majority of *OCRL* mutations associated with Lowe syndrome are located in exons 8–23, which comprises the inositol polyphosphate 5-phosphatase and the ASPM, SPD-2, Hydin (ASH), and RhoGAP-like domains, whereas the majority of mutations that cause Dent disease 2 are located in exons 1–7, which encompass the pleckstrin homology (PH) domain (148). Of note, mutations in the phosphatase domain of *OCRL* have been described both in patients with Lowe syndrome and in patients with Dent disease 2, but such mutations in patients with Dent disease 2 are always missense mutations (298). A number of evidences suggest that OCRL plays a role in the endocytic pathway and the coordination of membrane dynamics with remodeling of the actin cytoskeleton (148, 193, 475). Therefore, it is likely that *OCRL* mutations in Lowe syndrome or Dent disease 2 lead to disruptions in the endosomal and/or lysosomal trafficking, i.e., an abnormality similar to that observed in Dent disease 1.

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. The clinical presentation Dent disease 1 reflects the predominant expression of ClC-5 in PT cells, where it codistributes with the V-ATPase in subapical, early endosomes (158, 271). Studies in two independent strains of *Clcn5* knockout (KO) mice have provided important insights into the mechanisms of PT dysfunction in Dent disease 1 (570, 794). The *Clcn5* KO mouse models recapitulate the LMW proteinuria and other manifestations of PT dysfunction associated with the disease **(FIGURE 4)**. In vitro experiments showed defective acidification of vesicles isolated from *Clcn5* KO mice, supporting a role for ClC-5 in acidification of early endosomes (272, 529). Although ClC-5 was initially considered as a simple Cl^- channel, later studies revealed that it is actually an electrogenic $2Cl^-/H^+$ exchanger, exploiting the H^+ gradient to move Cl^- into endosomes (567, 652) **(FIGURE 3)**. To better understand the biological role of this exchange activity and its relevance for Dent disease, Novarino et al. (529) generated a knock-in (KI) mouse model carrying a point mutation (E211A) affecting a glutamate residue that is crucial for the gating of CLC exchangers. The replacement of this glutamate by an alanine converts ClC-5 into a pure, uncoupled Cl^- conductor. The E211A mutant ClC-5 did not affect endosomal acidification, in contrast with the severe defect observed in ClC-5 KO. However, despite the normal endosomal acidification, the KI mice showed the same phenotype as that of *Clcn5* KO mice, including LMW proteinuria, glycosuria, hyperphospha-

turia, and hypercalciuria. Furthermore, a similar uncoupling mutation (E211Q) has been reported in a Japanese patient with Dent disease (672) supporting that PT dysfunction in Dent disease may thus occur despite normal endosomal acidification. Instead of the simple Cl^- shunt hypothesis, the disease may be caused by defective exchange activity, i.e., uncoupling of Cl^- from H^+ gradients and defective endosomal Cl^- accumulation. ClC-5 could actually mediate endosomal acidification independently of the V-ATPase in the early endosomes, with luminal H^+ uptake driven by the favorable gradient for Cl^- (652) **(FIGURE 3)**. Recent studies in conditionally immortalized PT cells from patients with mutations involving different domains of ClC-5 showed differing effects on endosomal acidification, uncoupled to defects in receptor-mediated endocytosis (257). A potential role of vesicular Cl^- concentration or transmembrane voltage of endosomes, which could affect other transport systems or vesicule recycling, has been hypothesized (350, 705).

Studies in *Clcn5* KO and KI mice have demonstrated that inactivation of ClC-5 is associated with a severe trafficking defect in PT cells **(FIGURE 4)**, with loss or reduced levels of megalin and cubilin at the brush border, impaired endocytosis and lysosomal processing of endocytosed ligands, and defective internalization of NaP_i-IIa and/or Na^+/H^+ exchanger 3 (NHE3) (121, 529, 570, 794). Importantly, mice lacking ClC-5 do not show ultrastructural alterations of the endocytic apparatus (121), a finding confirmed in kidney biopsies from patients with Dent disease and established mutations in *CLCN5* (501). The use of differentiated primary PT cells grown on filters evidenced that the endocytic defect observed in *Clcn5* KO mice was retained in vitro (225, 594, 738). The link between ClC-5 expression, receptor-mediated endocytosis, and PT dysfunction was further supported by a proof-of-concept study investigating the effect of bone marrow transplantation in *Clcn5* KO mice (225). Transplantation of wild-type bone marrow in *Clcn5* KO mice significantly improved PT dysfunction, with bone marrow-derived cells engrafted in the kidney, surrounding PT cells which showed a rescue of the apical expression of ClC-5 and megalin receptors. The improvement of PT dysfunction correlated with the rescue of *Clcn5* gene expression in kidneys. Coculture of *Clcn5* KO mouse PT cells (mPTCs) with bone marrow-derived cells confirmed rescue of ClC-5 and megalin, resulting in improved endocytosis. Nanotubular extensions between the engrafted bone marrow-derived cells and PT cells were observed in vivo and in vitro, playing a key role in the rescue mechanism (225).

Despite their vulnerability, PT cells are able to recover from an ischemic or toxic insult, as surviving cells dedifferentiate and proliferate to eventually restore tubular integrity (66). A similar process occurs in Dent disease, with a fourfold increase in the proliferative activity of PT cells [assessed by transcription of proliferating cell nuclear antigen (PCNA), KI-67, and cyclin E] paralleled by dedifferentiation (expression of osteopontin and the mesodermal marker carbonic anhydrase type III, CA3). The induction of the latter was also linked to an increased production of superoxide anion and the induction of type I superoxide dismutase and thioredoxin, pointing to increased oxidative stress and solicitation of cell oxidative defenses in *Clcn5* KO kidneys (229). Of note, these modifications occurred at a time when no visible alterations in cell morphology or renal failure were observed in *Clcn5* KO mice, and neither was there any change in the apoptotic rate. Albumin is also known to exert a potent survival activity in mouse PT cells, most likely through scavenging of reactive oxygen species (335), so that a reduced capacity of albumin uptake may be deleterious.

The potential link between the functional loss of ClC-5 and PT dysfunction can be proposed as follows. The defective Cl^- transport in early endosomes leads to impaired trafficking and recycling of apical receptors, defective receptor-mediated endocytosis, and ensuing urinary loss of LMW ligands (121). The functional loss of ClC-5 is also associated with impaired lysosomal function, as shown by the defective processing of endocytosed LMW ligands (121). The lysosome defect may at least in part be due to defective megalin which is critical for reabsorbing (mannose 6-phosphate devoid) lysosomal enzymes that are continuously filtered from the circulation, providing a major source of lysosomal enzymes in PT cells (521). In turn, the lysosomal defect might compromise autophagy, the cytoprotective mechanism for the degradation of damaged organelles through lysosome-mediated self-digestion (674). The defective lysosomal-mediated clearance of autophagosomes, containing ubiquitinated proteins and dysfunctional mitochondria, may lead to oxidative stress as observed in ClC-5 KO kidneys (229). It was recently shown that oxidative stress disrupts the integrity of the junctional complex [i.e., zonula occludens 1 (ZO-1) protein] (845), which might activate an abnormal signaling cascade involving the ZO-1-associated nucleic acid binding protein (ZONAB, also called Y-box protein 3, YBX3), a transcription factor known to cause proliferation (increased transcription of cyclin D1 and PCNA) and apical dedifferentiation (repression of the transcription of megalin and cubilin) in proximal tubule cells (433). The crucial pathogenic role of oxidative stress in mediating the epithelial dysfunction associated with endolysosomal diseases will be elaborated in the section dealing with nephropathic cystinosis (207, 591). Of note, the fact that ClC-5 is also detected in cells lining the thick ascending limb of Henle's loop and in the α-type intercalated cells of the collecting ducts (CD) (158) may explain some of the distal tubular manifestations of the disease, including defects in urinary acidification (458).

Inactivating mutations in the inositol polyphosphate 5-phosphatase OCRL induce defects in the endolysosomal system

which generally mimicks the PT dysfunction encountered in Dent disease 1. The similar phenotype is explained by the association of OCRL with early endosomes, where it acts to maintain low levels of $PI(4,5)P_2$ for proper endocytic trafficking (754, 774). The functional loss of OCRL induces an increase in $PI(4,5)P_2$ levels in early endosomes, which stimulates uncontrolled actin polymerization and impairs the trafficking of different receptors including megalin (774). These events lead to the trapping of megalin in early endosomes, reducing its recycling to the plasma membrane, impairing receptor-mediated endocytosis and causing PT dysfunction (148). The absence of OCRL is also leading to $PI(4,5)P_2$ accumulation on autolysosomal membranes, causing defective autophagic flux and increased levels of autophagosomes, which could be toxic for PT cells (146).

If the link between deficient ClC-5 or OCRL and defective PT apical endocytosis has been established, the transition between such PT dysfunction and progression to CKD in Dent disease remains to be deciphered. Atypical features (nephrocalcinosis, fibrosis) are observed in the few kidney biopsies available (858). The classical mechanisms of albumin toxicity on PT cells, which are considered in case of glomerular proteinuria, cannot be evoked here, since PT cells in Dent disease are prevented from endocytosis-mediated albumin overload. Presumably, early changes in PT cells, including proliferation, dedifferentiation, autophagy, and metabolic adaptation, may become maladaptive and promote inflammation and progression of tubulointerstitial fibrosis by various mechanisms (241, 436). The role of tubular proteinuria, a universal feature of the disease, should also be considered, as increasing evidence suggests that distal nephron segments may elicit specific stress response when exposed to proteinuria (178, 185a).

3. Cystinosis

A) BRIEF CLINICAL DESCRIPTION. Cystinosis is a rare disease (incidence: 1:100,000–1:200,000 live births) that is caused by recessive mutations in the *CTNS* gene that encodes the lysosomal cystine-H^+ cotransporter cystinosin (111, 364, 748). *CTNS* is expressed in all tissues: mutations causing cystinosis result in a lysosomal storage disorder characterized by a multi-systemic accumulation of cystine crystals. Children with infantile cystinosis (MIM no. 219800), the most frequent and most severe form of cystinosis, develop RFS typically around age 6 to 12 mo, with accompanying polyuria, polydipsia, failure to thrive, and rickets. The GFR begins to deteriorate from 5 to 6 yr of age, leading to ERSD by ~10 yr of age if untreated (188, 227). In addition to the kidney manifestations, patients present early depositions of cystine crystals in the cornea, and can develop retinopathy, hypothyroidism, hypogonadism, diabetes, myopathy, and deterioration of the central nervous system (227, 515). The juvenile (MIM no. 219900) and the ocular (MIM no. 219750) forms of cystinosis are milder and rarer than the typical, infantile cystinosis (227). There is a specific treatment for cystinosis: cysteamine, an aminothiol that can deplete the intralysosomal cystine through the reduction of cystine, and the formation of cysteine and a cysteamine-cysteine mixed disulfide which exits the lysosome via the cationic amino acid transporter PQLC2 (352, 435). Most of these complications, with the exception of the RFS, can be delayed or attenuated with cysteamine therapy (81, 414).

B) GENETICS. More than 100 pathogenic mutations of the *CTNS* gene (17p13.2) have been reported (188). Founder mutations, including a 57-kb deletion in *CTNS* which affects 65% of patients of northern European descent but is almost completely absent in patients from other origins, have been described (110). Genotype-phenotype correlation revealed that severe or truncating mutations on both alleles are usually associated with infantile cystinosis, while juvenile and ocular forms of cystinosis are usually associated with at least one mild mutation. However, some missense mutations in *CTNS*, which result in mutated forms of cystinosin located in lysosomes but unable to carry cystine transport, have been found in patients with juvenile cystinosis, suggesting that cystinosin exerts functions beyond cystine transport (365).

Cystinosin is a 367-amino acid protein, with seven predicted transmembrane domains, a luminal NH_2-terminal region bearing seven *N*-glycosylation sites and a cystolic COOH-terminal GYDQL lysosomal targeting signal (748). An additional lysosomal targeting motif, YFPQA, reinforces association with lysosomes (111). A longer CTNS isoform (cystinosin-LKG) can be generated by alternate splicing of exon 12, localized into lysosomes, the secretory apparatus, and the plasma membrane (734). Cystinosin is a high-affinity cystine-proton symporter that uses the proton gradient to export cystine from the acidic lysosome to the cytosol **(FIGURE 4)**. Since the low abundance of cystinosin transporters in lysosomes is the rate-limiting step for cystine transport, the disruption of cystine transport results in intralysosomal accumulation of cystine, reflecting the lysosomal degradation of disulfide-bearing proteins, such as albumin which is internalized via receptor-mediated endocytosis. In turn, cystine may organize into crystals within the lysosomal matrix: although these crystals are specific for cystinosis, they are probably not instrumental for the development of PT dysfunction. They are indeed not detected despite early manifestations of PT cell dysfunction in patients and mouse models of cystinosis (110). This conclusion is supported by the lack of effect of cysteamine, which decreases cystine levels, on the manifestations of RFS (81). Instead, multiple alterations in cystinosis cells are probably involved in the functional defects that characterize the early stage of cystinosis. These defects include impaired lysosomal dynamics, with lysosomes engorged by undigested proteins and clustered around the nuclei; defective clearance of endocytic cargo, with also a decreased expression of apical receptors; impaired proteolysis and limited amino acid and cysteine availability in the cytosol, causing redox imbalance and oxi-

dative stress; abnormal clearance of autophagic vesicles and accumulation of damaged mitochondria, which further increases ROS production (see below). In the long term, these modifications may also activate the inflammasome and apoptosis, leading to cell atrophy and irreversible tissue damage (110).

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. Studies based on a *Ctns* KO mouse model that recapitulates multiple features of cystinosis have demonstrated that the functional loss of cystinosin is reflected by enlarged, perinuclear lysosomes, abnormal proliferation and dysfunction of PT cells, which showed a progressive loss of the apical expression of megalin and of the glucose (SGLT2) and phosphate (NaP_i-IIa) cotransporters (228, 591). Despite the identification of cellular defects associated with cystinosis in different models and cell systems (see above), a unifying mechanism linking loss of cystinosin, lysosomal dysfunction, and defective transport by PT cells had not been deciphered until recently.

An essential role of the endolysosomal system is to capture and degrade intracellular worn-out constituents through autophagy, particularly in PT cells, whose intense reabsorptive and transport properties require the maintenance of mitochondrial network (215). The autophagy-mediated turnover of damaged mitochondria is required for protecting PT from acute tubular injury (340). Accumulation of distorted mitochondria and of autophagy receptor SQSTM1/p62 in kidney biopsies and urinary cells from cystinotic patients (640) suggested that autophagy could play a role in the PT dysfunction due to cystinosis. Recent studies confirmed that the genetic deletion of cystinosin impaired the autophagy-mediated clearance in vitro and in vivo, due to defective lysosomal degradation capacity (207). In turn, the defective autophagy clearance led to the accumulation of damaged and dysfunctional mitochondria in *Ctns* KO cells, overproducing mitochondrial-derived ROS. A signaling cascade bridging excessive mitochondrial ROS and epithelial dysfunction was deciphered, involving the tight junctions. In differentiated epithelial cells, tight junctions repress the nuclear translocation of ZONAB/YBX3, a transcriptional factor that promotes cell proliferation and represses PT differentiation during kidney development (433). The increased levels of mitochondrial ROS enhanced GNA12/Gα_{12}-SRC-mediated phosphorylation of the tight junction protein ZO-1 and its subsequent misrouting to enlarged, nondegradative endolysosomes. In turn, the disruption of tight junction integrity promotes ZONAB/YBX3 signaling, with increased proliferation (e.g., *Ccnd1*, *Pcna*) and decreased differentiation (e.g., *Lrp2*) targets, resulting in defective endocytosis in *Ctns* KO cells. The biological relevance of the YBX3 signaling for maintaining PT cell integrity was confirmed by gain- and loss-of-function approaches and pharmacological interventions. In particular, treatment of *Ctns* KO mice and their derived PT cells with the mitochondrial-targeted antioxidant MitoTempo, which is clinically tested in various mitochondrial diseases, not only repairs dysfunctional mitochondria and averts mitochondrial oxidative stress, but also rescues the integrity of tight junctions, cell differentiation, and endocytic uptake (207). The identification of this signaling cascade **(FIGURE 5)** substantiates the role of lysosomes in preserving the autophagy-mediated quality control of mitochondria that are crucial for the high transport activities performed by specialized epithelial cells.

4. Other genetic disorders associated with defective receptor-mediated endocytosis

Recent studies have extended the role of receptor-mediated endocytosis in association with other genetic disorders that mimick the PT dysfunction associated with Dent disease. Inactivation of the chloride channel cystic fibrosis transmembrane conductance regulator (CFTR) causes cystic fibrosis (CF) (MIM no. 219700), the most common autosomal recessive disease in Caucasian individuals (613). CFTR is a 1,480-amino acid protein that belongs to the ATP-binding cassette (ABC) family of integral membrane proteins. It is located mainly in the apical membrane area of secretory epithelia, where it functions as a cAMP-dependent chloride channel and as a conductance regulator via interactions with other ion channels (683). CFTR is significantly expressed in the kidney, located in the apical area of PT cells, where it codistributes with ClC-5 in PT endosomes **(FIGURE 3)** (357). Defective receptor-mediated endocytosis has been demonstrated in CFTR-null mice, with impaired LMW protein (β2-microglobulin) uptake and a waste of cubilin and its LMW ligands into the urine. A significant LMW proteinuria (and particularly transferrinuria) was also documented in the *Cftr*$^{delta/delta}$ mice and in a cohort of patients with CF. Several reasons could explain the milder renal phenotype that is observed in *Cftr* KO mice and patients with CF in comparison with *Clcn5* KO mice and patients with Dent disease. First, the difference could reflect the more distal distribution of CFTR as compared with ClC-5 along the PT. Indeed, although ClC-5 is distributed evenly in the S1 to S3 parts of the PT, CFTR seems to be most abundant in the S3 segment of the PT, which displays lower endocytic activity (357). Second, CFTR functions as a cAMP-regulated, ATP-dependent chloride channel, whereas the flux of chloride through ClC-5 depends constitutively on transmembrane Cl^- and H^+ concentration gradients, together with the membrane voltage. Third, the discrete nature of renal manifestations in CF might be due to tissue-specific protective mechanisms, such as the occurrence of functional CFTR splice variants (493), or alternative pathways for Cl^-.

Hepatocyte nuclear factor 1α (HNF1α) is a homeodomain-containing transcription factor expressed in the liver, pancreas, and proximal tubule of the kidney (749). HNF1α binds to DNA as a homodimer or a heterodimer with the

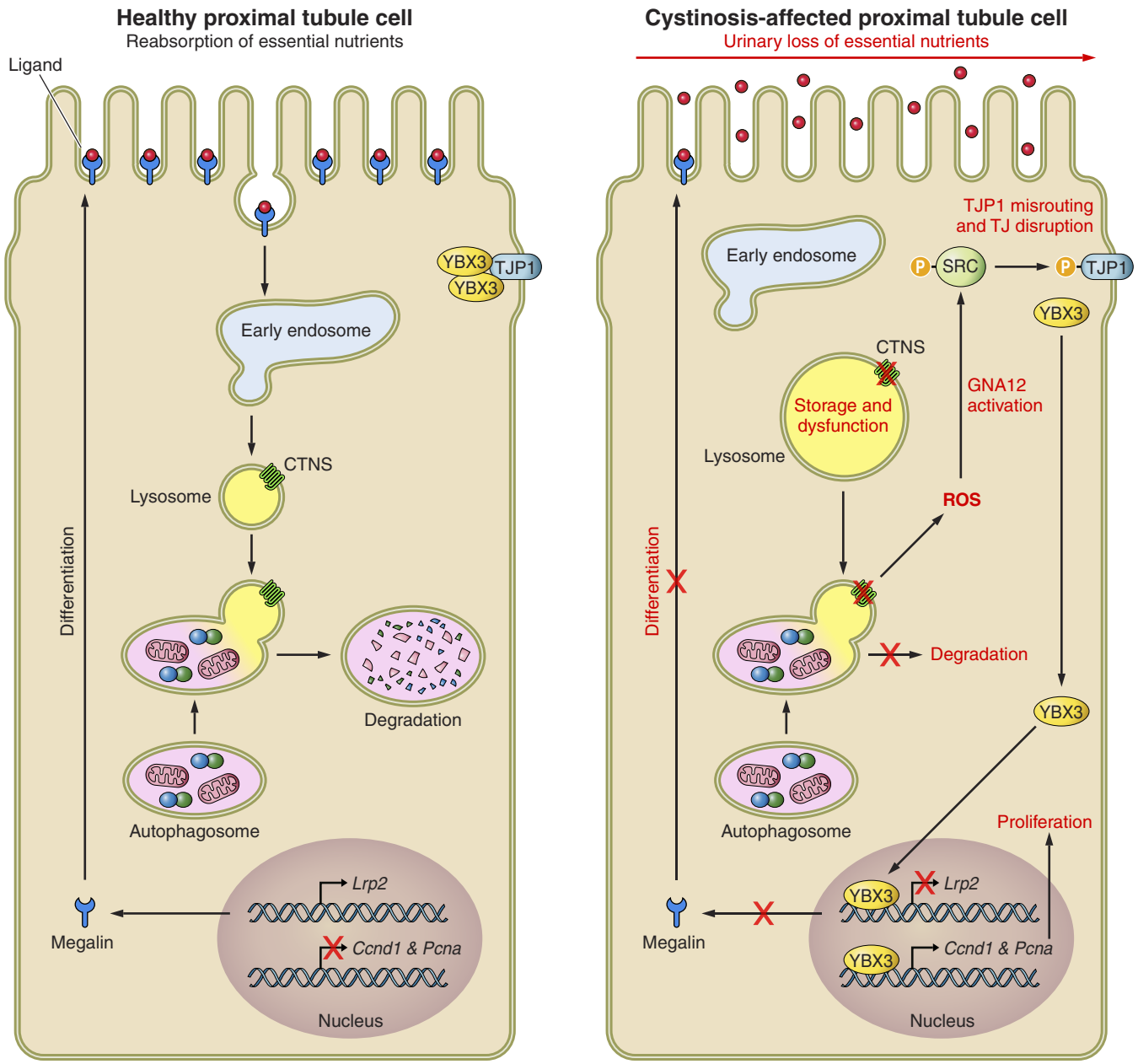


FIGURE 5. Cascade linking primary lysosomal defect and proximal tubule dysfunction in cystinosis. Inactivating mutations in the lysosomal transporter cystinosin (CTNS) cause lysosomal dysfunction storage disease within proximal tubule cells. The ensuing lysosomal dysfunction impairs the cellular degradation of autophagosomes containing SQSTM1$^+$ aggregates and/or damaged mitochondria, promoting the generation of reactive oxygen species (ROS). In turn, the ROS stimulate GNA12-SRC-mediated phosphorylation of the TJP1 adapter protein, resulting in its misrouting to an endolysosomal compartment. The disruption of tight junction integrity releases the transcription factor YBX3, which induces abnormal cell proliferation (induction of the transcription of *Ccnd1* and *Pcna*, coding for proliferation factors) and represses apical endocytic receptors such as megalin (M coded by *Lrp2*), causing epithelial dysfunction in cystinosis cells. TJ, tight junction. [Adapted from Festa et al. (207).]

closely related HNF1β. HNF1α is only found in PT cells, whereas HNF1β is expressed in most nephron segments. Heterozygous mutations of HNF1α cause an autosomal dominant form of diabetes mellitus (MODY-HNF1A) and kidney tubular dysfunction (574). The *Hnf1*α KO mice show LMW proteinuria and decreased uptake of β2-microglobulin, indicating a major endocytic defect due to decreased expression of megalin/cubilin receptors (739). The promoters of the *LRP2* and *CUBN* genes coding for megalin and cubilin, respectively, contain binding sites for HNF1α. The functional interaction of HNF1α with these promoters was demonstrated in vitro. The expression of *Clcn5* was reduced in the proximal tubule segments of HNF1α-null kidneys, and it was rescued, with a parallel

increase in receptor-mediated endocytosis, upon transfection of HNF1α-null cells with wild-type but not with mutant HNF1α. Importantly, LMW proteinuria was consistently detected in individuals with HNF1A mutations compared with healthy controls and patients with non-MODY-HNF1A diabetes mellitus (739). Thus HNF1α plays a key role in the constitutive expression of megalin and cubilin, hence regulating receptor-mediated endocytosis in the kidney.

B. Disorders of Uric Acid Handling

1. Uric acid regulation by the kidney

Uric acid is produced by dietary and endogenous purine metabolism mostly in the liver, where it is generated from xanthine by the xanthine oxidase. In most mammals, uric acid is further metabolized by the hepatic enzyme uricase (encoded by the *Uox* gene) to highly soluble allantoin, which can be readily excreted in the urine. In humans, this uricase is inactive as a result of mutational silencing making uric acid the final breakdown product of purine metabolism (826, 827). Uric acid is a weak diprotic acid which exists predominantly as monosodium urate anion at physiological pH of 7.4. The terms urate and uric acid are often interchangeably used to refer to the total pool of dissociated and undissociated uric acid in the circulation, since the ratio of urate to uric acid remains stable with constant pH. This ratio is much more variable in the urine with broader range of pH. Lower urinary pH values result in a larger proportion of uric acid in the undissociated form (60). Hyperuricemia has been linked to various diseases including gout, hypertension, as well as cardiovascular and renal disease (200, 355, 699). In particular, the issue of whether urate contributes to kidney disease, hypertension, or diabetes remains controversial (354). On the other hand, urate seems to have a protective role as a potent antioxidant, and low serum urate concentrations have been associated with several neurological diseases (548). Serum urate levels depend on both urate production and its removal by the kidney and intestine. Although production of urate through dietary purine intake or alterations in purine metabolism affect serum urate concentrations, changes in serum urate levels are mostly due to impaired renal excretion (333, 669).

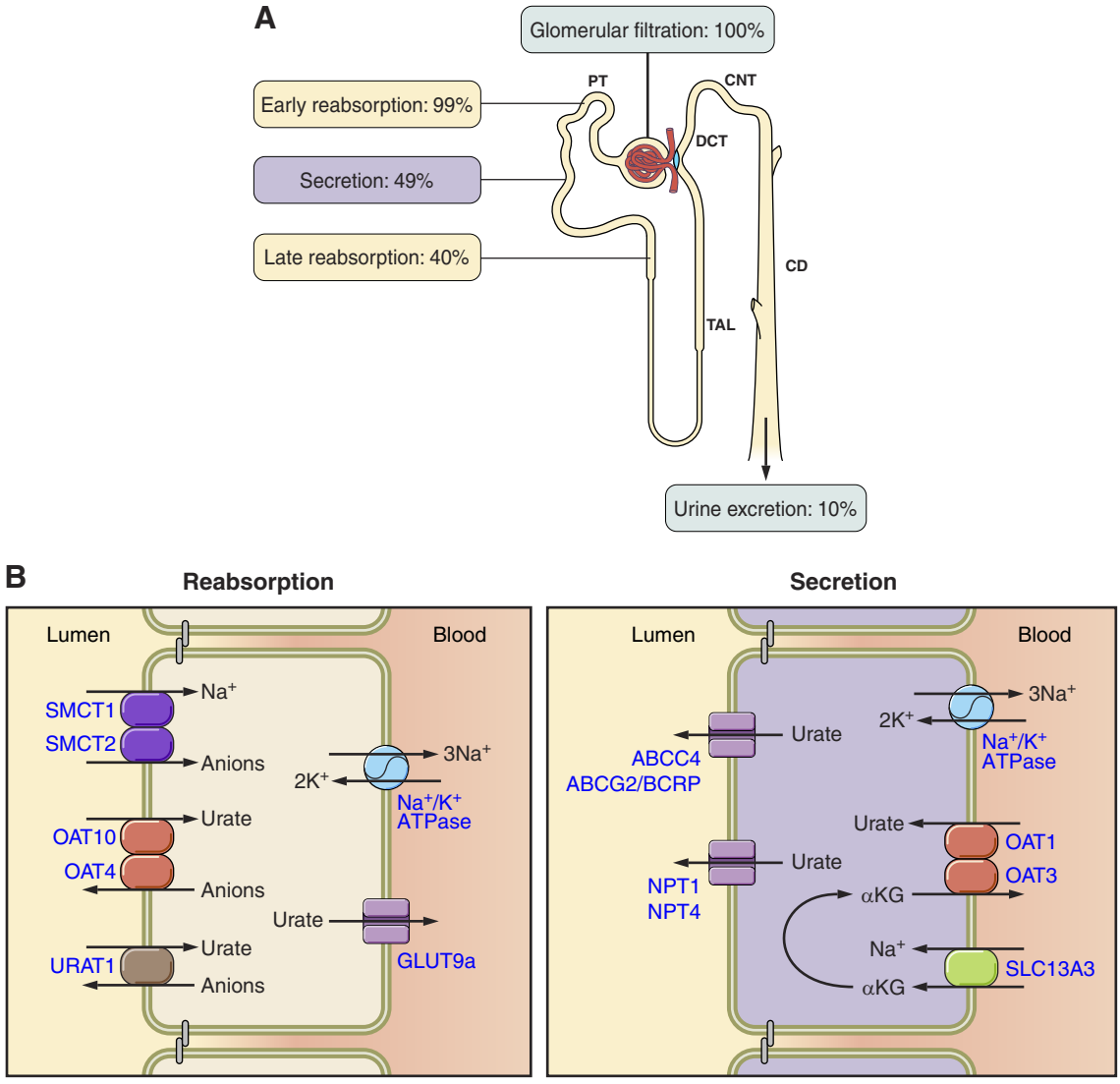
Approximately two-thirds of daily urate production is excreted by the kidney, the remainder being eliminated by the gastrointestinal tract. Previous physiological and pharmacological studies have suggested a bidirectional transport of urate in the PT. A four-component model has been accepted for many years, which proposed that urate handling by the kidney consists of four steps: glomerular filtration, reabsorption of nearly all of the filtered urate in the early PT, subsequent tubular secretion of up to half of this amount, and finally postsecretory reabsorption of the majority of the secreted urate in the late PT with only ~10% of the filtered urate being excreted into the urine **(FIGURE 6)**. This model was based on an interpretation of the pharmacological interactions of antiuricosuric and uricosuric agents (169, 612, 689, 706). Secreted urate was suggested to contribute moderately to urate excretion, implying that the excreted urate represents mainly the filtered urate that escapes reabsorption (60, 502, 503, 589, 617, 618). However, the recent molecular identification of key urate transporters allowed a better understanding of urate handling in the kidney, showing the importance of urate secretion in urate homeostasis.

The exact molecular mechanisms that control urate handling in the kidney are not yet completely understood, although the molecular identification of the kidney-specific urate/anion exchanger URAT1 in 2002 by Enomoto et al. promoted the discovery of several transporters involved in urate transport (17, 191). These transporters include NPT1 (360), ABCC4 (761), SMCT1 (253), SMCT2 (254), OAT10 (29), GLUT9 (16, 99, 778), ABCG2/BCRP (816), as well as urate transport-related scaffolding protein PDZK1 (18). Their identification promoted the idea of a urate-transporting multimolecular complex, the "urate transportome" (17) **(FIGURE 6)**

In plasma, urate mostly exists as an organic anion, which is freely filtered by the glomerulus. In the PT, a complex interplay of various transport pathways is involved in the reabsorption of filtered urate. The PT cells are primed for apical urate transport by the Na^+-dependent absorption of lactate and other monocarboxylate anions, which increases the intracellular concentration of anions that exchange with luminal urate. This process is mediated by the apical Na^+-coupled monocarboxylate cotransporters 1 (SMCT1) and 2 (SMCT2), respectively, encoded by the *SLC5A8* and *SLC5A12* genes, which colocalize with urate transporters at the apical membrane of PT cells (503). Urate-anion exchange in turn involves the urate transporter URAT1, encoded by the *SLC22A12* gene, and the organic anion transporters OAT4 and OAT10, which are encoded respectively by the *SLC22A11* and *SLC22A13* genes (29, 191, 278). Exit of urate from the PT cell is mediated by the basolateral voltage-dependent urate transporter GLUT9a (15, 503, 633, 778). The secretion of urate by the PT is a mirror image of the urate uptake. It involves the basolateral urate transporters OAT1 and OAT3, transporting the anion into the cell in exchange for α-ketoglutarate, followed by secretion via the ATP-driven efflux pumps ABCC4 (ATP-binding cassette C4, encoded by the *ABCC4* gene) and ABCG2/BCRP (ATP-binding cassette subfamily G member 2 or breast cancer resistance protein, encoded by the *ABCG2* gene) and the electrogenic apical urate transporters NPT1 and NPT4 (encoded by the *SLC17A1* and *SLC17A3* genes) (336, 359, 360, 503, 761, 816) **(FIGURE 6)**.

Serum urate levels display a strong genetic predisposition, with a heritability of ~40–70% (405). Various GWAS

pointed to several genetic loci associated with serum urate concentration. These loci include urate transporter-coding genes including *SLC2A9* (GLUT9), *ABCG2* (ABCG2/BCRP), *SLC17A1* (NPT1), *SLC17A3* (NPT4), *SLC22A11* (OAT4), *SLC22A12* (URAT1), and *PDZK1* (PDZK1/NHE-RF3) (17, 106, 151, 179, 395, 405, 430, 542, 744, 778, 837). A very large effect was identified for the *SLC2A9* and *ABCG2* loci, explaining respectively 3 and 1% of the variance in serum urate concentration (405). The important role of GLUT9 (*SLC2A9*) in urate handling will be de-



C

	RHUC type 1	RHUC type 2
Gene	*SLC22A12*	*SLC2A9*
Protein	URAT1	GLUT9
Effect of mutation	Loss-of-function Dominant-negative effect	Loss-of-function
Serum UA	0.5-1.0 mg/dL	0-0.2 mg/dL
FE_{UA}	40-90%	~150%
UA transport defect	Early reabsorption defect	Total reabsorption defect

scribed below (see sect. III*B2*B*II*). ABCG2 was initially identified as a multidrug resistance protein (181). Dehghan et al. (151) were the first to indicate a role for ABCG2 in urate handling through a GWAS showing that the *ABCG2* locus is associated with serum urate level and gout. ABCG2 was subsequently found to be a high-capacity urate transporter. Using a *Xenopus* oocyte expression system, Woodward et al. (816) demonstrated that ABCG2 mediates urate efflux. The role of ABCG2 as a high-capacity urate transporter was verified by Matsuo et al. (469) using membrane vesicles from transfected HEK293 cells. Several loss-of-function *ABCG2* variants that confer a risk of hyperuricemia and gout have been identified, including the common variant Q141K, which reduces urate efflux by 54% (816).

Matsuo et al. (469) investigated the relationship between ABCG2 dysfunction and renal urate excretion in hyperuricemia patients. Surprisingly, hyperuricemic patients with graded levels of ABCG2 dysfunction, stratified by genotype for dysfunctional single nucleotide polymorphisms (SNPs), exhibited elevated urinary urate excretion and fractional excretion of urate (FE_{UA}) levels (332, 817). Furthermore, *Abcg2* KO mice showed increased renal urate excretion and serum urate levels and reduced intestinal excretion compared with wild-type mice. Thus ABCG2 dysfunction appeared to cause decreased extrarenal urate excretion (332, 817). It was shown subsequently that ABCG2 dysfunction can also impair renal excretion of urate in patients with lesser degrees of function (468).

The neurohumoral regulation of urate homeostasis involves angiotensin II, the sympathetic tone, insulin, and PTH (503). Alterations in volume status and/or dietary salt intake affect serum urate concentrations via modifications of its urinary excretion. Angiotensin II and epinephrine are the potential mediators (496, 833). The retention of urate by the kidney stimulated by insulin may play a crucial role in the associations between metabolic syndrome, hyperuricemia, and gout (115, 503). Elevated PTH levels also decrease urate excretion, in primary hyperparathyroidism and during pharmacological therapy for osteoporosis, which may be relevant for the association between gout and CKD (325, 503, 510). Finally, sex hormones appear to regulate urate transporters in mouse (309, 730), which could possibly explain why urate levels are higher in men compared with women (190, 633).

Here, we will address inherited disorders primarily involving renal urate transporters, resulting in hypouricemia. We will not discuss inborn errors of purine metabolism such as phosphoribosylpyrophosphate synthetase (PRPPS) superactivity (MIM no. 300661) characterized by congenital hyperuricemia and hyperuricosuria (575); nor familial juvenile hyperuricemic nephropathy (HNFJ1) (MIM no. 162000), a form of tubulointerstitial kidney disease caused by dominant mutations in the *UMOD* gene encoding uromodulin (Tamm-Horsfall protein), in which hyperuricemia is secondary to inappropriate tubular reabsorption of urate (low FE_{UA}) (162).

2. Renal hypouricemia

A) BRIEF CLINICAL DESCRIPTION. Renal hypouricemia (RHUC) is an autosomal recessive kidney disorder characterized by defective reabsorption of urate in the PT, resulting in increased urate clearance associated with hypouricemia. The first RHUC case was reported by Greene et al. in 1972 (261), but the molecular mechanisms and defective genes associated with this disorder were only identified 30 yr later. The majority of reported cases were initially reported in Japanese patients and non-Ashkenazi Jews (171, 191, 330, 331, 342, 396, 427, 726). However, recent studies suggested that RHUC is not restricted to East Asian populations, as the condition has been reported in various ethnic groups (e.g., Arab Israelis, Iraqi Jews, Caucasians, and Roma) and in geographically noncontiguous countries such as Macedonia, the United Kingdom, the US, the Czech Republic, and Spain (127, 226, 708).

The diagnosis of RHUC is based on hypouricemia (<119 μM or 2 mg/dl) with an increased fractional excretion of urate (FE_{UA} >10%) without any underlying renal or systemic diseases, such as RFS, or drug-induced tubulopathy. RHUC can be subdivided into two categories based on the molecular abnormalities (see below): renal hypouricemia type 1 (RHUC1) (MIM no. 220150) and renal hypouricemia type 2 (RHUC2) (MIM no. 612076). RHUC2 is char-

FIGURE 6. Handling of uric acid by the kidney. *A*: the classical four-component model of uric acid transport in the proximal tubule (PT), including glomerular filtration of urate, reabsorption of nearly all of the filtrated urate in the early PT, subsequent tubular secretion of up to half of this amount and final, postsecretory reabsorption of the majority of the secreted urate in the late part of PT. CD, collecting ducts; CNT, connecting tubule; DCT, distal convoluted tubule; TAL, thick ascending limb. *B*: molecular mechanism of urate reabsorption and secretion in PT. The reabsorption of urate involves the Na^+-dependent monocarboxylate anion transporters SMCT1 and SMCT2, which increase the intracellular concentration of anions and drive urate uptake via the apical exchange mediated by the urate transporter URAT1 and the organic anion transporters OAT4 and OAT10. GLUT9a is the exit pathway for urate at the basolateral membrane. The secretion of urate involves a basolateral entry in exchange with α-ketoglutarate (αKG), mediated by OAT1 and OAT3. The α-ketoglutarate gradient is provided by SLC13A3. On the apical side, the secretion of urate involves the ATP-driven efflux pumps ABCC4 and ABCG2/BCRP, as well as the electrogenic urate transporters NPT1 and NPT4. *C*: characteristics of renal hypouricemia (RHUC) type 1 and 2. ABCC4, ATP-binding cassette subfamily C member 4; ABCG2, ATP-binding cassette subfamily G member 2; BCRP, breast cancer resistance protein; GLUT9a, glucose transporter 9a; OAT, ornithine aminotransferase; SLC13A3, Na^+-dependent dicarboxylate transporter; SMCT, Na^+-coupled monocarboxylate transporter; NPT, Na^+-dependent phosphate transport protein; URAT1, urate transporter-1. [Adapted from Mandal and Mount (453) and Dinour and co-workers (171, 172).]

acterized by much lower serum urate levels and a FE_{UA} of ~150%, compatible with a total urate reabsorption defect, compared with RHUC1 (171) **(FIGURE 6*C*)**.

The majority of patients with RHUC remain clinically silent, and the disorder is often recognized during screening procedures of various unrelated diseases (700). Some patients may present nephrolithiasis, hypercalciuria, and hematuria. It is not completely clear why these manifestations are associated with RHUC, but a possible explanation is that a high rate of urate excretion results in stone formation followed by hematuria. Therapy is based on alkalinization of the urine and high fluid intake to prevent the precipitation of urate and the formation of urate nephrolithiasis. Indeed, elevated urinary concentration of urate, reduced urine ouput and low urine pH are major risk factors for the development of urolithiasis (190, 669, 700). Although not frequent, exercise-induced acute kidney injury (AKI) is a potential complication of RHUC (330, 396, 541, 669, 682, 700). The AKI typically develops after acute anaerobic exercise in previously healthy young adults and is associated with severe loin pain, nausea and vomiting, but without evidence of massive rhabdomyolysis. There is a marked male preponderance in such exercise-induced AKI (109). Contrast computed tomography of the kidneys demonstrates wedge-shaped defects, suggesting patchy renal vasoconstriction. The prognosis of exercise-induced AKI in patients with hypouricemia is good, with >80% of subjects recovering without dialysis therapy. The mechanisms of exercise-induced AKI associated with RHUC remain unclear; they could involve *1*) urate nephropathy resulting from an increase in urate production during exercise or *2*) renal reperfusion injury due to vasoconstriction caused by an exercise-induced increase in oxygen free radicals and a lack of urate, free radical scavengers (171, 330).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Hereditary renal hypouricemia is a heterogeneous, autosomal recessive disease that can be caused by mutations in the *SLC22A12* gene encoding the urate transporter URAT1 (RHUC1), or by mutations in the *SLC2A9* gene encoding the voltage-driven urate transporter GLUT9 (RHUC2).

I) Renal hypouricemia type 1 (RHUC1). Enomoto et al. (191) were the first to identify the urate transporter URAT1 and to demonstrate that mutational alterations in the gene *SLC22A12* (solute carrier gene family 22, 12th member; located at chromosome 11q13) coding for URAT1 are associated with RHUC1. URAT1 is a urate/anion exchanger, member of the organic anion transporter (OAT) family. It belongs to the amphiphilic solute carrier family (SLC22A) together with the organic cation transporters (OCT) (631, 671). The OAT family plays a crucial role in the transepithelial transport of various organic anions in the kidney. URAT1 is a membrane protein consisting of 553 amino acid residues with 12 putative transmembrane domains (TM). Similarly to other OAT family members, URAT1 has a large extracellular loop between transmembrane domain TM1 and TM2, and an intracellular loop between TM6 and TM7 (330, 396). The COOH-terminal end of URAT1 contains a binding motif for PDZ domain-containing proteins (190). The PDZ domain-containing protein PDZK1 interacts with URAT1 via this motif, and coexpression experiments demonstrated that URAT1 transport activity is increased by PDZK1/URAT1 interactions. PDZK1 may thus be as a scaffolding protein regulating the function of URAT1 (190). URAT1 is expressed specifically in the kidney where it is located in the apical membrane of PT cells. URAT1 transports urate from the lumen to the cytosol of the PT in exchange for monovalent organic anions, such as lactate and nicotinate. Pyrazinoate and several uricosuric agents such as probenecid and benzbromarone share the affinity for the URAT1 transporter (700).

The importance of URAT1 for the handling of urate was demonstrated by genetic analyses of Japanese patients with RHUC (191). These individuals harbour homozygous, heterozygous, or compound heterozygous loss-of-function mutations in the *SLC22A12* gene. Ichida et al. (330) showed that the p.W258X mutation predominates in Japanese patients with renal hypouricemia. This nonsense mutation produces a largely truncated protein (396). Expression of the mutant cDNA in *Xenopus* oocytes revealed that the truncated protein could not be targeted to the cell membrane, suggesting loss of function of the mutant protein (190). The p.W258X mutation is also predominant in Koreans with hypouricemia, indicating that the mutation originated in Asia (109) and expanded in the Japanese population either by founder effect or by genetic drift, or both (331). Studies in which mutant URAT1 proteins were expressed in *Xenopus* oocytes showed various degrees of residual transport activities, probably explaining the wide range of FE_{UA} values observed in RHUC patients (700). Ichida et al. (330) demonstrated a gene dosage effect of *SLC22A12* on C_{UA}/C_{cr} (urate clearance/creatinine clearance), correlating with the difference in serum urate levels. Serum urate levels were significantly lower and C_{UA}/C_{cr} was significantly higher in heterozygotes compared with healthy subjects. These changes were even more significant in homozygotes and compound heterozygotes (330)

Various types of *SLC22A12* mutations have been reported, including missense, nonsense, splice-site mutations, as well as short deletions and one gross deletion, and they are scattered along the 10 exons of the *SLC22A12* gene (856). Zhou et al. (856) recently summarized the clinical features and *SLC22A12* gene mutations reported up to now in RHUC patients. They showed that the frequency of the p.W258X mutation was very high (79.7%), as initially described by Ichida et al. (330). Patients with at least one p.W258X mutation were more likely to present urolithiasis, hematuria, or AKI (856). This mutation was predominant in patients of Jap-

anese and Korean origin, but was not found in patients of Chinese origin. The second most prevalent mutation, p.R90H, was found in patients of Japanese, Korean, and also Chinese origin. These two mutations were not observed in patients from other racial origins, including Czech Roma, Iraqi-Jews, and patients of European origin (856). Recently, Stiburkova et al. (710) suggested that not only loss-of-function mutations of *SLC22A12* but also dominant-negative effects cause RHUC1. Indeed, by coexpression and colocalization studies, they showed an accumulation and retention of the wild-type URAT1 protein in the ER by the p.G366R and p.R477H variants, which were detected in Czech family with an extremely rare coincidence of RHUC1 and autosomal dominant polycystic kidney disease (710).

Interestingly, *Urat1* KO mice exhibit a slightly higher FE_{UA} but do not develop significant hypouricemia (192, 310). The differences in plasma urate levels due to the loss of URAT1 in these mice are blunted by the degradation of urate in the liver. Indeed, in contrast to humans, mice possess the hepatic enzyme uricase (encoded by the *Uox* gene) which metabolizes urate to allantoin (311). Recently, a double KO mouse model for *Urat1* and *Uox* was developed, which may represent a suitable experimental model for RHUC type 1 (311). Administration of allopurinol was necessary to obtain plasma urate and urate excretion levels comparable to RHUC type 1 patients, since uricase deficiency in mice causes extreme hyperuricosuria and urate nephropathy (311, 825). Transgenic mice overexpressing *Urat1* showed no significant changes in plasma urate levels or urinary urate excretion, suggesting that URAT1 plays a less important role in the mouse kidney (383).

II) Renal hypouricemia type 2 (RHUC2). It was recently discovered that RHUC2 is caused by mutations in the *SLC2A9* gene (mapped to chromosome 4p15.3-p16), which encodes the urate transporter GLUT9 (172). GLUT9 is a member of the solute carrier family 2 (SLC2) of hexose facilitative transporters and consists of 12 transmembrane domains, a large extracellular loop between TM1 and TM2, and both NH_2- and COOH-terminal ends on the cytoplasmic side. Initially, GLUT9 was reported to be a glucose and/or fructose transporter (172). However, GWAS conducted to identify new genes in urate homeostasis showed significant association between variants in *SLC2A9* and serum urate levels (182, 366, 395, 405, 430, 778). Expression studies in *Xenopus* oocytes confirmed the role of GLUT9 as a urate transporter, with urate uptake significantly increased in GLUT9-expressing oocytes compared with control and URAT1-expressing oocytes (778). Increased urate uptake by overexpression of GLUT9 was also demonstrated in transfected human and mouse cells (99). The significance of GLUT9 function for human urate handling was further supported by the discovery of loss-of-function *SLC2A9* mutations in patients with RHUC (172, 173, 467).

The *SLC2A9* gene contains 14 exons and encodes 2 GLUT9 isoforms, a long (GLUT9a, 540 amino acids) and a short (GLUT9b, 512 amino acids) one, generated by alternative splicing and differing only in their NH_2-terminal region (26). The NH_2-terminal amino acids seem to play a role in their membrane trafficking and protein stability (51, 384). GLUT9a has a broad tissue distribution including the kidneys, liver, placenta, and leukocytes, whereas GLUT9b has been observed only in kidney and placenta (709). In the human kidney, GLUT9a is expressed at the basolateral membrane of PT cells **(FIGURE 6*B*)**, whereas GLUT9b was shown at the apical membrane of CD cells (384).

At least 10 different mutations in *SLC2A9* (including missense/nonsense mutations, 1 insertion, 1 deletion, and 1 duplication) associated with RHUC2 have been identified (172, 344, 467, 709). Most of these mutations have been functionally studied. However, interpretation of the pathogenicity of the identified variants remains difficult (629). Recently, Ruiz et al. (629) analyzed the function of known GLUT9 mutants using using [^{14}C]urate uptake assay and two-electrode voltage clamp in *Xenopus* oocytes. They demonstrated decreased urate transport by flux studies for most of the variants. None of the variants was permissive for glucose transport. Furthermore, two main categories of GLUT9 mutants were oberved: those harboring poor overall and cell-surface expression leading to low activity and those with preserved expression at the cell surface, but exhibiting decreased activity. Both mutant types are associated with a decreased urate transport ability, explaining the loss-of-function phenotype in RHUC patients (629).

Preitner et al. (579) investigated the renal phenotype of *Glut9* KO mice. Mice lacking GLUT9 are characterized by moderate hyperuricemia, massive hyperuricosuria, and early-onset obstructive nephropathy. However, the phenotype of these mice is modulated by the expression of *Glut9* in the liver, where it plays a role in the uptake of urate thereby facilitating its subsequent uricase-catalyzed degradation into allantoin (453). The liver-specific inactivation of *Glut9* led to severe hyperuricemia and hyperuricosuria, in the absence of urate nephropathy or structural changes in the kidney (579). Furthemore, the expression of GLUT9 in mouse kidney is different than in humans. In mouse, GLUT9 is mostly detected in the distal convoluted tubules (DCT) and connecting tubules, (CNT), with only limited expression in the PT (17, 579).

C. Disorders of Glucose Transport

1. Renal glucose handling

Glucose is a major source of metabolic energy for most cells of the body and is of critical importance in the brain. Glucose homeostasis is maintained by a complex interaction between gluconeogenesis in liver and kidney, absorption of

glucose by the kidney and intestine, as well as tissue storage and consumption. The kidney contributes to glucose homeostasis by reabsorption of virtually all the filtrated glucose at the PT level. Several transporters ensure the movement of glucose across PT cells, since cell membranes are impermeable to glucose. The rate-limiting step for PT reabsorption of glucose is its influx across the apical membrane via the Na^+-coupled glucose cotransporters SGLT1 and SGLT2 (295, 820, 821) **(FIGURE 7*A*)**. SGLT2 is a low-affinity/high-capacity cotransporter, which controls the bulk (90%) of glucose reabsorption and is expressed almost exclusively in the kidney, more particularly in the S1 segment of the PT (295, 820, 821). The remaining filtered glucose is reabsorbed by SGLT1, a high-affinity/low-capacity Na^+-glucose cotransporter, which is expressed more distally in the S2/S3 segment of the PT but is also strongly expressed in the intestine and which transports also galactose (295, 821). After the apical uptake, the transporters GLUT2 and GLUT1 facilitate the basolateral exit of glucose (113). The low-affinity glucose transporter GLUT2 works in synergy with SGLT2 in the S1 segment of the PT, whereas the high-affinity GLUT1 cooperates with SGLT1 in the S2/S3 segment (30, 459, 592) **(FIGURE 7, *A* AND *B*)**. This efficient and highly adaptive transport system ensures that glucose cannot be detected in the urine at below plasma glucose concentrations of 200 mg/dl. Glycosuria occurs when plasma glucose levels exceed the maximal reabsorptive capacity of the SGLT transport system, in the kidney PT, for known as the transport maximum for glucose, ranging from 260 to 350 mg/min/1.73 m^2 and corresponding to a plasma glucose level of 200 mg/dl (459, 490) **(FIGURE 7*C*)**.

Mutations in the gene encoding SGLT1 have been shown to cause glucose-galactose malabsorption, charcaterized by significant gastrointestinal dysfunction, but only mild renal glycosuria (752). Mutations in the gene encoding the GLUT2 transporter are associated with Fanconi-Bickel syndrome, a glycogen-storage disease with general PT dysfunction (484, 644). In this review we focus on familial renal glycosuria, involving the SGLT2 cotransporter.

2. Familial renal glycosuria.

A) BRIEF CLINICAL DESCRIPTION. Familial renal glycosuria (FRG) (MIM no. 233100) is an inherited disorder characterized by persistent glycosuria in the absence of both hyperglycemia and generalized PT dysfunction. The condition was first described by Hjärne in 1927 (301) and was historically classified into three different types (A, B, and O), based on the severity of glycosuria (88, 537, 602, 641). However, current molecular findings have enabled appropriate genotype-phenotype correlations in the vast majority of cases. Accordingly, a simpler and easier classification of FRG has been developed, based on the genetic defect (heterozygous, homozygous, or compound heterozygous *SLC5A2* mutations) (641). Glycosuria in FRG patients can range from <1 to >150 g/1.73 m^2 per day (855). No major clinical consequences are associated with FRG, which is considered to be a benign condition (641). However, clinical information is mainly based on case reports as an extensive evaluation of the phenotype associated with FRG in large cohorts is still lacking (88). Enuresis, polyuria, and a mild growth retardation and pubertal maturation delay were the only clinical manifestations observed during a 30-yr follow-up period of the originally described FRG patient (662). Other manifestations have occasionally been reported in severe forms of FRG (641), such as episodic dehydration and ketosis during pregnancy and starvation (537), the presence of autoantibodies without clinical evidence of autoimmune disease (149), an increased incidence of urinary tract infections (147, 149), as well as activation of the renin-angiotensin-aldosterone system (RAAS) secondary to natriuresis and possible extracellular volume depletion (87, 90). Moreover, selective aminoaciduria and even generalized aminoaciduria have been described in some cases, although it is not a general finding (88, 258, 452, 639). Interestingly, aminoaciduria has also been reported in patients with diabetes, and is most likely a consequence of the impaired glucose reabsorption in the PT rather than a primary defect (54, 641). Moreover, *Sglt2* KO mice, who mimic the glycosuric phenotype of patients with FRG, do not exhibit increased urinary excretion of amino acids (756). Hypercalciuria has also been reported in some patients with FRG, possibly indicative of further PT dysfunction (659, 662). Of note, it was recently shown that chronic loss of glucose in the urine did not protect from deterioration of the glucose tolerance in a large pedigree with FRG during a follow-up period of more than 10 yr (545).

B) GENETICS. FRG is caused by mutations in the *SLC5A2* gene, which is mapped to 16p11.2 and consists of 14 exons spanning 7.7 kb of genomic DNA. *SLC5A2* encodes the 672-amino acid Na^+-glucose cotransporter SGLT2 (642, 805, 806). *SLC5A2* was proposed as a major candidate gene for FRG in 1994 (368), and the first *SLC5A2* mutation in FRG was reported in 2000 by Santer et al. (643). Since then, molecular evaluation of small series of FRG patients (87, 90, 418, 452, 642, 796, 842, 843, 855) as well as several case reports supported the role of SGLT2 in this disorder (89, 216, 380, 388, 762, 840, 841, 844). More than 70 mutations, scattered throughout the *SCL5A2* gene, have been described up to now, including missense and nonsense mutations, small deletions (in-frame and frameshift), and splicing mutations (88, 418, 842, 855). Most of the reported mutations are missense mutations. The intron 7+5G>A (c.885+5G>A) mutation, reported in several unrelated pedigrees of different ethnic origins, might be a mutational hotspot (90, 642). Recently, Zhao et al. (855) reported another high-frequency mutation, a deletion in intron 7 resulting in abnormal splicing in *SLC5A2* gene, which might be another mutational hotspot. The mode of inheritance has long been debated, but FRG has now been shown to be inherited as a codominant trait with incom-

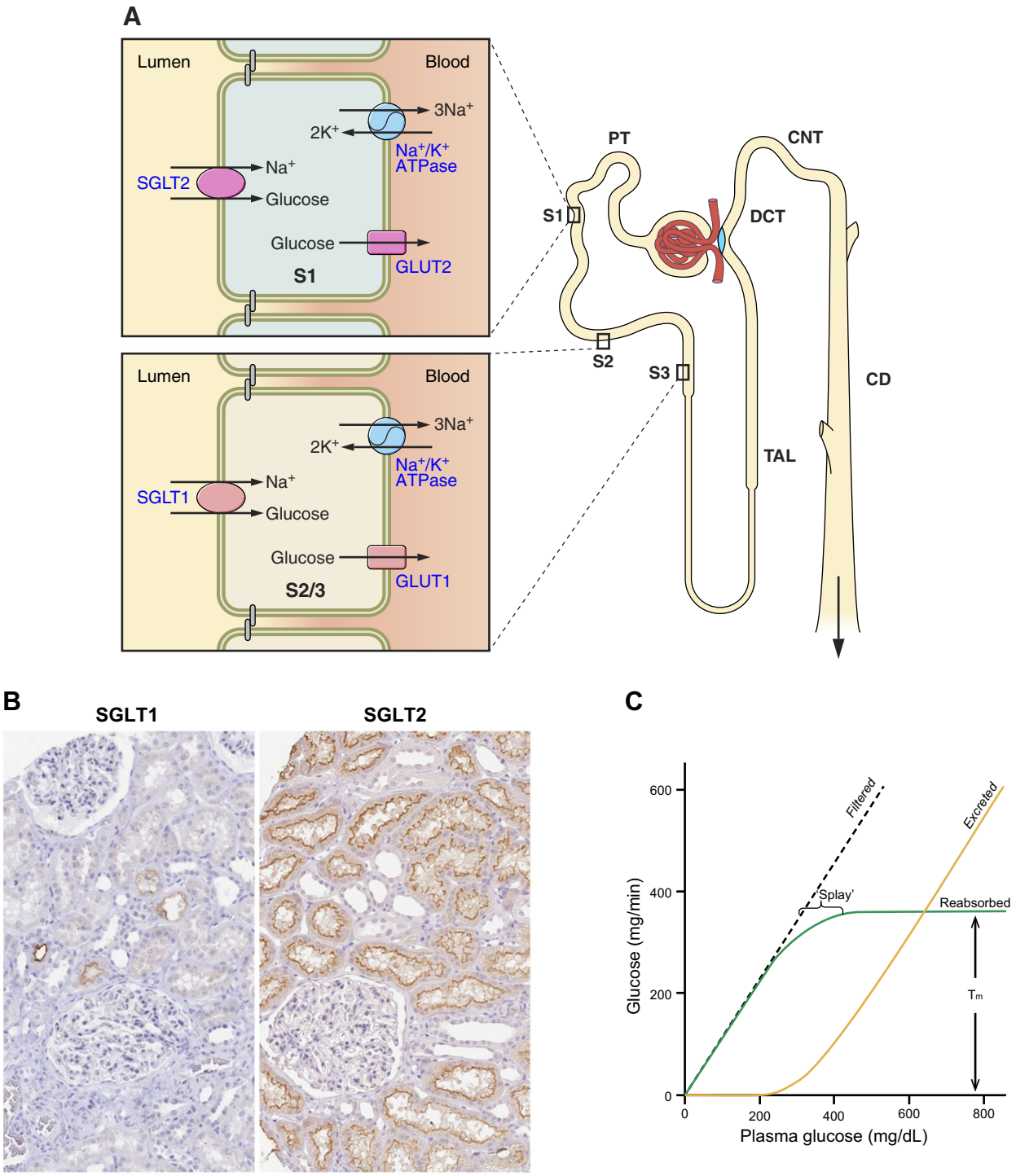


FIGURE 7. Glucose transport in the proximal tubule. *A*: molecular mechanisms of glucose transport. Glucose enters the cell via the apical Na^+-coupled glucose cotransporter SGLT2 that is expressed in the S1 segment of the proximal tubule (PT) and is responsible for the vast majority of glucose reabsorption. SGLT2 cooperates with the basolateral glucose transporter GLUT2. More distally, in the S3 segment of PT, the apical reabsorption of glucose occurs via the Na^+-coupled glucose cotransporter SGLT1, in synergy with the basolateral transport of glucose by GLUT1. *B*: segmental distribution of SGLT1 and SGLT2 in the PT segments of the human kidney. Note that SGLT2 is in fact much more abundant and located in the convoluted (S1-S2) parts of the proximal tubule. *C*: glucose handling in the kidney. The rate of glomerular filtration of glucose is proportional to the plasma glucose level. Glycosuria occurs when the transport maximum (Tm) for glucose in PT is approached, corresponding to a plasma glucose level of ~200 mg/dl. Image credit: Human Protein Atlas (www.proteinatlas.org), https://www.proteinatlas.org/ENSG00000100170-SLC5A1/tissue/kidney#img; https://www.proteinatlas.org/ENSG00000140675-SLC5A2/tissue/kidney#img.

plete penetrance (88, 641, 642, 842). Patients with mild glycosuria (<10 g/1.73 m^2 per day) are usually heterozygous for *SLC5A2* mutations, whereas homozygosity or compound heterozygosity is associated with severe glycosuria (>10 g/1.73 m^2 per day) (87, 88, 90, 642). However, a variable expressivity of mutations in FRG have been reported since patients with similar or identical mutations, especially in the heterozygous state, do not display similar degrees of glycosuria. Modifier genes, including other *SLC5* genes known to be expressed in the kidney and the involvement of which remains elusive, may explain this variable expressivity (88).

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. The Na^+-glucose cotransporter SGLT2 accounts for the vast majority of glucose reabsorption in the PT. SGLT2 is a 672-amino acid protein, which belongs to the SLC5 family, also known as the Na^+ substrate symporter gene family. The SLC5 family compromises more than 230 members, including 12 members identified in humans that are expressed in tissues such as the small intestine, kidney, brain, muscle, and thyroid gland (820, 822). The SGLT members of the SLC5 family transport a vast variety of solutes ranging from sugars to inorganic ions. They share a common core structure of 13 transmembrane helices, although some members have one or two additional COOH-terminal helices. SGLT1 and SGLT2 both have 14 transmembrane helices with extracellular NH_2- and COOH-terminal domains (641, 819). Only a few studies investigated the functional consequences of *SLC5A2* variants (842, 843). All the *SLC5A2* variants tested exhibited lower transport activity upon reconstruction in cultured cells. The expression levels of the variants were significantly decreased, and some variants showed altered expression pattern with a loss of the typical punctuate membrane pattern seen in wild-type *SLC5A2* (842). These in vitro studies matched the evidence of a markedly lowered SGLT2 expression in PT cells in a kidney biopsy from a FRG patient (843).

Up to now, the mechanism of action of SGLT2 remains poorly understood. SGLT2 expresses only weakly in either transfected mammalian cells or *Xenopus* oocytes, rendering its characterization difficult. Coady et al. (128) recently identified an accessory protein, 17-kDa membrane-associated protein (MAP17), which is required for the normal function of SGLT2 in oocytes and mammalian cells. MAP17 was first identified as a protein with upregulated transcription in kidney, colon, breast, and lung cancer (392). In the PT, MAP17 interacts with the scaffolding protein PDZK1, which is linked to other transporters such as NHE3 and URAT1. Coady et al. (128) showed the physiological relevance of this MAP17-SGLT2 interaction studying a cohort of 60 patients with FRG in which they identified one patient homozygous for a splicing mutation in the MAP17 coding gene (*PDZK1IP1*), pointing to a genetic heterogeneity for FRG.

SGLT2 is localized to the brush-border membrane of the cells lining the early PT in mouse kidney. *Sglt2* KO mice exhibit glycosuria, polyuria, and increased food and fluid intake without differences in blood pressure, GFR, or plasma levels of Na^+ and K^+, and no significant increase in urinary excretion of other PT substrates such as amino acids (756). The genetic deletion of *Sglt2* in mice reduced blood glucose levels in streptozotocin-induced diabetes mellitus and attenuated glomerular hyperfiltration, but it did not prevent the increase of kidney growth or the rise of markers of kidney injury (758).

Pharmacological inhibition of SGLT2 has recently emerged as an innovative therapeutic strategy for the management of type 2 diabetes by increasing renal glucose excretion (30, 107, 150, 204, 242, 334, 465, 759, 760, 853). Compounds that enhance renal glucose excretion and promote weight loss, such as the natural occurring phenolglycoside phlorizin, have been known for a long time (105, 711). However, mechanisms of phlorizin-induced renal glycosuria were only recognized after the characterization of SGLT2 in the early 1990s (421). To date, three highly selective SGLT2 inhibitors, dapagliflozin, canagliflozin, and empagliflozin, have been approved for patient use. SGLT2 inhibitors have been demonstrated to reduce glycated hemoglobin (HbA1C), along with fasting and postprandial plasma glucose, as well as body weight and blood pressure in patient with type 2 diabetes (13). In addition to their antihyperglycemic properties, this emerging class of drugs shows renoprotective effects and cardiac benefits in patients with type 2 diabetes (150, 204, 760, 853). The SGLT2 inhibitors empagliflozin and canagliflozin have been evaluated in two major clinical trials, the EMPA-REG OUTCOME trial (551, 857) and the CANVAS Program (509), and showed clinically significant advantages over other antidiabetic drugs in protecting patients with type 2 diabetes against heart and kidney failure (760).

During the EMPA-REG OUTCOME trial and the CANVAS Program trial, the cardioprotective effect of SGLT2 inhibitors developed in the course of the treatment and can probably not be explained by the reduction of cardiovascular risk factors. Instead, they may be due to the metabolic properties of SGLT2 inhibitors: by increasing glucose excretion in the urine, these drugs induce a mild ketogenesis that in turn reduces blood glucose and insulin levels. The use of ketone bodies as an energy source might contribute to the cardiac benefit of SGLT2 inhibitors by improving the performance of cardiomyocytes (760).

A number of trials are currently ongoing to investigate whether the SGLT2 inhibition may also provide renal and cardiac benefits in a nondiabetic CKD setting. The renoprotective effects of SGLT2 inhibition are commonly explained by several pathways, including the tubular regulation of glomerular filtration. The SGLT2 inhibitors increase the

delivery of NaCl and fluid to the macula densa which reduces the GFR through tubuloglomerular feedback (TGF), thereby supressing the diabetes-induced hyperfiltration known to induce renal damage (152, 760, 853). However, the decrease of GFR induced by SGLT2 inhibitors may not necessarily reflect activation of the TGF. Indeed, micropuncture studies in a diabetic rat model have shown that increased reabsorption of solutes and water in the PT results in a reduced hydrostatic pressure in Bowman's space and in the PT in these diabetic animals compared with the nondiabetic rats (757). This reduced hydrostatic pressure will in turn increase the net filtration pressure, thereby contributing to the development of diabetic hyperfiltration. Inhibition of PT reabsorption allows the hydrostatic pressure in Bowman's space and in the PT to rise, thereby decreasing net filtration pressure and GFR. Interestingly, A1 adenosine receptor (A1AR) KO mice, which lack a functional TGF mechanism, still display pronounced glomerular hyperfiltration when diabetes is induced, indicating a TGF-independent mechanism in the development of diabetic hyperfiltration (198, 648). Moreover, inhibition of proximal sodium-linked glucose reabsorption by phlorizin in diabetic *A1ar* KO mice has been shown to reduce diabetes-induced glomerular hyperfiltration (649). Mathematical modeling proposes that effects of diabetes on GFR via TGF and hydrostatic pressure contribute each ~50% when both mechanisms are intact (280).

D. Disorders of Sodium Chloride Transport

1. Salt reabsorption processes

Salt (NaCl) is essential for life. The tight regulation of the body's Na^+ and Cl^- concentrations is so important that multiple mechanisms work in concert to control them. Na^+ and Cl^- are the primary ions in the extracellular fluid, including blood plasma. As such, they are central in a number of physiological mechanisms that regulate blood volume and blood pressure. The kidney is the main organ responsible for maintaining this vital balance. In general, active reabsorption of Na^+ generates the driving force for the passive reabsorption of water. Under physiological conditions, renal tubules are capable of reabsorbing 99% of filtered Na^+ and Cl^-. This is performed by a combination of several Na^+ and Cl^- channels and Na^+- or Cl^--coupled transport systems along the tubular segments of the nephron. Overall, the energy needed for the transport derives from the basolateral Na^+-K^+-ATPase, which is expressed in all tubular segments (180, 373).

The major part of the filtered Na^+ (~65%) is reabsorbed in the PT, via symporter and antiporter mechanisms. The latter is regarded as the most important Na^+ flux in the PT and is mediated by NHE3 (53, 506). The other main mechanism is the 1:1 Na^+-glucose cotransport that is mediated by SGLT2 (368, 839) **(FIGURE 8)**. The reabsorption of Na^+ and accompanying solutes creates a small transepithelial osmotic gradient, which drives water reabsorption primarily through the water channels AQP1, which are massively expressed in the apical and basolateral membranes of PT cells. Reabsorption of Na^+ together with uncharged solutes (e.g., glucose), HCO_3^- and water in the early PT establishes an electrochemical gradient that drives diffusion of Cl^- in the (mid-to-late) PT from the lumen to the peritubular interstitium, mainly via a paracellular pathway.

The TAL is responsible for reabsorbing 25–30% of the filtered NaCl load, which results in a diluted pro-urine as the TAL is essentially water impermeable (264). The apical entry of Na^+ is essentially mediated via the Na^+-K^+-Cl^- cotransporter (NKCC2) (230, 252), with a small contribution of NHE3 (~10% of the net Na^+ reabsorption in a microperfused rat study, see Ref. 687). A key feature of NKCC2 is the sensitivity to the loop diuretic furosemide. The net driving force for NKCC2 transport originates from low intracellular Na^+ concentration (263), which is established by the Na^+-K^+-ATPase activity at the basolateral membrane. Next, Cl^- exits the cell through the basolateral Cl^- channels ClC-Ka and ClC-Kb (5, 729), and via electroneutral K^+-Cl^- cotransporters (KCCs) (262) **(FIGURE 8)**. KCC4 has been detected at the basolateral membrane of the TAL (63, 243). The activity of NKCC2 and the apical renal outer medullary K^+ channel (ROMK), together with Cl^- efflux, generates a lumen-positive transepithelial voltage that drives paracellular transport of Ca^{2+} and Mg^{2+}.

The final 5–10% of the filtered Na^+ is actively reabsorbed by the apical Na^+-Cl^- cotransporter (NCC) and the epithelial Na^+ channel ENaC expressed in the distal nephron (187, 230, 771). Despite its short length (5 mm in humans), the DCT can be further subdivided into two distinct segments: DCT1 and DCT2 (717). NCC expression is confined to DCT1 and DCT2, while ENaC is expressed in DCT2 and in the downstream CNT and CD (135, 464) **(FIGURE 8)**. At the basolateral membrane, Na^+ is extruded by the Na^+-K^+-ATPase. Cl^- transport in the DCT1 is carried out by NCC and the Cl^- channel ClC-Kb at the apical and basolateral membranes, respectively. Furthermore, the basolateral membrane expresses KCC, and paracellular Cl^- transport has also been reported in the CD (318, 772). Additionaly, Cl^- is counter-transported with bicarbonate by pendrin in the intercalated cells of the CD (382, 560). Genetic or acquired defects in any of these transport systems, which are specific for individual nephron segments, lead to distinct salt-losing nephropathies. Here, we will consider the different renal genetic disorders affecting salt reabsorption.

2. Bartter syndrome

A) BRIEF CLINICAL DESCRIPTION. In 1962 Bartter et al. (36) reported two unrelated children with a new syndrome, characterized

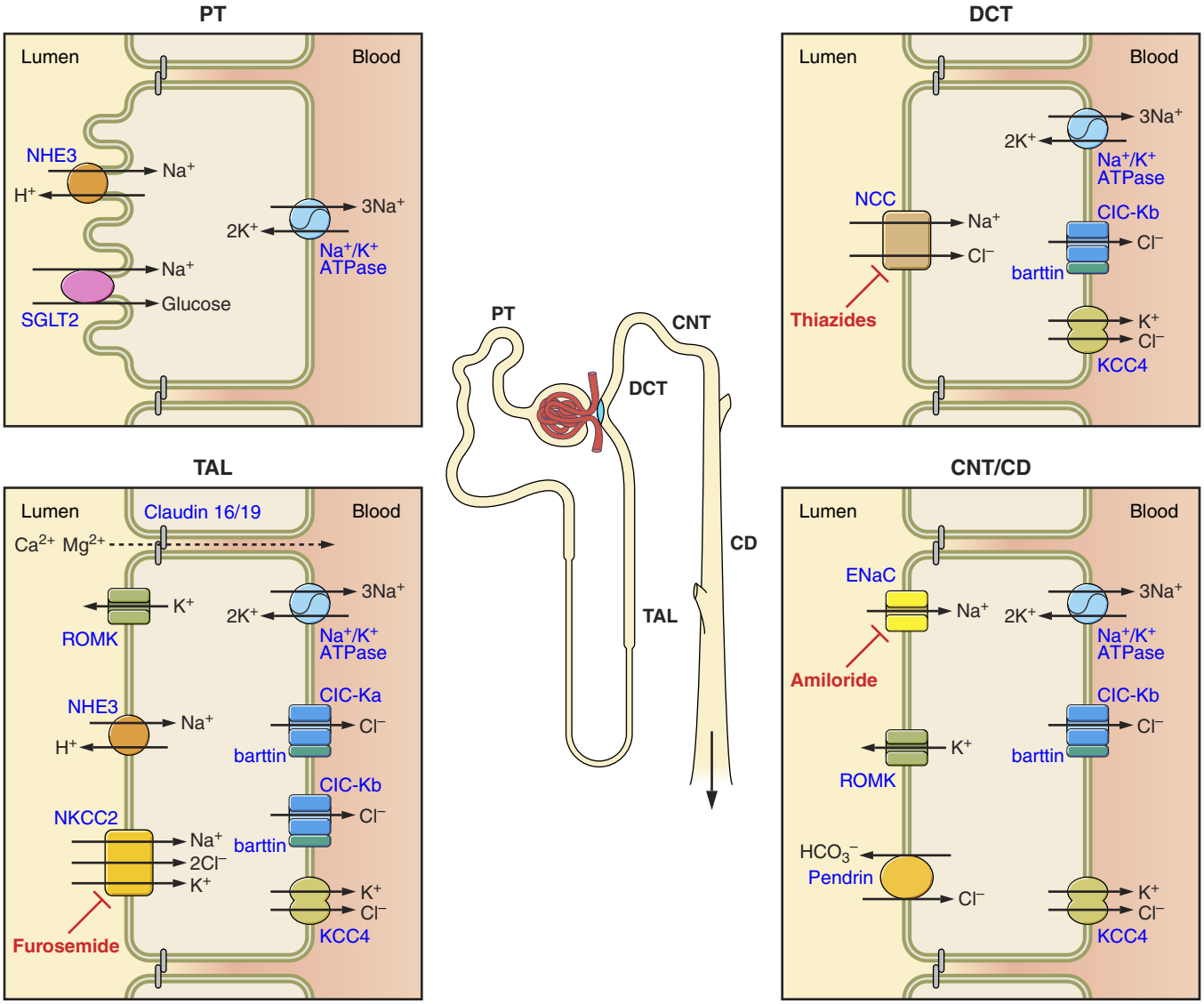


FIGURE 8. Sodium and chloride transport along the nephron segments. Reabsorption of Na^+ in the proximal tubule (PT) is mediated by the Na^+-H^+ exchanger NHE3 and coupled to glucose transport through SGLT2. In the thick ascending limb (TAL), Na^+ and Cl^- are essentially transported over the apical membrane by NKCC2, followed by efflux of Cl^- through ClC-Kb and Na^+ via the Na^+-K^+-ATPase. An estimated 10% of the apical uptake of Na^+ is mediated by NHE3. Barttin is an accessory protein regulating ClC-Kb function. The K^+ ions that enter the cell through NKCC2 are recycled back into the lumen via ROMK. Together, a lumen-positive transepithelial voltage is generated in the TAL that drives paracellular reabsorption of Ca^{2+} and Mg^{2+} through claudins 16/19. In the distal convoluted tubule (DCT), Na^+ and Cl^- are reabsorbed through the thiazide-sensitive NCC. The Na^+-K^+-ATPase and ClC-Kb, associated with its regulatory subunit barttin, mediate transport of Na^+ and Cl^- into the blood compartment. The Na^+ reabsorption in the connecting tubule (CNT) and collecting duct (CD) occurs via Na^+ entry through ENaC that is expressed at the apical membrane and the Na^+-K^+-ATPase that extrudes Na^+ at the basolateral side. The ENaC-mediated electrogenic Na^+ transport creates an electrical driving force for K^+ secretion via ROMK. Diuretics targeting Na^+ transport include furosemide for NKCC2, thiazides for NCC, and amiloride for ENaC. CD, collecting duct; ClC-Kb, chloride channel Kb; CNT, connecting tubule; DCT, distal convoluted tubule; ENaC, epithelial Na^+ channel; NCC, Na^+-Cl^- cotransporter; NHE3, Na^+-H^+ exchanger 3; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; PT, proximal tubule; ROMK, renal outer medullary K^+ channel; SGLT2, sodium glucose transporter 2; TAL, thick ascending limb of the loop of Henle.

by hypokalemic metabolic alkalosis, renal K^+ wasting, hypertrophy and hyperplasia of the juxtaglomerular apparatus, and normotensive hyperaldosteronism. The disorder also featured increased urinary excretion of prostaglandins and high plasma renin activity (36). In the following decades, many similar cases and phenotypic variants have been described and included in a group of hypokalemic salt-losing tubulopathies, referred to as Bartter-like syndromes (270, 347). All these disorders are recessively inherited and associated with hypokalemia and hypochloremic metabolic alkalosis due to stimulation of the RAAS. However, they markedly differ in terms of age of onset, severity

of symptoms, presence of urinary concentrating defect, other electrolyte abnormalities (including hypomagnesemia), and magnitude of urinary Ca^{2+} excretion. Over the years, it became apparent that these tubular disorders may affect salt handling in distinct nephron segments, based on striking comparisons between the patient's symptoms and the effects of loop and thiazide diuretics affecting the TAL and DCT, respectively.

Based on clinical manifestations, the Bartter-like syndromes were grouped into two major groups: the antenatal Bartter syndrome (aBS), which can be associated or not with sensorineural deafness (SND); and the classic Bartter and Gitelman syndromes (cBS and GS, respectively) **(TABLE 3** and **FIGURE 9)**.

The aBS type 1 and type 2 (MIM nos. 601678 and 241200) are rare, life-threathening disorders characterized by massive polyuria that manifests in utero with the development of polyhydramnios and premature delivery in almost all cases. Affected neonates rapidly develop salt wasting, hypokalemic metabolic alkalosis, and profound polyuria (473, 583, 769). A majority of patients have hypercalciuria and nephrocalcinois, with increased risk for kidney stones (583). Mg^{2+} wasting is not a common finding in aBS (564). Failure to thrive and growth retardation are invariably observed (451, 583). The disorder is accompanied by markedly elevated urinary prostaglandin E_2 (PGE_2) excretion, and treatment with PG synthesis inhibitors effectively reduces clinical and biochemical manifestations (675). As patients with aBS failed to respond to loop diuretics such as furosemide, a defective NaCl reabsorption in the TAL was suspected (404). The two forms of aBS, due to mutations in the genes encoding NKCC2 or ROMK, are clinically and biochemically similar, with the exception of transient neonatal hyperkalemia that is only associated with mutations in *KCNJ1* (encoding ROMK) (210). Typically, hypokalemia in ROMK-deficient patients is less severe than that observed in NKCC2-deficient patients (564).

In 1995, Landau et al. (413) described a subtype of aBS associated with SND in five affected subjects from an inbred kindred. These patients show a severe salt wasting and fluid loss, and they most often develop progressive renal failure (346, 413). In 2001, Birkenhager et al. (55) detected inactivating mutations in a novel gene, *BSND*, in affected individuals. The gene encodes barttin, a regulatory beta-subunit of the basolateral ClC-Ka and ClC-Kb channels. This subtype of aBS was named aBS with SND, or type 4 BS (MIM no. 602522).

BS type 3, also referred to as cBS (MIM no. 607364), usually presents during infancy or early childhood, with a phenotype similar to the original description given by Bartter et al. (36), but without the prenatal onset and the

Table 3. *Genotypic and phenotypic characteristics of the different types of Bartter and Gitelman syndromes*

Disease	Inheritance	Gene	Protein	Affected Tubular Segment	Phenotype								Other
					Serum				Urine				
					Na^+	K^+	Mg^{2+}	Ca^{2+}	pH	Na^+	K^+	Mg^{2+}	Ca^{2+}	
Bartter type 1 (aBS)	AR	*SLC12A1*	NKCC2	TAL	–	↓	–	–	↑	↑	↑	↑	↑	Polyhydramnios, fetal polyuria, nephrocalcinosis
Bartter type 2 (aBS)	AR	*KCNJ1*	ROMK	TAL, DCT, CNT	↓	↑ (Initial)	–	–	↑	↑	↑	↑	↑	Polyhydramnios, fetal polyuria, nephrocalcinosis
Bartter type 3 (cBS)	AR	*CLCNKB*	ClC-Kb	TAL+DCT	–	↓	–	–	↑	↑	↑	–	–/↑	
Bartter type 4 (aBS with SND)	AR	*BSND*	Barttin	TAL+DCT	–	↓	–	–	↑	↑	↑	–	–/↑	Sensorineural deafness
Bartter type 4b (cBS)	AR	*CLCNKA-CLCNKB*	ClC-Ka/ClC-Kb	TAL+DCT	–	↓	–	–	↑	↑	↑	–	–/↑	Sensorineural deafness
Autosomal dominant hypocalcemia with Bartter	AD	*CASR*	CaSR	TAL+DCT	–	↓	–	↓	↑	↑	↑	–	–/↑	Nephrocalcinosis
Gitelman	AR	*SLC12A3*	NCC	DCT	–	↓	↓	–	↑	↑	↑	↑	↓	Chondrocalcinosis

↓, Decreased; ↑, increased; –, unchanged.

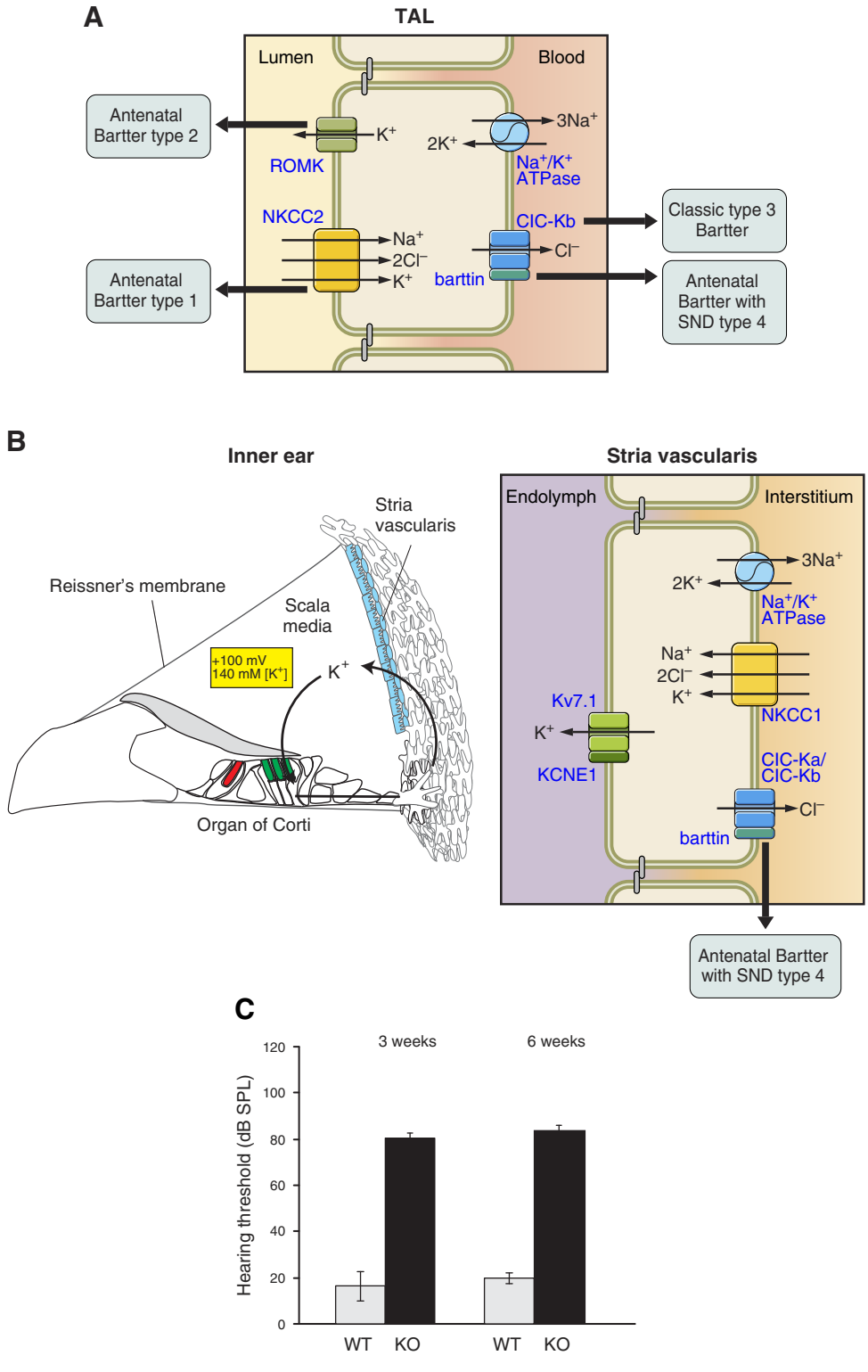


FIGURE 9. Various types of Bartter syndrome. *A*: in the TAL, Na^+ and Cl^- are transported over the apical membrane by NKCC2, followed by efflux of Cl^- through ClC-Kb and Na^+ via the Na^+-K^+-ATPase. Of note, barttin is identified as an accessory protein regulating ClC-Kb function. The K^+ that enter the cell through NKCC2 are recycled back into the lumen via ROMK. Mutations in either of the genes expressing these proteins result in the development of different types of Bartter syndrome. *B*: barttin is also expressed as a regulatory subunit for ClC-Kb and ClC-Ka in the inner ear and is thereby involved in sensory function. It is crucial for inner ear K^+ secretion. Patients with mutations in *BSDN*, encoding barttin, suffer from sensorineuronal deafness, as a result of barttin affecting both Cl^- channels in the inner. *C*: bar graphs depict the hearing thresholds in 3- and 6-wk-old wild-type (WT) and inner-ear-specific *Bsdn* knockout (KO) mice measured by auditory brainstem responses (ABR). ClC-Kb, chloride channel Kb; NKCC1 and NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; KCNE1, voltage-gated K^+ channel subfamily E regulatory subunit 1; Kv7.1, voltage-gated K^+ channel. [Adapted from Rickheit et al. (608), with permission from John Wiley and Sons.]

nephrocalcinosis seen in the aBS variant. The electrolyte abnormalities are usually severe at presentation, including hypokalemic alkalosis and increased plasma renin levels (564). Most patients with cBS show growth retardation and failure to thrive (45, 621, 667). Polyuria is not uniformly found in cBS. Lower urinary osmolality, either iso- or hyposthenuria, was only evidenced in approximately one-third of the patients, whereas some achieved urinary osmolality above 700 mOsm/kgH_2O (347). The persistance of such a urine concentrating ability suggests that patients have residual TAL function. This is further supported by the fact that only ~20% of patients have sustained hypercalciuria (564), and nephrocalcinosis was not detected in most cases (45, 621, 667).

In addition to these types of Bartter syndrome, gain-of-function mutations in the *CASR* gene encoding the extracellular calcium-sensing receptor (CaSR) cause autosomal dominant hypocalcemia with Bartter syndrome (previously named Bartter type 5) (MIM no. 601198) (294, 770, 800). In addition to clinical manifestations of Bartter syndrome, these patients present with hypocalcemia, reflecting the crucial role of the CaSR in divalent mineral homeostasis. The inherited disorders associated with the CaSR will be discussed in section III*E*.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Despite some overlapping features, the aBS group included disorders affecting the TAL, with furosemide-like manifestations, whereas the cBS group including GS is related to a defect in the DCT, with thiazide-like manifestations. A comprehensive classification of these salt-losing tubulopathies, based on the genetic, physiological, and molecular insights discussed below, provides a basis to understand the distinct phenotypes of these disorders **(TABLE 3)**.

I) Antenatal Bartter syndrome: type 1 (NKCC2) and type 2 (ROMK). Simon et al. (691) discovered that aBS type 1 (MIM no. 601678) is caused by loss-of-function mutations in the *SLC12A1* gene, located on 15q15-q21.1 and encoding NKCC2. This form of antenatal Bartter syndrome, also called hyperprostaglandin E syndrome (675), is one of the most severe forms that can be life-threatening for newborns when associated with fetal polyuria, polyhydramnios, and premature delivery (157, 538, 582, 676). Phenotypic variability among patients includes absence of hypokalemia and metabolic alkalosis within the first years, as well as an observed metabolic acidosis or hyponatremia (46). A late onset of the disease has been reported in two patients (aged 13 and 15 yr) harboring compound heterozygous mutations (580).

NKCC2 is a 121-kDa membrane protein comprising 12 putative transmembrane domains that form a transport pathway through dimerization of two homologous domains (702). It conducts the electroneutral transport of 1 Na^+, 1 K^+, and 2 Cl^- ions across the apical membrane of the TAL and thereby functions as the main salt reabsorption pathway in the kidney. Loop diuretics such as furosemide and bumetanide bind to portions of transmembrane domains 11 and 12, whereas portions of transmembrane domains 2, 4, and 7 are involved in ion transport (681). There have been numerous mutations in *SLC12A1* reported, mostly missense or frameshift, and they are essentially distributed throughout the entire encoded protein (4). The functional consequence of some of these mutations has been investigated in *Xenopus laevis* oocytes, demonstrating either impaired transporter function, reduced Na^+ affinity, or defective processing and misrouting of NKCC2 (3, 491, 580, 701). Recent studies have demonstrated that the phosphorylation and activity of NKCC2 is regulated by uromodulin, the most abundant protein in normal urine. Uromodulin is a GPI-anchored, ZP-domain protein encoded by the *UMOD* gene that is essentially expressed in the cells lining the TAL. In the TAL cells, uromodulin is trafficked to the apical membrane where, after proteolytic cleavage, it is released into the lumen to form multimeric filaments in the urine (162). Transient overexpression of uromodulin in heterologous cell systems increased the phosphorylation and activation of NKCC2 (507). *Umod* KO mice showed a discrete salt-losing phenotype with impaired response to furosemide and decreased levels of phosphorylated NKCC2 (507), whereas transgenic mice overexpressing *Umod* showed the opposite, i.e., higher level of phospho-NKCC2 and increased response to furosemide (750). The cross-talk between uromodulin and NKCC2 is potentially important for blood pressure regulation, as indicated by the association of common variants in the promoter of the *UMOD* gene with blood pressure and response to furosemide (162, 547, 750).

The aBS type 2 (MIM no. 241200), which can present with transient neonatal hyperkalemia, is caused by inactivating mutations in *KCNJ1*, which codes for ROMK (339a, 692). These mutations include missense and nonsense, as well as frameshift and deletions (294). Functional studies of mutated ROMK proteins showed that the loss-of-function originates from either an altered channel function or impaired plasma membrane abundance (563, 664, 668, 703). ROMK (also named Kir1.1) is an ATP-sensitive, inwardly rectifying renal K^+ channel that is critical for K^+ recycling in the TAL and K^+ secretion in the CNT and CD (219, 393, 420). ROMK channels are assembled from four subunits, each consisting of two transmembrane domains flanking a conserved loop that contributes to the pore and selectivity filter, and cytoplasmic NH_2 and COOH termini that contain regulatory and oligomerization domains (516a). In the TAL, ROMK plays a dual role as it supports NKKC2 transport activity essential for salt reabsorption, and also contributes to a positive transepithelial membrane potential important for paracellular reabsorption of Ca^{2+} and Mg^{2+} (264, 294, 803) **(FIGURE 8)**. Indeed, patients with Bartter syndrome (type 1 and type 2) often present with hypercalciuria, which increases the predisposition to nephrocalcinosis (583). Salt wasting, volume contraction, and metabolic alkalosis are explained by disrupted NaCl transport in the TAL, which in turn results in distal Na^+ delivery that drives ENaC function at the expense of increased K^+ and H^+ excretion.

The importance of NaCl handling in the TAL has been further demonstrated by screening members of the Framingham Heart Study (353). In that cohort, heterozygote carriers of inactivating mutations in *SLC12A1* and *KCNJ1* had significantly lower systolic and diastolic blood pressure, and a significant reduction in the risk of developing hypertension compared with non-carriers. The effects of the

carrier state on systolic and diastolic blood pressure at different age were similar to that of antihypertensive agents (353). Furthermore, Tobin et al. (745) showed that five polymorphisms in *KCNJ1* were associated with mean 24-h systolic or diastolic blood pressure. Two of these SNPs were located in the 3′ untranslated region and the remaining three SNPs were intronic. The strongest association was between the intronic variant (rs2846679) whose minor allele (frequency, 16%) was associated with a significant change in mean 24-h systolic blood pressure, after accounting for age, sex, and familial correlations. While the precise nature of the mechanisms by which variants in *KCNJ1* affect BP remains to be elucidated, these data suggest that these transporters involved in renal NaCl handing may exert a profound influence on blood pressure regulation in the general population (166).

Elevated PGE_2 levels are considered instrumental for most clinical abnormalities in Bartter patients. Prostaglandins increase K^+ secretion by activating the RAAS and are known to decrease Na^+ reabsorption in TAL, likely via inhibition of NKCC2 (379). Hence, treatment focuses on blocking the prostaglandin production with indomethacin, as it enhances the urinary concentrating ability by increasing the expression of NKCC2 in the TAL and the water channel aquaporin-2 in CD (203, 381). This is often started in infants of 4–6 wk old to reduce polyuria and hypercalciuria, improve hypokalemia, and normalize the plasma renin levels. However, care should be taken with newborns and prenatal indomethacin treatment as it might result in gastrointestinal complications, renal failure, and potentially hyperkalemia. Generally, a combination of indomethacin and K^+ supplementation results in management of the disease and stimulates development of growth and intellectual ability (583, 755).

Both *Slc12a1* and *Kcnj1* KO mice have comparable phenotypic characteristics to Bartter patients as they display hypokalemia in combination with extreme polyuria, hypercalciuria, and nephrocalcinosis (443, 725). Although 95% of these mice die within 2 wk of birth, micropuncture studies in the surviving mice demonstrated significantly impaired NaCl transport in the TAL (443). The development of another colony of *Kcnj1* KO mouse with higher survival rates, due to adaptative mechanisms and upregulation of Na^+ transport in the downstream DCT segment, offers more opportunity to study the pathophysiology of Bartter syndrome (448, 782).

In addition to the above-mentioned phenotype, patients with a transient form of aBS have been described (598). A recent study characterized this phenotype in six families and described a novel *X*-linked disease of severe polyhydramnios with prematurity and transient renal salt wasting (MIM no. 300971) that is caused by *MAGED2* mutations (410). The *MAGED2* gene (located on Xp11.21) encodes the melanoma-associated antigen D2 (MAGE-D2) protein that belongs to the MAGE family and has previously been reported in relation to cell-cycle regulation, apoptosis, and neurogenesis (33). Laghmani et al. (410) showed expression of MAGE-D2 in fetal and adult kidneys and found diminished expression of NKCC2 and NCC in a fetus with the disease, which might explain the severe renal salt wasting. Recently, Legrand et al. (422) detected mutations in *MAGED2* in 17 patients from 16 families in France. The *MAGED2* mutations explained 9% of cases of aBS, accounting for 38% of patients without identified genetic cause. The phenotype was variable and could also be observed in females (422). Further investigations are needed to understand the transient nature of the phenotype.

II) Classic Bartter syndrome: type 3. The cBS type 3 (MIM no. 607364) originates from mutations in the *CLCNKB* gene (located on 1p36) coding for the ClC-Kb Cl^- channel that mediates the basolateral Cl^- efflux from the cells lining the TAL and the DCT (400, 690). Patients harboring mutations in *CLCNKB* present a broad spectrum of clinical features that range from the aBS phenotype with polyhydramnios, isosthenuria, and hypercalciuria over to the classic BS phenotype with less impaired concentrating ability and normal urinary Ca^{2+} excretion, to a GS-like phenotype with hypocalciuria and hypomagnesemia (347, 400, 564, 621).

A relatively large number of *CLCNKB* mutations have been reported, which include frequent gene deletions but also nonsense, missense, small insertions/deletions, frameshift, and splice-site mutations (14, 80, 400, 530, 690). Interestingly, no genotype-phenotype correlations have been described yet. Similar to aBS, therapy involves a combination of indomethacin and high doses of KCl that is sometimes complemented with K^+-sparing diuretics to correct severe hypokalemia (45, 599). In cases with hypomagnesemia, supplementation with Mg^{2+} is recommended, but the correction is usually difficult (564). A followup study of patients harboring mutated *CLCNKB* showed persistently increased plasma renin levels as well as secondary hyperaldosteronism, and most patients developed proteinuria despite the control of other symptoms (45).

ClC-Kb belongs to the CLC family of chloride channels/exchangers, which includes nine isoforms in mammals (348). Both ClC-Kb and the closely related ClC-Ka isoform (encoded by *CLCNKA*) are expressed predominantly in the kidney, located on the basolateral membrane of the thin ascending limb (ClC-Ka only), TAL, and DCT cells, as well as in the intercalated cells of the collecting duct. Both ClC-Ka and ClC-Kb require the beta-subunit barttin to facilitate their insertion in the plasma membrane and generate Cl^- currents (195). Estevez et al. (195) showed that disease-causing missense mutations of *CLCNKB* resulted in significant reductions (or the loss) of ClC-Kb/barttin chan-

nel activity. Detailed studies of *CLCNKB* mutations in *Xenopus laevis* oocytes and HEK293 cells revealed two classes of mutants: nonconducting mutants associated with low total protein expression and partially conducting mutants with unaltered channel properties and ClC-Kb protein abundance (375). Thus inactivating mutations in *CLCNKB* affect the basolateral exit of Cl^-, which in turn reduces the reabsorption of NaCl in the TAL and DCT. The phenotypic variability of type 3 BS may thus be explained by the wide distribution of ClC-Kb (400, 564). Alternative pathways for Cl^- exit, which include ClC-Ka (348), KCC4 (772), or the Cl^-/H^+ exchanger ClC-5 (158) in the TAL, could partially compensate for ClC-Kb inactivation in the kidney.

Mice lacking *Clcnk2* (corresponding to *CLCNKB* in humans) have been generated that exhibited a Bartter syndrome phenotype, characterized by salt wasting, hypokalemia, and metabolic alkalosis (297). These mice did not show a natriuretic response to furosemide and had a significantly reduced response to thiazide. On the other hand, *Clcnk1* KO mice (corresponding to *CLCNKA*) exhibit polyuria but no signs of salt wasting or hypokalemic alkalosis (466). Together, this suggests that ClC-Kb is the critical Cl^- channel responsible for salt reabsorption in the TAL and DCT.

III) Antenatal Bartter syndrome with sensorineural deafness: type 4. Type 4 aBS (MIM no. 602522) is typically the most severe form of Bartter syndrome with early maternal polyhydramnios, prematurity, severe neonatal episodes of dehydration, and progressive renal failure (346, 347, 678). Moreover, these patients are deaf and have seriously impaired motor development and growth defect. An additional form of type 4 Bartter with SND (also termed type 4b, MIM no. 613090) is caused by coinciding mutations in *CLCNKA* and *CLCNKB* (532, 657).

The *BSND* gene (located on 1p32.3) consists of four exons. It encodes barttin, a 320-amino acid protein that contains two putative transmembrane domains and is expressed in the thin limb, TAL, and DCT in the kidney and in the stria vascularis surrounding the cochlear duct in the inner ear (55, 195). Barttin is a beta-subunit required for the expression and function of the Cl^- channels ClC-Kb and ClC-Ka (195, 785). Functional analysis of the identified *BSND* mutations revealed that missense mutations can either affect the channel properties of ClC-K/barttin channels despite normal membrane abundance or result in disturbed trafficking to the cell surface (343, 603, 660, 785). Hence, the severity of the disease is likely due to a loss of both ClC-K channels in all nephron segments. In contrast to patients harboring mutations in *SLC12A1* and *KCNJ1*, barttin-deficient patients exhibit only moderate and transient hypercalciuria and do not show nephrocalcinosis (347, 678). This could be due to defective NaCl transport in both the TAL and DCT, with divergent effects on urinary Ca^{2+} excretion that is somehow similar to a combined action of loop and thiazide diuretics. Barttin-deficient patients may show a severe Mg^{2+} wasting, caused by a defect in both the paracellular (TAL) and transcellular (DCT) pathways of Mg^{2+} reabsorption (347). Furthermore, a lack of diuretic response to furosemide and to hydrochlorothiazide was evidenced in one barttin-deficient patient, supporting a defect in both TAL and DCT (846).

Apart from the kidney, ClC-K channels are expressed in the inner ear, where they play a role in the secretion of K^+-rich endolymph required for the function of the inner hair cells (195, 608). Defective ClC-K/barttin channels will therefore eliminate this K^+ recycling in the inner ear and cause the SND **(FIGURE 9)**. A conditional *Bsnd* KO mouse model with specific deletion of barttin in the inner ear had no renal phenotype, but displayed congenital deafness (608). Importantly, none of the type 3 BS patients with *ClCKB* mutations is deaf because the function of ClC-Kb/barttin channels in the inner ear can be replaced by ClC-Ka/barttin. Only the disruption of barttin (195) or the combined loss of ClC-Ka and ClC-Kb (532, 657) results in a Cl^--recycling defect that lowers K^+ secretion in the stria vascularis to a pathogenic level.

While *Bsnd* KO mice die within a few days after birth (608), the generation of a KI mouse model that carries the R8L mutation provided in vivo evidence for the role of barttin (528). The mutant mice display Bartter syndrome characteristics like hypokalemic metabolic alkalosis and decreased salt reabsorption under a low-salt diet (528). A significantly reduced plasma membrane abundance of the CLC-K/mutant-barttin channels was observed in the TAL and distal nephron. The disease-causing R8L mutation was shown to result in ER-localized barttin that cannot recruit ClC-K to the plasma membrane in vitro (289). The KI mouse model was recently used to test a potential new drug, 17-allylamino-17-demethoxygeldanamycin (17-AAG), which is a 90-kDa heat shock protein inhibitor known to rescue ER-trapped proteins. Nomura et al. (527) demonstrated that treatment with 17-AAG enhanced the plasma membrane expression of barttin R8L and improved the electrolyte disturbances and hearing loss. New treatment regimes are highly valuable for the patients with type 4 BS, as the effect of indomethacin and K^+ supplementation on recovering growth and correcting electrolyte disorders is rather poor (346, 678).

3. Gitelman syndrome

A) BRIEF CLINICAL DESCRIPTION. Gitelman syndrome (GS) (MIM no. 263800) was first described in 1966 by Gitelman and co-workers as a familial disorder in which patients presented with hypokalemic alkalosis and a susceptibility to carpopedal spasm and tetany due to hypomagnesemia (244). The disease was long considered as a variant of Bartter syndrome with hypomagnesemia and hypocalciuria

(TABLE 3). In 1992 Bettinelli and co-workers concluded that GS could be distinguished from BS, based on low urinary Ca^{2+} excretion and frequent tetanic episodes (44). The dissociation of renal Ca^{2+} and Mg^{2+} handling in GS, together with the subnormal response of these patients to thiazides (720, 751), pointed to a primary defect in the DCT. GS is arguably the most frequent inherited tubulopathy detected in adults, with a prevalence of ~1 per 40,000 and a prevalence of heterozygous carriers in the Caucasian population estimated at ~1% (56).

Classically, GS has been considered as a mild variant of Bartter-like syndromes, often detected fortuitously during adolescence or adulthood. The GS patients are often asymptomatic or present with mild symptoms such as weakness, fatigue, salt craving, thirst, nocturia, constipation, or cramps (56). They may also present with growth retardation and short stature (247). Typical manifestations include low blood pressure, muscle weakness, carpopedal spasms, or tetanic episodes that are related to profound hypomagnesemia (138, 390, 401). Since Mg^{2+} ions increase the solubility of calcium pyrophosphate crystals and are important for the activity of pyrophosphatases, hypomagnesemia may promote the formation of calcium pyrophosphate crystals in joints and sclera, leading to chondrocalcinosis (586) and sclerochoroidal calcifications (71). Patients with GS have higher bone mineral density, similar to chronic thiazide treatment, which likely arises from increased renal Ca^{2+} reabsorption and a decreased rate of bone remodeling (518). K^+ and Mg^{2+} depletion result in prolonged QT interval in ~50% of the patients, which could lead to an increased risk for ventricular arrythmias (47, 213). The classical biochemical features of GS include hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. The presence of both hypomagnesemia and hypocalciuria is highly predictive for the diagnosis of GS (44).

The view that GS is a benign condition has been challenged by reports emphasizing the phenotype variability and the potential severity of the disease. GS is associated with a significant reduction in the quality of life, similar to that associated with congestive heart failure or diabetes (138). Manifestations such as early onset (before age 6 yr), growth retardation, invalidating chondrocalcinosis, tetany, rhabdomyolysis, seizures, and ventricular arrhythmia have been described (56). The phenotype of GS is highly heterogeneous in terms of age at presentation, nature/severity of biochemical abnormalities, and nature/severity of the clinical manifestations, not only between patients carrying different *SLC12A3* mutations, but also between affected family members (614).

Because GS is primarily caused by salt wasting, patients are encouraged to follow their propensity for salt consumption. Lifelong oral Mg^{2+} and K^+ supplementation is the mainstay of treatment (56, 390). In the presence of hypomagnesemia, Mg^{2+} supplementation should be considered first, because Mg^{2+} repletion will facilitate K^+ repletion (808). Many symptoms are improved by K^+ or Mg^{2+} supplementation or both, but there is no evidence correlating the severity of blood levels with the intensity of symptoms. In cases of persistent, symptomatic hypokalemia when supplements are not sufficient, the use of K^+-sparing diuretics (e.g., amiloride, spironolactone, potassium canrenoate, and eplerenone) can be useful (58, 130).

B) GENETICS. GS is caused by loss-of-function mutations in the *SLC12A3* gene, which codes for the thiazide-sensitive Na^+-Cl^- cotransporter NCC (424, 694). At present, over 250 disease-causing mutations have been identified in GS, of which a large part are missense mutations. GS is recessively inherited, and the majority of patients are compound heterozygous for different *SLC12A3* mutations. Of note, 15–20% of patients with GS are found to carry only a single mutation in *SLC12A3*, instead of being compound heterozygous or homozygous (423, 600, 614). It is likely that the second mutation resides either in gene regulatory fragments, 5′ or 3′ untranslated regions, or intronic sequences, or that there are large genomic rearrangements. Few studies have provided evidence for this hypothesis (440, 531, 768). The possibility of a heterozygous mutation in another gene should also be considered, as the clinical representation of the disease is highly heterogeneous. Mutations in *CLCNKB* have, for example, been reported in patients that have common characteristics of classic Bartter and Gitelman syndromes (345, 849). The distribution of ClC-Kb in both the TAL and DCT, and potential compensation by other Cl^- transporters, may probably explain these overlapping syndromes (347). In addition to *CLCNKB*, other genes participating in the complex handling of Na^+, Ca^{2+}, and Mg^{2+} in DCT are potential candidates to account for disease-causing or disease-modifying genes in GS (615). For instance, Belge et al. (38) showed that mice lacking parvalbumin, a cytosolic Ca^{2+}-binding protein that is selectively expressed in the DCT, had a phenotype resembling GS. These mice exhibited volume contraction, aldosteronism, and renal K^+ loss at baseline; an impaired response to hydrochlorothiazide; and higher bone mineral density. They demonstrated that these modifications were due to decreased expression of NCC, secondary to modifications in intracellular Ca^{2+} signaling in the DCT (38).

NCC belongs to the SLC12 family of electroneutral cation-chloride cotransporters that also contains the NKCC2 and KCC proteins (292). The identified *SLC12A3* mutations are spread throughout the entire protein. A limited number of mutations have been functionally analyzed for alterations in the plasma membrane expression and transport activity of mutant NCC. There appear to be different classes of *SLC12A3* mutations. First, they can affect the synthesis and target NCC for degradation, resulting in ablated plasma

membrane expression. Second, some mutants display impaired trafficking and membrane insertion, while they have normal function if they do reach the plasma membrane. Third, it is observed that NCC mutants reach the plasma membrane but show diminished transporter activity. And finally, there are splicing mutations that lead to truncated transcripts which are degraded before the translation process (144, 246, 614, 632).

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. NCC includes 12 predicted transmembrane domains with intracellular NH_2 and COOH termini, and it likely functions as a dimer at the plasma membrane (145, 230, 231). The Cl^- affinity of NCC resides within the transmembrane 1–7 region, and the sensitivity for thiazide is located between transmembrane domain 8 and 12, whereas both areas appear to be involved in Na^+ affinity (494). The regulation of NCC involves posttranslational modifications including glycosylation, phosphorylation, and ubiquitination. NCC contains a large extracellular hydrophilic loop between transmembrane domain 7 and 8 holding two glycosylation sites (N404 and N424) that are essential for the function and membrane expression of the protein (307). Several *SLC12A3* mutations result in impaired glycosylation and defective trafficking of the protein to the plasma membrane (246, 632). The NH_2 terminus contains key phosphorylation sites, including T55 and T60 and S73 and S91, that stimulate NCC activity (546, 607). Indeed, a mutation in T60 is commonly found in patients with GS (434). The exact contribution of each phosphorylation site remains to be resolved, but the intracellular signaling cascade has largely been unraveled. Richardson et al. (607) have shown that activation of SPAK (STE20/SPS1-related proline-alanine-rich protein kinase) and OSR1 (oxidative stress responsive kinase) results in phosphorylation and activation of NCC **(FIGURE 10)**. This involves binding of a unique conserved COOH-terminal (CCT) domain within SPAK and OSR1 to the RFTI motif in the NH_2 terminus of NCC (607). The with-no-K (lysine) (WNK) family of serine-threonine kinases is found to play a role upstream in this process as they can induce phosphorylation of SPAK and OSR1 (495, 777). Here, the CCT domain is also required for binding and activation by the WNKs, which contain RFXV/I motifs as well. More details on the current model of NCC regulation will be discussed in section III*D4*.

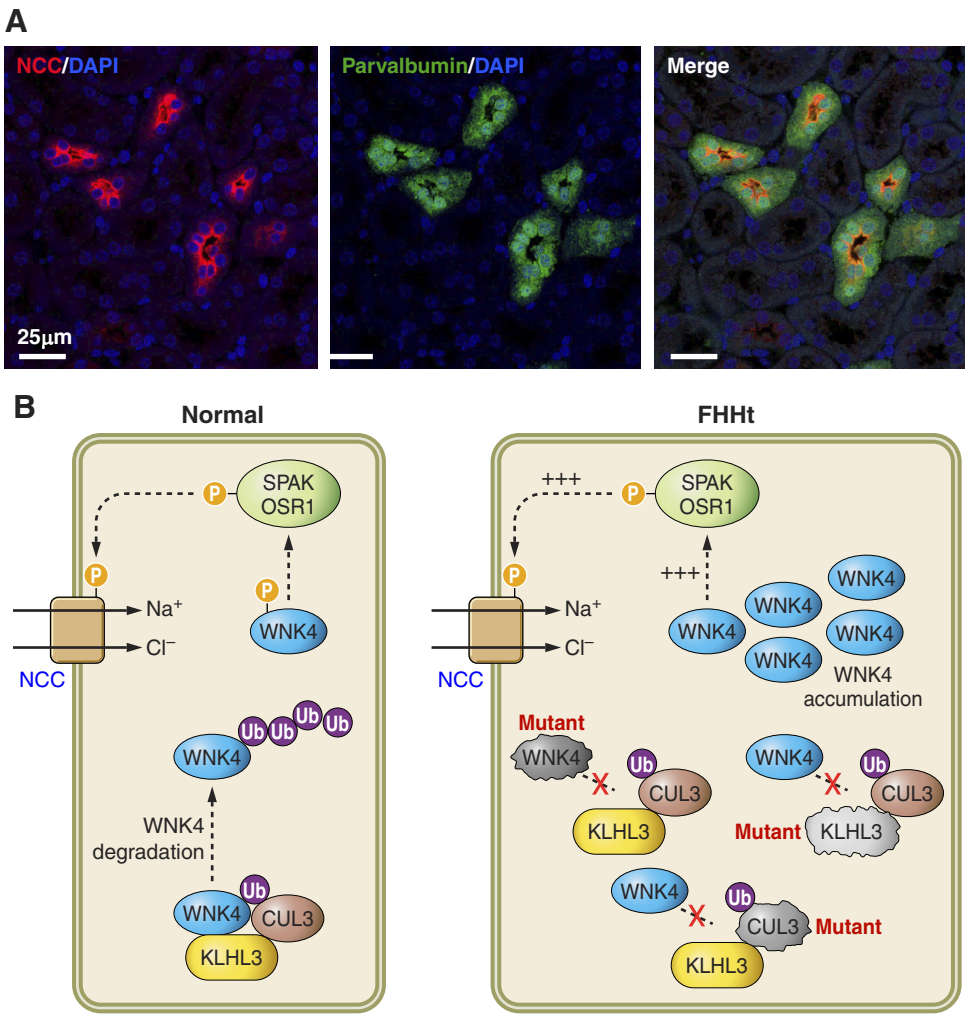


FIGURE 10. NCC-mediated Na^+ transport. *A*: immunohistochemical staining for NCC and the cytosolic protein parvalbumin in the epithelial cells lining the DCT. *B*: stimulation of WNK4 will phosphorylate SPAK/OSR1, which in turn activate NCC via phosphorylation and increased plasma membrane trafficking. On the other hand, the KLHL3/CUL3 complex can ubiquitylate the WNKs, thereby decreasing its expression and hampering the pathway that leads to NCC activity. In familial hyperkalemic hypertension (FHHt, also named Gordon syndrome), mutations in either *WNK4*, *KLHL3*, or *CUL3* result in increased WNK activation, which leads to enhanced NCC phosphorylation and activity, thereby explaining the hypertensive phenotype in FHHt patients. CUL3, cullin 3; FHHt, familial hyperkalemic hypertension; KLHL3, kelch-like family member 3; NCC, Na^+-Cl^- cotransporter; OSR1, oxidative stress responsive kinase; SPAK, STE20/SPS1-related proline-alanine-rich protein kinase; Ub, ubiquitin; WNK, with no lysine kinase.

The regulation of NCC by ubiquitination is a growing field of research. Ko et al. (391) were the first to suggest that NCC is modulated by ubiquitination, via a mechanism involving RasGRP1-mediated ERK1/2 activation. Further studies identified a role for the aldosterone-SGK1-Nedd4–2 pathway, which is also described to regulate ENaC activity (616). The E3 ubiquitin ligase Nedd4–2 (neural precursor cell expressed developmentally downregulated protein 4) was shown to interact with NCC and induce ubiquitination of the protein at the plasma membrane. This ubiquitination primes removal and degradation of NCC and thus reduces its activity. The activation of Nedd4–2 is known to result from phosphorylation by serum/glucocorticoid regulated kinase 1 (SGK1), which has an enhanced expression upon stimulation with the mineralocorticoid hormone aldosterone (50, 108, 697). Recent evidence suggests that phosphorylation and ubiquitination could have adverse effects on NCC: phosphorylated NCC had decreased ubiquitination (312), whereas WNK1 and WNK4 were shown to phosphorylate Nedd4–2 that ultimately promotes ubiquitination (296).

The pathophysiology of GS can be explained by the specific expression of NCC at the luminal membrane of the DCT, where it mediates the reabsorption of Na^+ and Cl^- (187) **(FIGURE 10)**. Loss of NCC function results in salt wasting, volume contraction, secondary hyperaldosteronism, and increased K^+ and H^+ secretion in the CD, resulting in hypokalemic metabolic alkalosis. As mentioned above, heterozygous carriers of mutations in *SLC12A3* from the Framingham Heart Study showed mean systolic blood pressure values that were below the entire cohort, with reduction in blood pressure being similar to values obtained with chronic thiazide treatment (353).

The importance of NCC as a highly-regulated, crucial player in NaCl handling by the DCT has been confirmed in different mouse models (773). Mice lacking NCC resemble a Gitelman phenotype with subtle changes in volume homeostasis, but clear alterations in the Ca^{2+} and Mg^{2+} balance (665). A later study showed that *Slc12a3* KO mice on a pure C57BL/6 background had a mild compensated alkalosis with increased levels of plasma aldosterone (442) and an increased sensitivity to develop hypokalemia when exposed to dietary K^+ reduction (499). These studies also demonstrated that loss of NCC results in hypertrophy of the distal tubule and that the observed hypocalciuria is caused by increased Ca^{2+} reabsorption in the PT (442). The latter hypothesis is supported by a study in which mice treated with thiazide diuretics developed hypocalciuria due to enhanced passive reabsorption of Ca^{2+} but independent of the distal expressed Ca^{2+} channel TRPV5 (transient receptor potential vanilloid 5) (522, 524). In addition, metabolic alkalosis is known to decrease renal Ca^{2+} excretion, which could also contribute to the observed hypocalciuria in Gitelman patients (64, 523). In contrast, the pathogenesis of hypomagnesemia observed in GS (and also after chronic thiazide administration) is likely due to a direct effect on DCT. Chronic thiazide treatment resulted in renal Mg^{2+} wasting and decreased expression of the epithelial Mg^{2+} channel TRPM6 (transient receptor potential melastatin 6) (524). TRPM6 is specifically expressed at the apical membrane of DCT1, the main site for active Mg^{2+} reabsorption (140, 780). Additionally, the TRPM6 mRNA levels were severely reduced in *Slc12a3* KO mice (524), which could reflect the atrophy of the DCT observed in these mice (442). This points towards a key role of TRPM6 in the development of hypomagnesemia in Gitelman patients, but further investigation is needed to unravel its exact underlying molecular mechanism.

4. Familial hyperkalemic hypertension

A) BRIEF CLINICAL DESCRIPTION. Although familial hyperkalemic hypertension (FHHt), also known as pseudohypoldosteronism type II (PHA2) (MIM no. 145260), was first described by Paver and Pauline in 1964 (556), Gordon delineated it as a new clinical condition, hence the term *Gordon Syndrome* (255, 256). It is characterized by hypertension, hyperkalemia, and metabolic acidosis; most patients have an early onset of the symptoms related to these electrolyte disturbances. The biochemical and clinical heterogeneity of the disease remains unclear due to the minimal number of families described so far. In general, hypertension appears in adult life and seems not prevented in patients in which the disease was diagnosed and treated before onset of hypertension (471). Untreated hypertensive individuals are at risk of developing complications related to the elevated blood pressure, like cardiac disease, renal impairment, and stroke. However, the electrolyte and blood pressure abnormalities can be corrected by treatment with thiazide diuretics, well-known inhibitors of NCC (419, 638, 673). This led to the initial idea that NCC plays a role in the pathogenesis of the disease, but no mutations in the gene encoding NCC have been identified in FHHt patients. Subsequent linkage analyses associated FHHt with several loci, and the disease was shown to have an autosomal dominant pattern of inheritance (176, 177, 457, 534).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. In 2001, disease-causing mutations in the *WNK1* and *WNK4* genes were identified in FHHt (814). These genes encode members of the WNK kinase family, WNK1 and WNK4, which are implicated in the regulation of epithelial transport of Na^+, K^+, and Cl^- in a variety of tissues (362).

WNK1 has two isoforms, namely, the long L-WNK1 isoform that is expressed ubiquitously, and the so-called kidney specific (KS) WNK1, whose expression is restricted to the kidney (114, 154, 718). The L-WNK1 isoform was shown to antagonize the inhibitory effect of WNK4 on NCC (836), thereby indirectly stimulating Na^+ reabsorp-

tion. In contrast, KS-WNK1 decreases NCC activity through antagonizing the L-WNK1 function (438, 718). L-WNK1 was also shown to activate ENaC via SGK1 phosphorylation (831), to inhibit ROMK (131, 437), and to decrease paracellular Cl^- transport via phosphorylation of claudin-4 (540).

The disease-causing *WNK1* mutations lead to large deletions in the first intron that have no effect on the final protein structure, but result in an overexpression of L-WNK1 in DCT and increased extrarenal expression of KS-WNK1 (153). Taken together, it is postulated that the net increase in L-WNK1 expression in the kidney will initiate FHHt pathogenesis via enhanced NCC activity (275). Interestingly, heterozygous *L-Wnk1*$^{+/-}$ mice showed a significantly reduced blood pressure compared with wild type (847), whereas mice KO for *Ks-wnk1* showed increased NCC activity in the DCT, as well as altered function of ROMK and decreased ENaC expression, in absence of hyperkalemic hypertension (276). Vidal-Petiot et al. (775) generated a mouse model with a heterozygous deletion of *Wnk1* that exhibited hyperkalemia, hypertension, and metabolic acidosis as a result of NCC activation. These mice had increased L-WNK1 expression and decreased ROMK expression in combination with unaltered ENaC function. Hence, the hypokalemia is suggested to be caused by inhibition of ROMK via L-WNK1.

The onset of FHHt by *WNK4* mutations was first considered to result from decreased inhibitory effect of WNK4 on NCC, as seen in *Xenopus* oocyte studies (815, 836). Furthermore, studies in oocytes showed that *WNK4* mutations increase the WNK4-mediated inhibition of ROMK (363), and an increased Cl^- permeability was demonstrated in MDCK cells (361, 834). Importantly, two independent groups generated KI mice harboring FHHt mutations that show phenotypes resembling FHHt as they exhibited increased blood pressure, hyperkalemia, and hypercalciuria (411, 838). This phenotype could be reversed by either treating the mice with thiazide or by backcrossing them with *Slc12a3*$^{-/-}$ mice (411, 838), which points towards a key role of NCC in FHHt. Interestingly, the *Wnk4*$^{-/-}$ mice have a Gitelman-like phenotype with mild hypokalemia, metabolic alkalosis, and hypomagnesemia but without hypocalciuria and hypotension (98). The K^+ wasting and normotension in the *Wnk4*$^{-/-}$ animals likely arise from increased ROMK and ENaC activities (98). A recent study by Takahashi et al. (723) postulates that WNK4, and not WNK1, is the major positive regulator of NCC, as they observed significantly decreased phosphorylated and total NCC levels despite an increase in WNK1 expression in their *Wnk4*$^{-/-}$ mice. Recently, it has been established that WNK4 exerts its action on NCC through the SPAK/OSR1 signaling cascade. Several mouse models have been generated with genetic alterations in WNK or SPAK/OSR1 to understand the role of these kinases in the regulation of NCC activity (274). While the exact physiological role of WNK1 and WNK4 is still a matter of debate, it is evident that these kinases are essential regulators of ion transport in the DCT, CNT, and CD. They were also shown to regulate the expression and function of ROMK and ENaC (274). Inhibition of these kinases would be a good target for regulating blood pressure (112, 590, 607).

Recent studies shed new light on the influence of dietary K^+ intake on blood pressure regulation through WNK signaling (736, 737, 781). They propose a link between the plasma K^+ concentration and NCC activity. Low dietary K^+ intake phosphorylates and activates NCC in the DCT despite high salt intake (737). Plasma K^+ levels can alter the intracellular Cl^- concentration via voltage-dependent Cl^- fluxes, which in turn modifies WNK activity. Piala et al. (566) demonstrated that Cl^- is able to bind the WNK1 catalytic domain, thereby inhibiting autophosphorylation and kinase activity. Hence, the DCT's ability to sense plasma K^+ levels is dependent on the WNK Cl^- responsiveness (737, 781). These studies support the role of WNKs in renal Na^+ and K^+ handling. The WNK activity is low when plasma K^+ levels are high. Following suppression of NCC, the Na^+ reabsorption occurs primarily along the CNT, not along the DCT. Na^+ reabsorption via ENaC is then exchanged for ROMK-mediated K^+ secretion **(FIGURE 11)**.

New insights into the mechanism of FHHt came from the identification of causative mutations in *KLHL3* and *CUL3* (73, 444). The encoded proteins kelch-like 3 (KLHL3) and cullin 3 (CUL3) function together in the cullin-RING E3 ligase complex that acts in the ubiquitin-mediated protein degradation pathway. Under normal conditions, the complex is able to interact and ubiquitinate the WNK kinases (724). Mutations in either *KLHL3* or *CUL3* disrupt the binding to WNKs, which subsequently leads to increased WNK1/WNK4 levels in the kidney that thereby control the activity of NCC and other ion transporters (539, 685, 784) **(FIGURE 10)**. The role of KLHL3 in the pathogenesis of FHHt was confirmed in vivo by generating *Klhl3*$^{R528H/+}$ KI mice that carry a mutation identified in FHHt patients. These mice have increased WNK1 and WNK4 levels, which indicates that both WNK1 and WNK4 are physiologically regulated by the KLHL3-mediated ubiquitination (719). Next, this group generated *Klhl3*$^{-/-}$ mice and demonstrated that lack of KLHL3 leads to increased WNK1 and WNK4 levels in the kidney, ultimately resulting in activation of the downstream OSR1/SPAK-mediated NCC phosphorylation (646). Of note, heterozygous *Klhl3*$^{+/-}$ mice did not exhibit a FHHt phenotype confirming that the previously observed phenotype in *Klhl3*$^{R528H/+}$ mice was caused by the dominant-negative effect of the *KLHL3* R528H mutation (646). As for *CUL3*, the mutations result in exon 9 skipping, which does not influence the binding of CUL3 to KLHL3, but it is suggested to disturb E3 ligase activity and

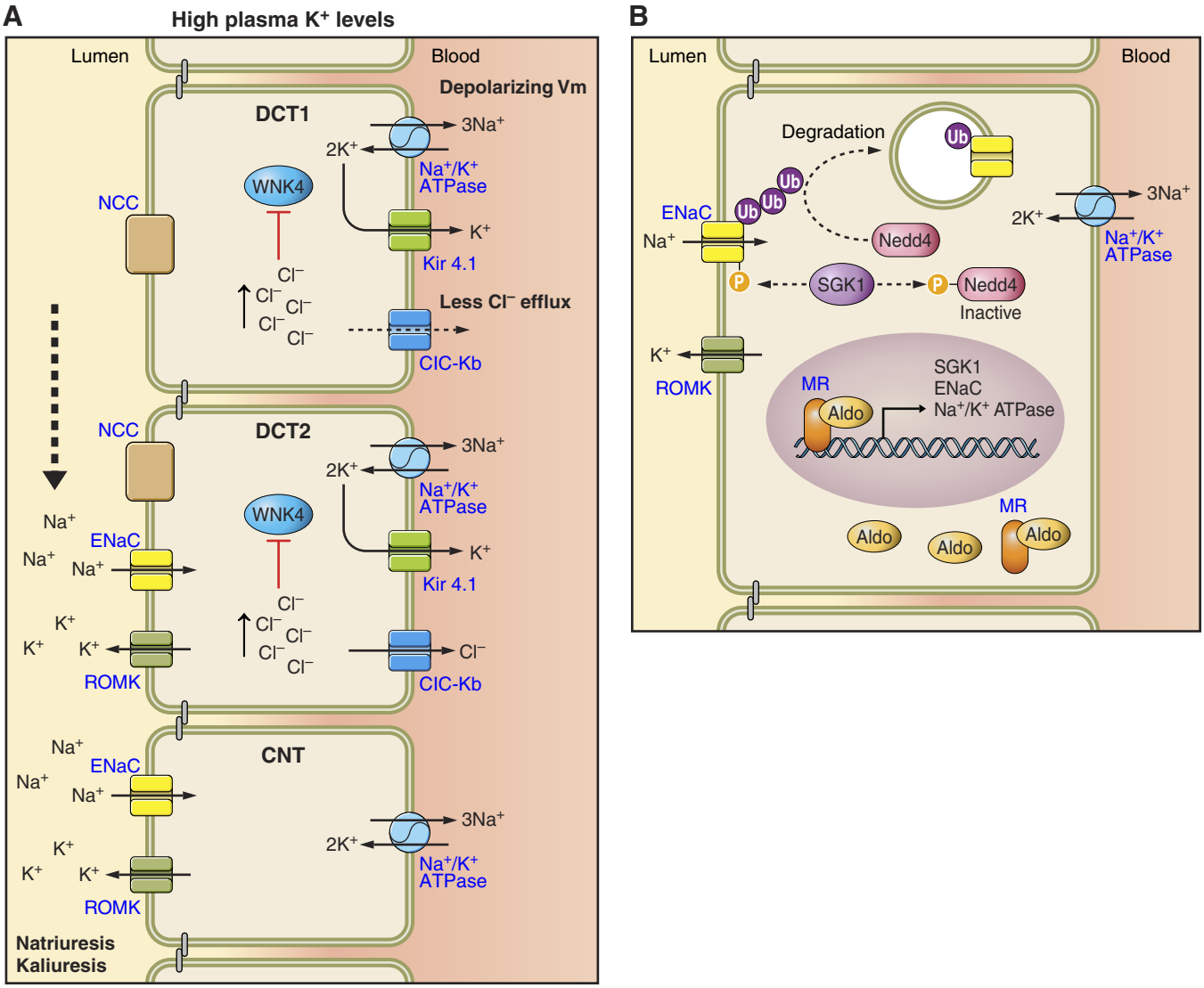


FIGURE 11. Mechanisms of sodium reabsorption in the distal nephron. *A*: the early part of the distal convoluted tubule (DCT1) is characterized by NCC expression at the apical membrane. Further downstream in the late DCT (DCT2) there is an overlapping expression of NCC and ENaC. Ultimately, ENaC is the sole Na^+ transport mechanism in the CNT and the CD. Here, ROMK colocalizes with ENaC and coordinates K^+ secretion. The K^+ channel Kir4.1 is expressed at the basolateral membrane where it extrudes K^+ into the blood compartment. Kir4.1 may also mediate the DCT's K^+ sensing which then controls intracellular Cl^- concentrations via affecting the membrane voltage. Increased plasma K^+ levels will depolarize the basolateral membrane, thereby reducing Cl^- efflux, and subsequent increased intracellular Cl^- levels reduce NCC activity via inhibition of the WNK pathway. *B*: aldosterone is identified as a key hormone binding to the intracellular mineralocorticoid receptor (MR) that is then translocated to the nucleus to induce the expression of ENaC, Na^+-K^+-ATPase, and SGK1. Activation of SGK1 leads to phosphorylation that inhibits the action of Nedd4, an ENaC interacting protein that controls the plasma membrane abundance of ENaC via ubiquitination and subsequent degradation. Aldo, aldosterone; ClC-Kb, chloride channel Kb; CNT, connecting tubule; DCT, distal convoluted tubule; ENaC, epithelial Na^+ channel; Kir4.1, inwardly rectifying K^+ channel; NCC, Na^+-Cl^- cotransporter; Nedd4–2, neural precursor cell-expressed developmentally downregulated gene 4–2; ROMK, renal outer medullary K^+ channel; SGK1, serum/glucocorticoid regulated kinase 1; Ub, ubiquitin; WNK, with no lysine kinase.

ubiquitination of at least a subset of KLHL3 targets (73, 784). Recently, a KI mouse model with specific targeting of exon 9 (*Cul3*$^{WT/\Delta 403-459}$) was generated that recapitulated the severe FHHt phenotype exhibiting hyperkalemia, hyperchloremia, and metabolic acidosis (666). Moreover, these mice showed a vascular phenotype that implies a stiffening of their arterial tree and suggests a vascular component contributing to the observed hypertension next to the salt retention mechanism in the DCT. Altogether, the identification of these novel proteins has given more insight into the renal regulation of salt balance and specifically the function of the distal part of the nephron, which might ultimately contribute to development of new drugs targeting high blood pressure in the general population.

5. Liddle syndrome

A) BRIEF CLINICAL DESCRIPTION. Another disorder characterized by early onset of hypertension is Liddle syndrome (MIM no. 177200), first described in 1963 by Liddle et al. (431). In addition to severe hypertension, patients suffer from hypokalemic metabolic alkalosis, reduced plasma renin activity, and diminished aldosterone secretion (70, 431, 799). Patients are most often treated with amiloride or triamterene, which normalizes their blood pressure and hypokalemia, but has only minimal effects on plasma aldosterone level or plasma renin activity (70, 351, 431). The effectiveness of this treatment had put the amiloride-sensitive Na^+ channel ENaC, located in the distal nephron, as a logical candidate gene for this disease.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Analyzing the original Liddle's pedigree, Shimkets et al. (686) showed complete linkage to the *SCNN1B* gene encoding the β-subunit of ENaC on chromosome 16p13–12. ENaC is comprised of three homologous subunits: α, β, and γ which act together to confer its low Na^+ conductance and its high selectivity for Na^+ and amiloride (91). In this pedigree and in other unrelated kindreds, a premature stop codon, a frameshift mutation, and other deleterious mutations were found, all located in the last exon of the gene encoding for the intracellular COOH-terminal domain of the β-subunit (351, 686). These dominantly inherited mutations were shown to be gain-of-function, with an increased amiloride-sensitive Na^+ current after transfection of the corresponding mutant subunits together with α and γ wild-type subunits. Other point mutations affecting the *SCNN1G* gene coding for same region of the γ-subunit of ENaC have also been found to cause Liddle syndrome (285).

The ENaC channel is responsible for Na^+ reabsorption across several epithelial tissues. Due to its apical localization in the cells lining the CNT and CD of the kidney, ENaC is regarded as a key player in the final regulation of Na^+ reabsorption (91, 123, 221, 234, 281). Mice that lack α-ENaC exhibit perinatal lethality due to impaired lung epithelial function (326), suggesting that the β- and γ-subunits alone are not sufficient for ENaC function. In comparison, the *Scnn1b*- and *Scnn1g*-null mice die within 48 h after birth because of an early renal dysfunction (34, 474), while low residual ENaC activity in the airway epithelia is likely due to the α-subunit.

Comprehensive studies have shown the mechanism by which the truncation or alteration of a conserved motif (PPxxY) in the COOH terminus of the β and γ subunits alters the function of ENaC (655, 698). Normally, a specific interaction between this PY motif and cytosolic proteins (Nedd4 isoforms 1 and 2, and other related WW proteins) leads to ubiquitination and then degradation of part of the newly synthetized subunits (626). Thus cell surface expression of ENaC is in part controlled by ubiquitination which is regulated by Nedd4–2 and SGK1 **(FIGURE 11)** (704). Both truncation or punctual mutations of the PY motif abrogate the Nedd4-mediated ubiquitination and increase surface expression of the mutant ENaC proteins, thus increasing the number of Na^+ channels in the apical membrane (2, 211). In turn, this promotes Na^+ reabsorption by the distal nephron, expansion of plasma volume, and hypertension which inhibits the secretion of renin and aldosterone. The fact that only one heterozygous mutation of either *SCNN1B* or *SCNN1G* is sufficient to lead to the pathology is probably due in part to the multimeric arrangement of the channel.

Shi et al. (684) generated *Nedd4–2* KO mice that displayed higher blood pressure than their wild-type littermates and had increased renal expression of all ENaC subunits, supporting the importance of Nedd4–2 in ENaC function and blood pressure regulation. Recently, an inducible kidney-specific *Nedd4–2* KO mouse model was developed, demonstrating the role of Nedd4–2 in the adult kidney tubules (623). These conditional KO mice maintain a normal Na^+/K^+ balance but develop increased blood pressure and hypercalciuria under high-Na^+ diet. They showed increased protein levels of β-ENaC and γ-ENaC but also of ROMK and of total and phosphorylated NCC in the kidney (623). The fact that Nedd4–2-dependent ubiquitination might also regulate NCC function is highly relevant when considering that mutations in *KLHL3* and *CUL3* are also linked to hypertension (73, 444).

Further evidence derived from the generation of KI mice carrying the *Scnn1b* R566stop mutation that displayed low plasma aldosterone and a salt-induced Liddle phenotype (576). Bertog et al. (42) found that the ENaC-mediated Na^+ transport in the colon of these mice was enhanced, together with an increased responsiveness to aldosterone. In addition to the colonic effect, it was recently demonstrated that DCT2/CNT is the primary nephron segment responsible for the disease-causing gain-of-function effect of the ENaC mutation (514). It will be interesting to unravel hormonal and/or molecular factors that regulate ENaC in that segment. Similarly, the recent discovery of a functional interaction between ENaC and NCC in the DCT also needs further exploration (487, 829).

6. Pseudohypoaldosteronism type 1.

A) BRIEF CLINICAL DESCRIPTION. Type 1 pseudohypoaldosteronism (PHA1) is a rare form of mineralocorticoid resistance characterized by neonatal renal salt wasting, failure to thrive, and dehydration. It is associated with hyponatremia, hyperkalemia, and metabolic acidosis, despite extremely high values of plasma renin and aldosterone (8, 850). There are two different clinical forms of PHA1: *1*) an autosomal dominant form, in which mineralocorticoid resistance is restricted to

the kidney, and 2) an autosomal recessive form, where mineralocorticoid resistance is systemic and salt loss occurs in multiple organs (288). Generally, treatment of PHA1 patients focuses on the replenishment of salt and water loss by salt supplementation, and on correction of hyperkalemia and acidosis. The correction of the generalized form usually requires high doses of Na^+ together with ion exchange resins and dietary changes to control hyperkalemia, throughout life (40, 287).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. *I) Autosomal dominant type 1 pseudohypoaldosteronism*. The renal, autosomal dominant PHA1 (MIM no. 177735) is caused by mutations in the *NR3C2* gene encoding the mineralocorticoid receptor (MR) (236, 585, 609). It is a mild form of the disease, and the most frequent. Treatment with Na^+ supplementation relieves patients from symptoms by 1–3 yr of age. Mutations are located throughout the *NR3C2* gene and result in a truncated or inactive MR that does not bind aldosterone, thereby hampering the aldosterone-induced transcription of hormone-responsive genes (137, 454, 609, 645) **(FIGURE 11)**. While haploinsufficiency is able to cause the disease, there are also reports of dominant-negative effects on the wild-type MR since the receptor functions as a dimer in transcription regulation (202, 237). Recent insight into the location and functional consequences of the *NR3C2* mutations revealed individual promoter-dependent effects on gene expression (202). This could explain the phenotypic differences that are observed in PHA1 patients; future studies in large patient groups should clarify any genotype-phenotype correlations.

The role of the MR in the maintenance of the Na^+ balance was demonstrated in the homozygous *Nr3c2* null mice that develop PHA1 symptoms within the first week after birth and later die from dehydration as a result of renal Na^+ loss (41). Conditional KO mice that lack expression of MR in the CNT and CD merely develop a PHA1 phenotype upon a low-salt diet (622). This highlights the refined mechanism of adaptation of the kidney tubule, and also the complex aldosterone signaling that likely regulates renal Na^+ transport through different pathways.

II) Autosomal recessive type 1 pseudohypoaldosteronism. The systemic, autosomal recessive variant of PHA1 (MIM no. 264350) is associated with ENaC loss-of-function mutations (103). Patients often have more severe symptoms due to disturbed Na^+ transport in all organs that express ENaC including lung, kidney, colon, and salivary glands (69, 378, 535, 650). Hence, the PHA1 phenotype includes serious respiratory tract illnesses and inflammation of eccrine sweat glands due to the high sweat salt concentration. Immediate diagnosis of the disease is essential to prevent neonatal death. If detected, the autosomal recessive PHA1 is a life-long disease that needs extensive salt supplementation in combination with K^+-lowering ion exchange resins (185, 286). Additional symptomatic treatment is often needed to relieve respiratory tract disturbances and improve the skin phenotype in these patients. In contrast to Liddle syndrome, mutations are found in all three ENaC subunits encoded by *SCNN1A*, *SCNN1B*, and *SCNN1G* (103). These are mainly frameshift or nonsense mutations that lead to truncated proteins or complete loss of ENaC expression. Loss-of-function mutations have been found in affected patients being either homozygous, in consanguineous families, or composite heterozygous (103, 715). Functional characterization of some identified missense mutations demonstrated reduced ENaC activity due to altered open probability or ion selectivity, highlighting a conserved His-Gly region in the cytoplasmic NH_2 terminus that is critical for ENaC function (267, 268, 376, 377). Recent cases have been reported that showed phenotypically distinct forms of systemic PHA1. Heterozygote carriers of a *SCNN1A* S562P missense mutation, originally identified in homozygous patients with autosomal recessive PHA1, show a subclinical salt-losing phenotype without additional features (610). A homozygous missense mutation (S243P) in *SCNN1A* that was associated with partial loss of ENaC channel activity resulted in a transient PHA1 phenotype in the premature infant, that could be corrected easily with salt supplementation stopped after 6 mo (175). These cases broaden the clinical spectrum of PHA1 and support further genetic screening as no clear genotype-phenotype correlation has been established so far (611, 850).

As mentioned above, the *Scnn1a*, *Scnn1b*, and *Scnn1g* KO mice all die soon after birth, and present with renal phenotypes similar to those observed in PHA1 patients (34, 326, 474). This did not allow detailed analysis of ENaC deletion specifically in the kidney and/or during adulthood. Hence, several transgenic mice with specific deletion of αENaC in renal tubules or only in the CNT were generated (119, 561). While CNT-specific *Scnn1a* KO mice only developed a mild PHA1 phenotype under low-salt diet, the renal tubule-specific *Scnn1a* KO model mimicked the severe PHA1. They suffered from severe hyperkalemia and decreased K^+ excretion, which could be rescued by high dietary Na^+ or low K^+ intake (561). A similar phenomenon was observed in nephron-specific *Scnn1b* KO mice (67). In contrast, the severe PHA1 phenotype cannot be rescued in nephron-specific *Scnn1g* KO mice upon high-Na^+ and/or low-K^+ diet (68). Hyperkalemia could only be avoided by preventive treatment with a K^+-deficient diet that restored NCC activity in these mice (68). This suggests that γ-ENaC is required for renal K^+ handling, and it supports the link between plasma K^+ levels and NCC regulation. A better understanding of the genetic background and biological outcome of PHA1 will be valuable to address blood pressure disturbances in the general population.

E. Disorders of Calcium Transport

1. The integrative network of renal calcium regulation

The Ca^{2+} balance depends on the interplay of intestinal absorption, renal excretion, and bone remodelling. Over 99% of the total body Ca^{2+} content is stored in the skeleton where it functions both as an essential element for skeletal strength, as well as a dynamic supply for the maintenance of circulating Ca^{2+} levels. Part of the non-bone Ca^{2+} is bound to calcium-binding proteins including albumin and globulin in plasma, and calmodulin and other calcium-binding proteins in the cells. Importantly, the free ionized Ca^{2+} needs to be tightly maintained within physiological range (1.10–1.35 mM) to prevent Ca^{2+} toxicity. This is regulated by a hormonal negative feedback mechanism involving the hormones PTH, fibroblast growth factor 23 (FGF23), and 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] that regulate Ca^{2+} transport processes in the intestine, kidney, and bone **(FIGURE 12)** (766). In short, a decline in plasma Ca^{2+} levels will stimulate the release of PTH via activation of the CaSR in the parathyroid gland (606). Subsequently, PTH regulates Ca^{2+} transport processes in bone and kidney and stimulates the production of $1,25(OH)_2D_3$ (505). $1,25(OH)_2D_3$ can enhance the expression of Ca^{2+} (and phosphate) transporters in kidney, bone, and intestine (118). In addition, $1,25(OH)_2D_3$ stimulates the production of FGF23 in bone, a key hormone in phosphate homeostasis. FGF23 also controls Ca^{2+} balance by regulating the expression of PTH in the parathyroid gland and has a negative feedback loop to inhibit $1,25(OH)_2D_3$ production (59).

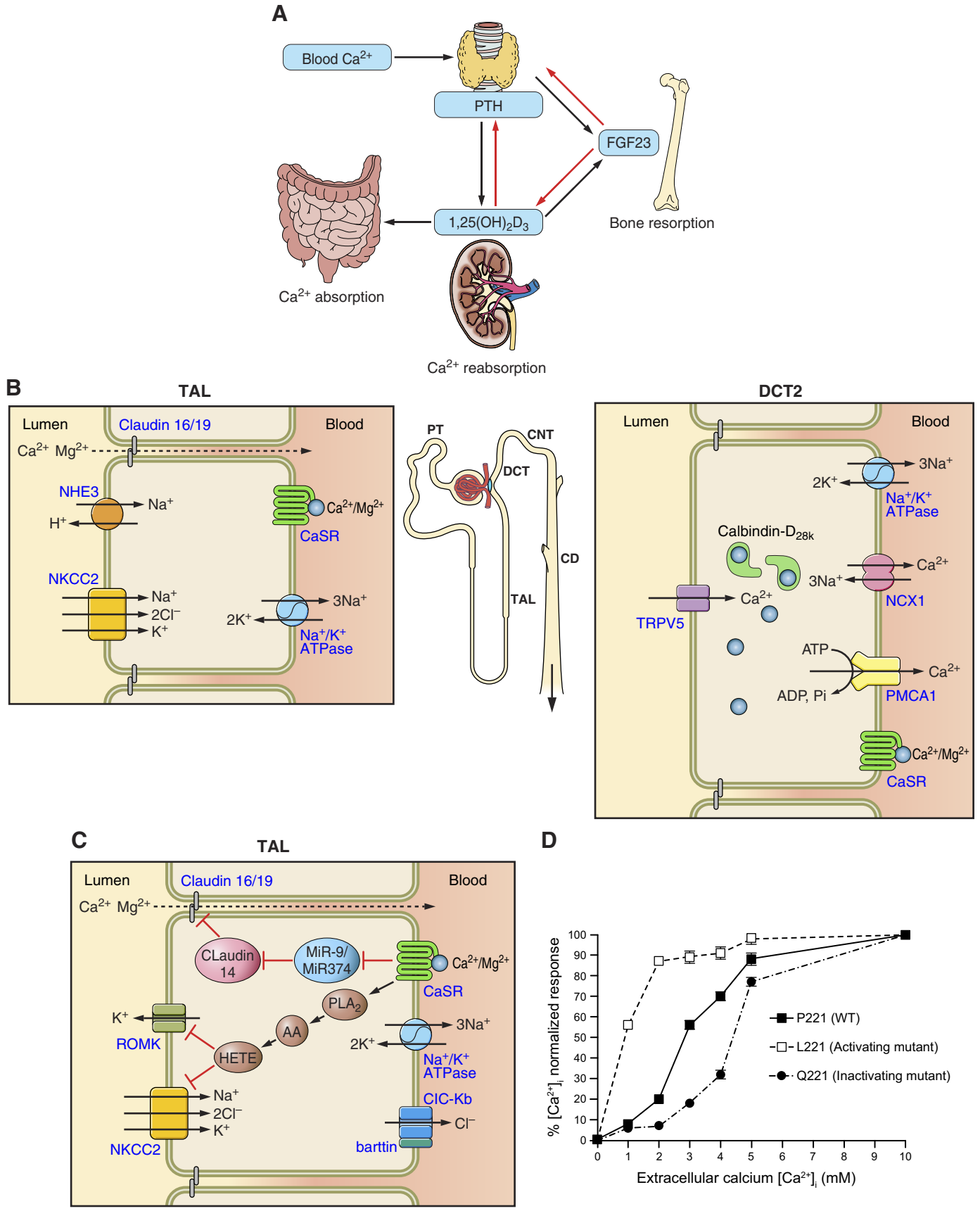
Within the kidney, glomerular filtration of Ca^{2+} includes its ionized form and Ca^{2+} complexed to small anions. The Ca^{2+} ions bound to plasma proteins are not filtered. Subsequently, the majority of the filtered Ca^{2+} is reabsorbed via passive paracellular transport in the PT that is mainly diffusive and in part facilitated by solvent drag. This is mainly influenced by Na^+ availability and Na^+ backleak. In addition, the paracellular transport of Ca^{2+} (and Mg^{2+} in more distal segments, see later) occurs via specialized tight junction proteins, the claudins. Claudins consist of four transmembrane helices, intracellular NH_2- and COOH-tails, and two extracellular loops that play a role in ion selectivity and interaction with the claudins of adjacent cells (721). Claudins usually associate into dimers or oligomers that involve either homo- or heteromeric interactions (223), which can form antiparallel double rows (722). The composition of tight junctions with different claudin members determines the characteristic properties regarding the paracellular permeability and/or transepithelial resistance in specific epithelia (250, 273). In the proximal tubule, the pore-forming claudins 2, 10a, 11, and 17 have been reported to be involved in paracellular Ca^{2+} transport (385, 409; for extensive review, see Ref. 314). Furthermore, microperfusion studies have suggested the presence of active Ca^{2+} transport in the pars recta of the PT, but the protein(s) responsible for this transport remain(s) to be identified (627).

Next, Ca^{2+} reabsorption takes place in the TAL and proceeds through the paracellular pathway driven by the positive transepithelial voltage that is established by the NKCC2-mediated Na^+ reabsorption and subsequent K^+ secretion via ROMK. The permeability for Ca^{2+} (and Mg^{2+}) is determined by specific tight junction proteins, claudin-16 and claudin-19. Recently, claudin-14 has been identified as inhibitor of the claudin-16/19 complex (251). Finally, a small portion (10–15%) of filtered Ca^{2+} is actively reabsorbed in the DCT2 and the CNT through a so-called three-step process. First, Ca^{2+} enters the cell via the epithelial Ca^{2+} channel TRPV5. Then Ca^{2+} is bound to calbindin-D_{28K} and diffuses to the basolateral side, where the extrusion process is mediated via the Na^+-Ca^{2+}-exchanger (NCX1) and the plasma membrane Ca^{2+}-ATPase PMCA1b (303) **(FIGURE 12)**.

An additional player is the CaSR that responds to changes in ionized plasma Ca^{2+}. As aforementioned, the CaSR regulates PTH release that stimulates Ca^{2+} mobilization from bone and leads to increased Ca^{2+} reabsorption via $1,25(OH)_2D_3$. Furthermore, the CaSR is expressed in the kidney where it participates in the Ca^{2+} homeostasis via a PTH-independent pathway (445). The underlying mechanism mainly involves an increase in Ca^{2+} reabsorption in the TAL, which has recently been shown to implicate regulation of claudin-14 expression via the calcineurin-NFATc1-microRNA pathway (248, 251). An additional mechanism evoked by the CaSR in the TAL involves phospholipase A_2 (PLA_2) activation and a subsequent increase in cytosolic arachidonic acid, which is then metabolized to 20-hydroxyeicosatetraenoic acid (20-HETE) (795). Both mechanisms will be discussed in more detail below, since abnormalities of the CaSR signaling are associated with hypercalcemic and hypocalcemic disorders.

2. Familial hypocalciuric hypercalcemia

A) BRIEF CLINICAL DESCRIPTION. Familial hypocalciuric hypercalcemia (FHH) (MIM no. 145980), initially referred to as familial benign hypercalcemia, is an autosomal dominant disorder that was first characterized in 1972 (214). Patients usually display a mild hypercalcemia, together with inappropriately low urinary Ca^{2+} excretion (214, 461, 552). The disease is often made after fortuitous discovery of hypercalcemia. As a result of hypercalcemia, patients may develop chondrocalcinosis and vascular calcification with age (291). Further biochemical characteristics consist of mild hypermagnesemia and normal to slightly elevated levels of serum PTH (291). FHH is usually asymptomatic, but fatigue, weakness, and excessive thirst may be experienced. Most of the time, treatment is not necessary. Yet, the calcimimetic (i.e., activator of the calcium-sensing receptor, see



below) cinacalcet appears to be an effective treatment in symptomatic FHH patients (472). Pregnant women with FHH must be monitored as an elevated hypercalcemia may inhibit PTH secretion in the developing fetus, which is then prone to developing severe hypocalcemia directly after birth (329). Importantly, Ca^{2+} levels should be monitored in newborns of two FHH parents as they can present the severe recessive disorder neonatal severe hyperparathyroidism (see below).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. FHH is a genetically heterogeneous disorder with three variants: types 1, 2, and 3. FHH type 1 (MIM no. 145980) is due to loss-of-function mutations in the *CASR* gene, coding for the CaSR (572). The CaSR is a guanine nucleotide-binding protein (G protein)-coupled receptor that signals through the G protein subunit α_{11} ($G\alpha_{11}$). FHH type 2 (MIM no. 145981) is due to mutations in *GNA11* (512), resulting in $G\alpha_{11}$ loss of function. Vice versa, *GNA11* mutations leading to $G\alpha_{11}$ gain of function, like *CaSR* mutations affecting CaSR gain of function that cause autosomal dominant hypocalcemia type 1, lead to hypocalcemia (282). FHH type 3 (MIM no. 600740) is associated with *AP2S1 (*adaptor-related protein complex 2, sigma 1 subunit) mutations that lead to altered CaSR endocytosis (283, 513).

The majority of FHH cases investigated to date are associated with loss-of-function mutations in the *CASR* (CaSR Database: http://www.casrdb.mcgill.ca/). In 1993, Brown et al. (82) cloned the CaSR from bovine parathyroid gland and demonstrated that it belongs to the G protein-coupled receptor family and responds to changes in extracellular Ca^{2+} (and Mg^{2+}). Subsequent cloning and characterization of the human CaSR revealed that it functions as a glycolysated dimer (233, 569). The receptor consists of a large extracellular NH_2-terminal domain, seven transmembrane spanning regions, and a long intracellular COOH terminus. Ligand binding at the extracellular domain activates either the G_q-, G_i-linked signaling, which in turn stimulates a variety of cell signaling pathways including the mitogen-activated protein kinases (MAPKs), PLA_2, phospholipase D, phosphatidylinositol 3-kinase (PI3K, leading to activation of the Akt pathway), and phospholipase C that increases the inositol 1,4,5-trisphosphate (IP_3)-dependent intracellular Ca^{2+} release (305).

Most missense mutations in *CASR* cluster within the extracellular domain of the CaSR that has a proposed role in Ca^{2+} sensing and binding (284, 323). Indeed, expression studies have demonstrated a right shift in the dose-response curve of mutant CaSR proteins compared with the wild-type, meaning a decrease in sensitivity towards the extracellular Ca^{2+} concentration (284, 558) **(FIGURE 12)**. Other mutations are localized in the transmembrane segments, which could inhibit the transmission of activation signals to the intracellular signaling pathways (320, 415). Additional missense mutations lead to impaired trafficking to the plasma membrane as a result of incorrect processing at either the ER or Golgi apparatus (324, 809). Interestingly, there seems to be a genotype-phenotype correlation in which the dominant-negative effect of missense mutations on wild-type CaSR function leads to a more severe phenotype than observed in patients harboring heterozygous truncating mutations (526, 797). It should be noted that common variants in the *CASR* gene have been consistently associated with serum Ca^{2+} levels in GWAS studies involving populations of European, Indian and Asian descent (371, 533, 776).

The CaSR mainly exerts its function in tissues directly related to Ca^{2+} homeostasis as it is highly expressed in the parathyroid gland and the kidney, but it can also be found in bone, colon, thyroid gland, brain, and pancreas (606). In the parathyroid gland, it regulates the secretion of PTH that can indirectly [via $1,25(OH)_2D_3$ production in the kidney] control intestinal Ca^{2+} absorption, Ca^{2+} release from bone, and also Ca^{2+} reabsorption in the kidney. PTH secretion is suppressed upon stimulation of the CaSR by high extracellular ionized Ca^{2+} concentrations, while low Ca^{2+} concen-

FIGURE 12. Calcium homeostasis. *A*: Ca^{2+} homeostasis is maintained through the coordinated actions of intestinal absorption, storage in bone, and urinary excretion by the kidney. Changes in serum Ca^{2+} are sensed by the parathyroid gland that can release PTH. The PTH-$1,25(OH)_2D_3$-FGF23 axis is an essential hormonal control mechanism that coordinates the Ca^{2+} balance. In short, release of PTH can stimulate bone resorption, renal Ca^{2+} reabsorption, and renal production of active vitamin D [$1,25(OH)_2D_3$] to increase intestinal Ca^{2+} absorption. Additionally, $1,25(OH)_2D_3$ stimulates FGF23 production in bone, which acts as a negative feedback loop to inhibit PTH and $1,25(OH)_2D_3$ production. The arrows indicate the direction of the pathway; red denotes inhibitory actions, and black depicts stimulatory actions. *B*: reabsorption of Ca^{2+} in the kidney occurs through a paracellular pathway in the PT and TAL, the latter involving the claudins 16/19. Fine-tuning of the final Ca^{2+} excretion occurs in the DCT via transcellular transport. Here, Ca^{2+} is reabsorbed at the apical membrane through TRPV5, is subsequently bound to calbindin-D_{28k}, and is transported to the basolateral where it is extruded via the Ca^{2+} pump PMCA and the NCX1 Ca^{2+} exchanger. *C*: activation of the CaSR at the basolateral membrane of the TAL inhibits the process of NaCl reabsorption via blocking NKCC2 and ROMK. This occurs via activation of HETE that is metabolized from AA, which in turn is produced by PLA_2. Furthermore, activation of the CaSR acts on the clauding16/19-mediated paracellular transport via inhibition of microRNA-claudin-14 pathway. *D*: functional analysis of the Ca^{2+} response, evoked by extracellular Ca^{2+} changes, of wild-type and various CaSR mutants in transfected HEK293 cells. The depicted CaSR mutants showed a leftward (activating mutant) and a rightward (inactivating mutant) shift in the concentration-response curve compared with the wild-type (wt) CaSR. AA, arachidonic acid; CaSR, calcium sensing receptor; DCT, distal convoluted tubule; FGF23, fibroblast growth factor 23; HETE, 20-hydroxyeicosatetraeonic acid; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; PLA_2, phospholipase A_2; PMCA, plasma membrane calcium ATPase; PT, proximal tubule; PTH, parathyroid hormone; ROMK, renal outer medullary K^+ channel; TAL, thick ascending limb of Henle's loop; TRPV5, transient receptor potential vanilloid type 5. [Adapted from Hannan et al. (284), with permission from Oxford University Press.]

trations result in the synthesis and secretion of PTH (488, 504, 511). The expression of the CaSR in the kidney has been widely studied, with the first studies showing a nephron-wide distribution with distinct cellular polarization per segment, but most significant abundance at the basolateral membrane in the TAL (445, 604, 605) **(FIGURE 12)**. The CaSR regulates the urinary Ca^{2+} excretion, and its mechanisms of action will be discussed in more detail in the forthcoming paragraphs. Overall, the inactivating *CaSR* mutations in FHH "reset" the Ca^{2+}-dependent setpoint for PTH release to a higher than normal plasma Ca^{2+} concentration, thereby explaining the inappropriate control of Ca^{2+} homeostasis and resulting hypercalcemia. In addition, defective CaSR in the kidney leads to increased tubular Ca^{2+} reabsorption. The renal Ca^{2+} handling in FHH seems independent of PTH, as parathyroidectomy did not improve the hypocalciuria (141, 463). Often, patients are treated with the loop diuretic ethacrynic acid that increases the urinary Ca^{2+} excretion. This occurs via inhibition of NKCC2 in the TAL, which in turn suppresses the passive Ca^{2+} reabsorption, suggesting that FHH patients have an abnormal TAL function (25).

The FHH type 2-causing mutations are located within the GTPase domain of the $G\alpha_{11}$-subunit, which are predicted to diminish CaSR signal transduction by influencing the interaction of $G\alpha_{11}$ with downstream effectors (282). Mutations in *AP2S1*, related to FHH type 3, were shown to disrupt the AP2 complex, which is a central component of clathrin-coated vesicles that facilitate endocytosis of plasma membrane proteins. The loss of interaction between the AP2 complex and the COOH terminus of the CaSR leads to impaired endocytosis and thus disrupts signal transduction in a dominant-negative manner (282).

3. Neonatal severe hyperparathyroidism

A) BRIEF CLINICAL DESCRIPTION. In contrast to FHH, the autosomal recessive disorder neonatal severe hyperparathyroidism (NSHPT) (MIM no. 239200) is a potentially life-threatening condition that is characterized by severe neonatal hypercalcemia and highly elevated serum PTH levels. Other phenotypic features include failure to thrive, markedly enlarged parathyroid glands, and undermineralization of bone resulting in bone abnormalities, multiple fractures, and ribcage deformities that may lead to respiratory problems (235, 299). The severe hypercalcemia and hyperparathyroidism associated with NSHPT are challenging and require specific measures. The acute management of hypercalcemia classically relies on saline perfusion and use of loop diuretics. Pamidronate, a biphosphonate drug that could halt the bone resorption process mediated by uncontrolled hyperparathyroidism, has been successfully used in NSHPT patients to control severe hypercalcemia before parathyroidectomy (790). Radical subtotal parathyroidectomy is often the treatment of choice in NSHPT (96). In addition, calcimimetic CaSR activators may be of interest in NSHPT (232). The disorder was originally described before the identification of FHH (235, 299), but later discovered to develop in children from consanguineous parents with FHH (462, 707). In line with this, *CaSR* mutations are shown to be the causative factor.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Pollak et al. (572) identified several homozygous and compound heterozygous mutations in the *CASR* gene in patients with NSHPT. To study the role of CaSR, various mouse models have been investigated over the past years. Mice heterozygous for the *Casr* gene mimic the FHH phenotype, while *Casr* KO mice exhibited a phenotype resembling NSHPT (302). These *Casr*-null mice have severe hyperparathyroidism and hypercalcemia, as well as bone abnormalities and growth retardation, and they die within a few days after birth. This lethality can be rescued by genetic ablation of *Pth* since double KO (*Pth* and *Casr*) mice have normal development compared with control littermates (402). Importantly, the serum Ca^{2+} levels and renal Ca^{2+} excretion remained affected, indicating that the CaSR has an additional role in renal Ca^{2+} handling independent of PTH (370, 402). Later studies found that targeting exon 5 of the *Casr* produced a truncated CaSR due to alternative splicing; this CaSR isoform is able to partly compensate for the loss of the CaSR in some tissues (536, 619). Additional mouse models have been generated that allowed inducible tissue-specific deficiency of the CaSR (104, 746). Toka et al. (746) studied kidney-specific *Casr* KO mice and found that serum levels of Ca^{2+}, Mg^{2+}, and PTH were unaltered compared with control mice. However, these mice display significantly diminished Ca^{2+} excretion when fed a high-Ca^{2+} diet. Furthermore, a marked downregulation of claudin-14, modest upregulation of claudin-16, and increased NKCC2 activity were observed (746). Claudin-16 can interact with claudin-19 to form a paracellular complex that regulates cation reabsorption in the TAL (315). Recently, claudin-14 was shown to control renal Ca^{2+} handling via negative regulation of the claudin-16/19 complex (249, 251). Together with its expression in the basolateral membrane of TAL cells (604, 605), it suggests that the CaSR plays a role in regulating paracellular Ca^{2+} transport in this segment.

The latter notion is supported by an in vitro study demonstrating that CaSR activation in MDCK cells results in deposition of tight junction components at the cell membrane, influencing the transepithelial electrical resistance (358). Another study used *Cldn14*-deficient mice and transgenic animals overexpressing claudin-14 to show that the CaSR alters the tight junction permeability via the calcineurin-NFATc1-microRNA-claudin-14 pathway (249) **(FIGURE 12)**. These investigators demonstrated that the *Cldn14* gene transcription is controlled by the microRNAs miR-9 and miR-374, which in turn are reg-

ulated by promoter binding of nuclear factor of activated T cell (NFAT) induced by CaSR signaling in the kidney (249, 251). This mechanism was substantiated by Gong et al. (248) demonstrating that the transcription of renal miR-9 and miR-374 can be stimulated by treatment with histone deacetylase (HDAC) inhibitors. This will downregulate claudin-14, thereby relieving its repression on paracellular transport and resulting in reduced urinary Ca^{2+} excretion in treated mice (248). In short, the targeted deletion of CaSR in mice has provided attractive models of the human syndromes and proved to be helpful in unraveling the role of the CaSR in the kidney. Furthermore, parathyroidectomized rats were shown to develop hypocalciuria and hypercalcemia despite PTH supplementation (445), thereby confirming a PTH-independent role of the CaSR in the regulation of the Ca^{2+} balance.

4. Autosomal dominant hypocalcemia

A) BRIEF CLINICAL DESCRIPTION. In contrast to the loss-of-function mutations that lead to hypercalcemic disorders, gain-of-function mutations in the *CASR* gene are associated with hypocalcemic defects. Autosomal dominant hypocalcemia (ADH) (MIM no. 601198), also referred to as autosomal dominant hypocalcemic hypercalciuria, is generally characterized by a mild asymptomatic hypocalcemia, together with renal Ca^{2+} wasting (559, 573). The phenotype and age of onset depend on the degree of hypocalcemia and are particularly variable, ranging from asymptomatic individuals to patients with rather mild symptoms (cramps, weakness, paresthesia) and patients with severe symptoms that include recurrent seizures, nephrocalcinosis, and impaired renal function. Neonatal seizures and carpo-pedal spasm have been reported in a few cases (559). Other biochemical features comprise hyperphosphatemia and hypomagnesemia, which are also observed in related diseases like hypoparathyroidism and pseudohypoparathyroidism that arise from tissue resistance to PTH (35, 209, 562). Appropriate diagnosis is important to avoid vitamin D analog treatment in ADH, as it worsens the hypercalciuria and may lead to complications such as nephrocalcinosis, nephrolithiasis, and renal failure (559). Instead, hypocalciuric compounds including PTH and thiazides are generally used, as well as calcilytics (CaSR antagonists) (425, 489, 647). Careful monitoring of urinary Ca^{2+} levels and regular kidney ultrasound are essential for the maintenance of Ca^{2+} homeostasis and treating the clinical signs of hypocalcemia.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Activating mutations of the *CASR* gene were first described in families affected with ADH (558, 573). These are most often missense mutations occurring in the extracellular NH_2-terminal domain and in the outer loops of the signal transduction domain of the CaSR (568). They may alter receptor conformation and were shown to cause a leftward shift in the dose-response curve towards the extracellular Ca^{2+} concentration (558, 573). In addition to this increased Ca^{2+} sensitivity, a large deletion of the intracellular COOH terminus was found to increase the cell surface expression of the CaSR (432). Gain-of-function mutations in *GNA11*, which encodes $G\alpha_{11}$ that mediates the signaling of the CaSR, were also recently reported in association with ADH (512). The altered CaSR activity results in inappropriately low serum PTH and decreased reabsorption of Ca^{2+} in the TAL, leading to Ca^{2+} wasting. The impaired reabsorption of Ca^{2+} in the TAL is thought to be due to a reduction of the paracellular permeability and/or to a decreased lumen-positive transepithelial voltage as a result of defective transcellular NaCl reabsorption (83).

Next to the typical mild form of ADH, some severe mutations have been identified in patients suffering from symptomatic hypocalcemia together with a Bartter-like syndrome that involves hypokalemic metabolic alkalosis, elevated plasma renin, and hyperaldosteronism (770, 800). This condition was previously known as Bartter syndrome type 5; functional analysis of these *CASR* mutations has demonstrated even higher affinity for extracellular Ca^{2+} than those observed for mutant receptors associated with ADH alone (319, 770, 800). These observations suggest that the additional features that occur in Bartter syndrome type 5 are due to severe gain of CaSR function (557). In a physiological setting, CaSR activation in TAL stimulates intracellular Ca^{2+} signaling that modulates PLA_2 activity, which in turn increases cytosolic arachidonic acid that is rapidly metabolized to 20-HETE or to prostaglandins (798). These signaling pathways have been linked to inhibition of NKCC2 and ROMK (9, 792, 793, 795). This means that enhanced activity of CaSR in TAL disturbs NaCl reabsorption directly mediated by NKCC2 and indirectly via ROMK channels, as K^+ recycling contributes to the NKCC2 transport rate. Furthermore, inhibition of ROMK and NKCC2 will lower the lumen-positive transepithelial voltage, which then diminishes paracellular Ca^{2+} and Mg^{2+} transport, resulting in TAL dysfunction resembling Bartter syndrome **(FIGURE 12)**.

A point of attention is that the intracellular signaling pathways activated by the CaSR are also stimulated by other receptor signaling involving angiotensin II and endothelin, which are not known to cause renal NaCl or K^+ wasting. This indicates that the CaSR functions via additional mechanisms, which could imply regulation of transporters in other nephron segments. There is some evidence of apical CaSR expression in the PT regulating the PTH-mediated phosphate excretion (28). A recent study suggested a new role of the CaSR in modulating fluid reabsorption as well as H^+ secretion in the PT, via stimulation of NHE3 (95). Activating the CaSR increased NHE3 activity leading to enhanced Na^+ reabsorption, which drives fluid reabsorption.

The concomitant H^+ secretion is thought to result in ionization of Ca^{2+}, which prevents its precipitation in the distal parts of the nephron (95). Thereby, CaSR activation would drive both fluid reabsorption in the PT and Ca^{2+} reabsorption in the distal nephron. Expression of the CaSR has also been reported on the apical and basolateral membranes of the DCT and CNT (604, 747), but its physiological role there remains to be established. Available evidence suggests the CaSR controls apical Ca^{2+} influx through TRPV5 and/or basolateral exit via NCX and PMCA in the DCT2/CNT (170, 747). An interaction of the CaSR with the inwardly rectifying K^+ channel Kir4.1, expressed at the basolateral membrane of the DCT, has also been demonstrated (100, 322). The CaSR was shown to block Kir4.1 channel activity by reducing its expression at the plasma membrane (100). Within the collecting duct, the CaSR is present in both principal and intercalated cells (604), where it is proposed to play a role in diuresis to prevent kidney stone formation upon hypercalciuria (581, 601, 636). The latest study suggests that activation of the CaSR leads to a reduced vasopressin response for aquaporin2 (AQP2) translocation, and subsequently reduces water reabsorption, functioning as a defense mechanism against kidney stones (581). This is in agreement with an earlier finding that mice deficient of *Trpv5* do not develop kidney stones despite the strong hypercalciuria (304). Instead, the *Trpv5*$^{-/-}$ mice have an enhanced urinary acidification and polyuria, likely due to the effects of the CaSR on the H^+-ATPase activity and AQP2 expression (601).

Together, these data suggest that the role of the CaSR in the kidney is not restricted to Ca^{2+} handling. Based on its basolateral expression in TAL and DCT, it may sense plasma Ca^{2+} levels in these segments and function as modulator of Ca^{2+} reabsorption by affecting either the passive or active transport pathways. In addition, the CaSR has antiphosphaturic effects in PT that might counteract possible Ca^{2+}-phosphate precipitation in distal tubular segments. Furthermore, it promotes acidification and polyuria through its action in the CD. Hence, the CaSR seems to have established an integrated system, regulating various levels of fluid and electrolyte management, to prevent nephrocalcinosis and kidney stone formation. Developing CaSR modulators with some specificity for the kidney could allow modulation of renal actions and function as therapeutics of the Ca^{2+}-related diseases.

F. Disorders of Magnesium Transport

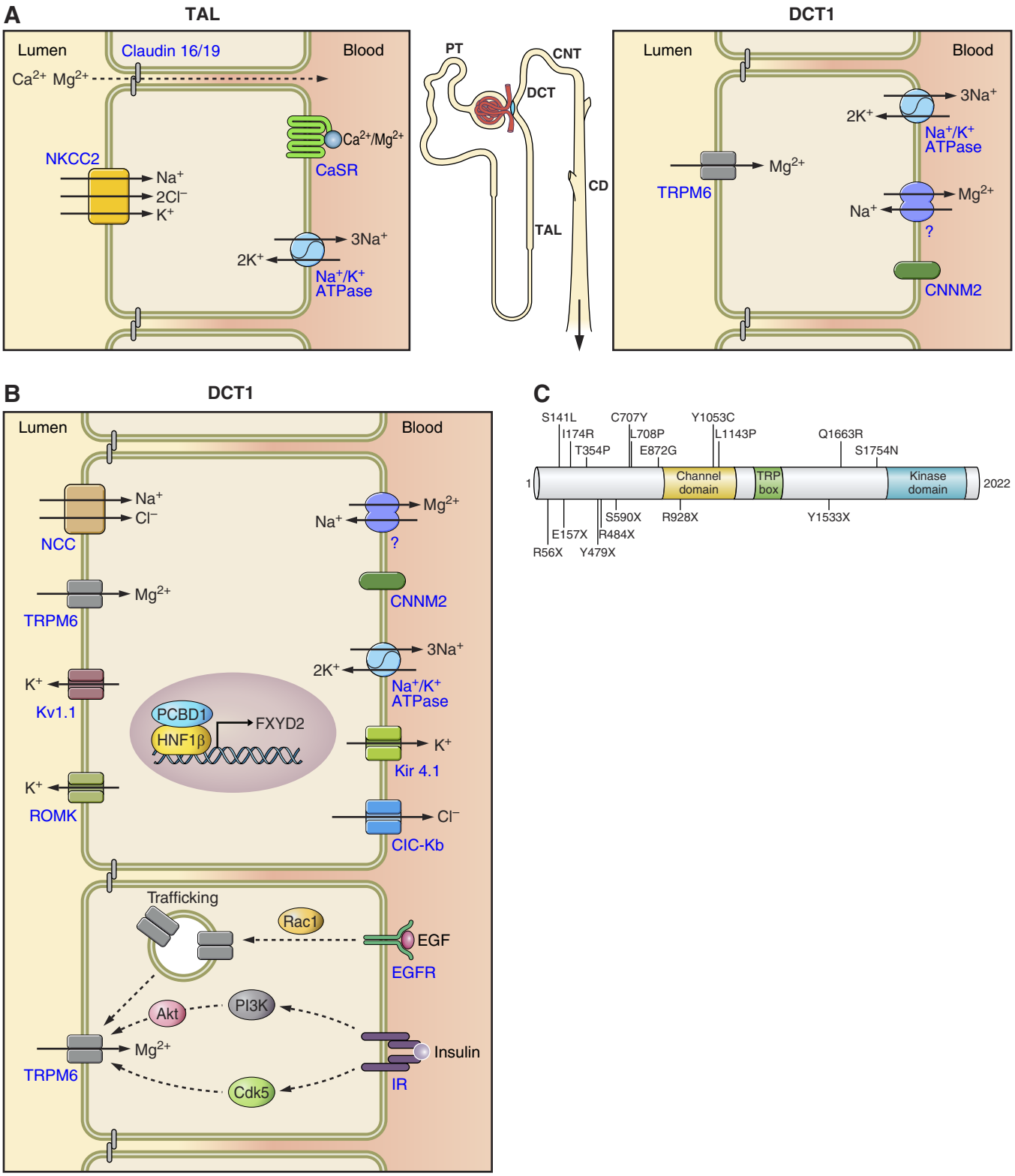
1. Renal magnesium handling

Mg^{2+} is an essential divalent cation that participates in a wide spectrum of processes involving intracellular signaling, neuromuscular excitability, bone formation, and enzyme activation (186, 212). The maintenance of the Mg^{2+} balance is crucial for many physiological functions, and plasma Mg^{2+} concentrations are kept within a defined range (0.7–1.1 mM) via (re)absorption in the intestine and kidney, and exchange with the bone. The skeleton functions as a major Mg^{2+} store, resulting in only 1% of the total body Mg^{2+} as the circulating plasma Mg^{2+} (789). Ultimately, these Mg^{2+} levels are defined by the final urinary Mg^{2+} excretion, which is tightly regulated by the kidney (174, 587). Here, the majority of filtered Mg^{2+} is reabsorbed in the PT (15–20%) and TAL (65–70%) via passive paracellular transport. Similar to Ca^{2+} transport, the claudin-16/19 complex is responsible for Mg^{2+} reabsorption in the TAL, which is driven by the positive transepithelial voltage. Several hormones, including PTH, glucagon, calcitonin, and insulin, were shown to stimulate Mg^{2+} reabsorption in this segment, either via influencing the transepithelial voltage by affecting NKCC2 transport or ROMK activity or by modifying the paracellular permeability through the claudins (168, 588). Similarly, activation of the CaSR in the TAL can inhibit paracellular Mg^{2+} transport (293). Furthermore, a number of other electrolyte disturbances like metabolic acidosis, K^+ depletion, and hypophosphatemia also affect renal Mg^{2+} transport by changing the transepithelial voltage or the permeability of the paracellular pathway. Final regulation of the urinary Mg^{2+} excretion takes place in DCT1 where the remaining 10% of filtered Mg^{2+} is reabsorbed by an active transcellular mechanism (140). Here, Mg^{2+} enters the cell via the epithelial Mg^{2+} channel TRPM6, dependent on the negative apical transmembrane potential. This is established by apical K^+ secretion via the K^+ channels Kv1.1 and/or ROMK (717). Furthermore, Mg^{2+} transport via TRPM6 can be stimulated by a number of hormones including epidermal growth factor (EGF), insulin, and estrogen (265, 266, 508). The mechanism of Mg^{2+} extrusion at the basolateral membrane is still not understood, but likely comprises a Na^+-dependent transporter. In addition, two other basolateral proteins, the K^+ channel Kir4.1 and γ-subunit of Na^+-K^+-ATPase, are identified as important factors in generating a Na^+ gradient that drives Mg^{2+} reabsorption in DCT1 (62, 477) **(FIGURE 13)**.

Disturbances in the Mg^{2+} balance are often secondary to diseases like diabetes mellitus, osteoporosis, asthma, and heart and vascular disease, or Mg^{2+} depletion occurs upon treatment with various drugs including loop diuretics, thiazides, immunosuppressants, anticancer drugs, proton pump inhibitors. Studies of inherited forms of hypomagnesemia and experimental findings of several animal models have greatly increased our knowledge of renal Mg^{2+} reabsorption mechanisms. Identification of the affected nephron segments, different modes of inheritance, and additional characteristic symptoms has helped in the classification of the Mg^{2+} wasting disorders, which is discussed in more detail in the forthcoming paragraphs.

2. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis

A) BRIEF CLINICAL DESCRIPTION. In 1975, a case report described the phenotype of a young man with hypomagnesemia and accompanying renal Mg^{2+} and Ca^{2+} wasting, that also exhibited progressive nephrocalcinosis and chondrocalcinosis (630). Subsequent studies enabled full characterization of the disorder named as familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC, also named



hypomagnesemia 3, HOMG3; MIM no. 248250) (517, 577, 620). The patients present in childhood with polyuria-polydipsia, urinary tract infections, and kidney stones, and extrarenal manifestations such as failure to thrive, tetany, seizures, and nystagmus have also been reported (517, 620). Additional biochemical characteristics include elevated PTH levels, incomplete distal tubular acidosis, hypocitraturia, and hyperuricemia in most patients. In addition to the classical FHHNC phenotype, a subset of patients was identified with severe ocular abnormalities. This appeared to be associated with a different genetic defect and was therefore termed FHHNC with severe ocular involvement (also named hypomagnesemia 5, HOMG5; MIM no. 248190) (399). Due to the hypercalciuria and nephrocalcinosis, patients often progress to chronic kidney disease within the first two decades of life, and a significant number of patients develop end-stage renal disease later in life. Initial therapy aims at restoring the plasma Mg^{2+} levels and reducing the hypercalciuria by chronic Mg^{2+} supplementation and thiazide treatment, respectively. However, this treatment is in general insufficient to prevent the progression of nephrocalcinosis and stone formation (577, 753, 801).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. By using a positional cloning approach, Simon et al. (693) found mutations in *CLDN16*, the gene encoding the tight junction protein claudin-16 (initially named paracellin-1) as associated with FHHNC/HOMG3. Claudin-16 is expressed in the TAL and plays a role in paracellular cation permeability (385, 693). Most reported *CLDN16* mutations are missense mutations that target either the transmembrane domains or the extracellular loops, with a clustering in the first extracellular loop that is important for ion selectivity. Within this domain, patients originating from Germany or Eastern European countries exhibit a common *CLDN16* mutation (L151F) due to a founder effect (801). As this mutation is present in ~50% of mutant alleles, molecular diagnosis is greatly facilitated in patients originating from these countries. A few years later, mutations were also identified in the *CLDN19* gene, coding for claudin-19, associated with HOMG5 (399). Claudin-19 colocalizes with claudin-16 in the kidney, but it is also highly expressed in the retina explaining the severe ocular problems observed in patients with *CLDN19* mutations (399). A cohort study presented a genotype-phenotype correlation demonstrating that FHHNC patients with *CLDN16* mutations leading to a complete loss-of-function on both alleles display a younger age onset as well as a more rapid decline in renal function compared with patients with residual claudin-16 function (398). On the other hand, phenotypical variability is even found in families with members having the same homozygous *CLDN16* or *CLDN19* mutation (20, 670).

The claudin-16 and -19 isoforms are both highly enriched in the TAL. Hou et al. (315) demonstrated that claudin-16 and claudin-19 interact to form a cation-selective pore. Overexpression studies showed that several FHHNC mutations in *CLDN16* and *CLDN19* disrupt this interaction and abolish the cation selectivity of the encoded claudins (316). However, other studies have shown conflicting results on the claudin-16/19 permeability properties, and the direct effects on Mg^{2+}/Ca^{2+} permeation do not fully explain the strong hypercalciuria and hypermagnesiuria observed in FHHNC patients (313, 337, 374). The idea is that the mutant claudin proteins impair the electrical driving force necessary for passive transport. Overexpression of claudin-16 significantly increased the Na^+ permeability (P_{Na}), which was not observed for the FHHNC disease mutants of claudin-16 (313). Furthermore, ex vivo perfusion measurements of TAL segments from *Cldn16* knockdown (KD) mice demonstrated that the ion permeability ratio for Na^+ over Cl^- (P_{Na}/P_{Cl}) was decreased (317). On the other hand, overexpression of claudin-19 led to a decrease in Cl^- permeability, meaning that coexpression with claudin-16 results in a large increase in P_{Na}/P_{Cl} that ultimately generates the transepithelial voltage (316, 680). Hence, loss-of-function mutations in *CLDN16* and *CLDN19* would abrogate this electrical driving force for paracellular Ca^{2+} and Mg^{2+} reabsorption in TAL.

The latter hypothesis has been supported by studies in mouse models. Hou et al. (317) used RNA interference to

FIGURE 13. Magnesium transport in the kidney. *A*: the major amount of filtered Mg^{2+} is reabsorbed through a paracellular route in the PT and TAL. Here, claudin-16 and claudin-19 constitute the paracellular Mg^{2+} pathway. The final reabsorption of Mg^{2+} takes place in the DCT via the apical Mg^{2+} channel TRPM6. *B*: Mg^{2+} reabsorption in DCT is mediated by TRPM6. Here, transport of Mg^{2+} is primarily driven by the electrical gradient over the apical membrane, which is established by the voltage-gated K^+ channels Kv1.1 and ROMK. Moreover, the hormones EGF and insulin are involved in the membrane expression of TRPM6 through intracellular signaling involving Cdk5, PI3K, Akt, and Rac1. Extrusion of Mg^{2+} at the basolateral membrane occurs via a yet unknown mechanism, possibly regulated by CNNM2 functioning as a Mg^{2+} sensor. The Na^+-K^+-ATPase generates the electrochemical gradient essential for the transport processes, and its activity is dependent on K^+ recycling via Kir4.1 at the basolateral membrane. Furthermore, FXYD2 is known as a regulatory subunit of the Na^+-K^+-ATPase, and its transcription is regulated by HNF1β and the cofactor PCBD1. *C*: schematic representation of the domain structure of TRPM6 depicting the missense mutations identified in patients suffering from hypomagnesemia with secondary hypocalcemia. Akt, protein kinase B; Cdk5, cyclin-dependent kinase 5; ClC-Kb, chloride channel Kb; CNNM2, cyclin M2; DCT, distal convoluted tubule; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FXYD2, FXYD-domain containing ion transport regulator 2; HNF1β, hepatocyte nuclear factor-1β; IR, insulin receptor; Kir4.1, inwardly rectifying K^+ channel; Kv1.1, voltage-gated K^+ channel 1.1; NCC, Na^+-Cl^- cotransporter; PCBD1, pterin-4 alpha-carbinolamine dehydratase 1; PI3K, phosphoinositide 3-kinase; PT, proximal tubule; Rac1, Ras-related C3 botulinum toxin substrate 1; ROMK, renal outer medullary K^+ channel; TAL, thick ascending limb of Henle's loop; TRPM6, transient receptor potential melastatin type 6.

generate *Cldn16*-deficient mice that had >99% knockdown (KD) of claudin-16 expression in the kidneys. These mice show typical FHHCN symptoms including hypomagnesemia, high urinary excretion of Ca^{2+} and Mg^{2+}, and nephrocalcinosis (317). Similarly, *Cldn19* KD mice exhibit low serum Mg^{2+} together with urinary Ca^{2+} and Mg^{2+} wasting (315). While the KD models favor a reduction in Na^+ selectivity as causative factor of renal wasting in FHHNC, a study on *Cldn16* KO mice demonstrated reduced Mg^{2+} and Ca^{2+} permeability in microperfused TAL segments (810). A third isoform enriched in the TAL, claudin-14, may interact with claudin-16, causing the inhibition of the claudin-16/19 complex. As described in section III*E3*, the expression of claudin-14 is positively regulated by the CaSR via a microRNA-dependent mechanism (251). Genome-wide association studies support the relevance of this mechanism, since common variants in *CLDN14* are associated with increased risk of kidney stones and the urinary Mg^{2+} to Ca^{2+} ratio in the general population (134).

The importance of claudins in electrolyte balance was further emphasized by the recent identification of mutations in *CLDN10*, encoding claudin-10, by three independent groups (65, 277, 386). Claudin-10 has two major isoforms that can form paracellular channels with different ion selectivity (767). Mutations in either of the isoforms were associated with an autosomal recessive disorder that is characterized by hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia (HELIX syndrome; MIM no. 617671). The patients had renal salt wasting, with hyperaldosteronism and hypokalemia, and mild Ca^{2+} and Mg^{2+} retention. Interestingly, the biochemical characteristics were in line with findings in the tubule-specific *Cldn10* KO mice (79). Functional analysis in isolated perfused TAL tubules of these mice demonstrated a decreased paracellular Na^+ permeability and a relatively increased permeability of Ca^{2+} and Mg^{2+} (79). Of note, claudin-10 shows a higher expression in the inner stripe of the outer medulla (ISOM), whereas claudin-16 and claudin-19 predominate in the outer stripe (OSOM) and the cortex. Furthermore, the channels formed by claudin-10b are selectively permeable for Na^+, whereas claudin-16 and -19 are permeable for Mg^{2+} and Ca^{2+} (485). These data, recently supported by studies using double KO mice for *Cldn16* and *Cldn10* (78), support the existence of a longitudinal specialization of paracellular transport within the TAL segment **(FIGURE 14)**. In addition to the paracellular reabsorption of Ca^{2+} and Mg^{2+} (in the OSOM and cortex) via the claudin-16/19 complex, the lumen-positive transepithelial potential drives the paracellular reabsorption of Na^+ (in the ISOM) via claudin-10b. Recently, Miltaz et al. (485) hypothesized that the high paracellular and transcellular Na^+ reabsorption without water in the ISOM leads to a hyposmotic luminal fluid in the cortical TAL, resulting in Na^+ diffusion from interstitium to lumen (via claudin-10b) along its concentration gradient, via the paracellular pathway created by claudin-10b. In turn, this Na^+ diffusion contributes to the lumen-positive potential as a driving force for Ca^{2+} and Mg^{2+} reabsorption (544). Together, these studies support further understanding of tight junction formation and provide essential information on the selectivity of the pore region.

3. Isolated dominant renal hypomagnesemia

A) BRIEF CLINICAL DESCRIPTION. Nearly three decades ago, two initially unrelated Dutch families were reported with dominant renal hypomagnesemia associated with hypocalciuria (IDH, also named hypomagnesemia 2, HOMG2; MIM no. 154020) (239). They had increased urinary Mg^{2+} values, showed lowered urinary Ca^{2+} excretion, and suffered from generalized convulsions, cramps, and chondrocalcinosis. The serum Mg^{2+} levels were <0.4 mM, without other plasma electrolyte abnormalities. A ^{28}Mg-retention study in one of the patients demonstrated that intestinal Mg^{2+} absorption was preserved, which was indicative for a renal defect (239). Other family members had low serum Mg^{2+} as well, but lacked symptoms of Mg^{2+} deficiency (239, 478). Detailed haplotype analyses identified the segregation of an affected haplotype in the two families, which is suggestive for a common ancestor (478). A recent study reported on two new Belgian and Dutch families with IDH that also shared this haplotype. Indeed, the same mutation was identified in all families (142, 477).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Linkage analysis followed by genetic candidate screening led to the discovery of a mutation in the *FXYD2* gene, resulting in amino acid substitution G41R in the encoded γ-subunit of the Na^+-K^+-ATPase (FXYD2) in the IDH patients (477). The Na^+-K^+-ATPase consists of α- and β-subunits that form a complex for the active transport of Na^+ and K^+ in opposite directions. The γ-subunit is a small, type I transmembrane protein of which the transmembrane domain binds to a groove formed by several helices of the Na^+-K^+-ATPase α-subunit (426). *Xenopus laevis* oocyte studies showed that this association is necessary for transport of the γ-subunit to the plasma membrane, but not for plasma membrane expression of functional Na^+-K^+-ATPase proteins (49). The γ-subunit is suggested to modulate the kinetics of Na^+-K^+-ATPase-mediated transport, with changes in the affinity to ATP or dependence to the membrane potential (23, 48, 49, 426, 584, 742). Expression studies in *Xenopus* oocytes and mammalian cells have shown that the G41R disease mutant is retained in the cytoplasm as it lacks interaction with the Na^+-K^+-ATPase α-β complex (86, 476). It is suggested that the dominant-negative G41R mutant protein can oligomerize with wild-type subunits, thereby abrogating the binding to the Na^+-K^+-ATPase (476). Immunolocalization studies in rat kidney showed that FXYD2 is highly expressed at the basolateral membrane of cells lining the TAL and DCT (23, 481, 584). It is, therefore,

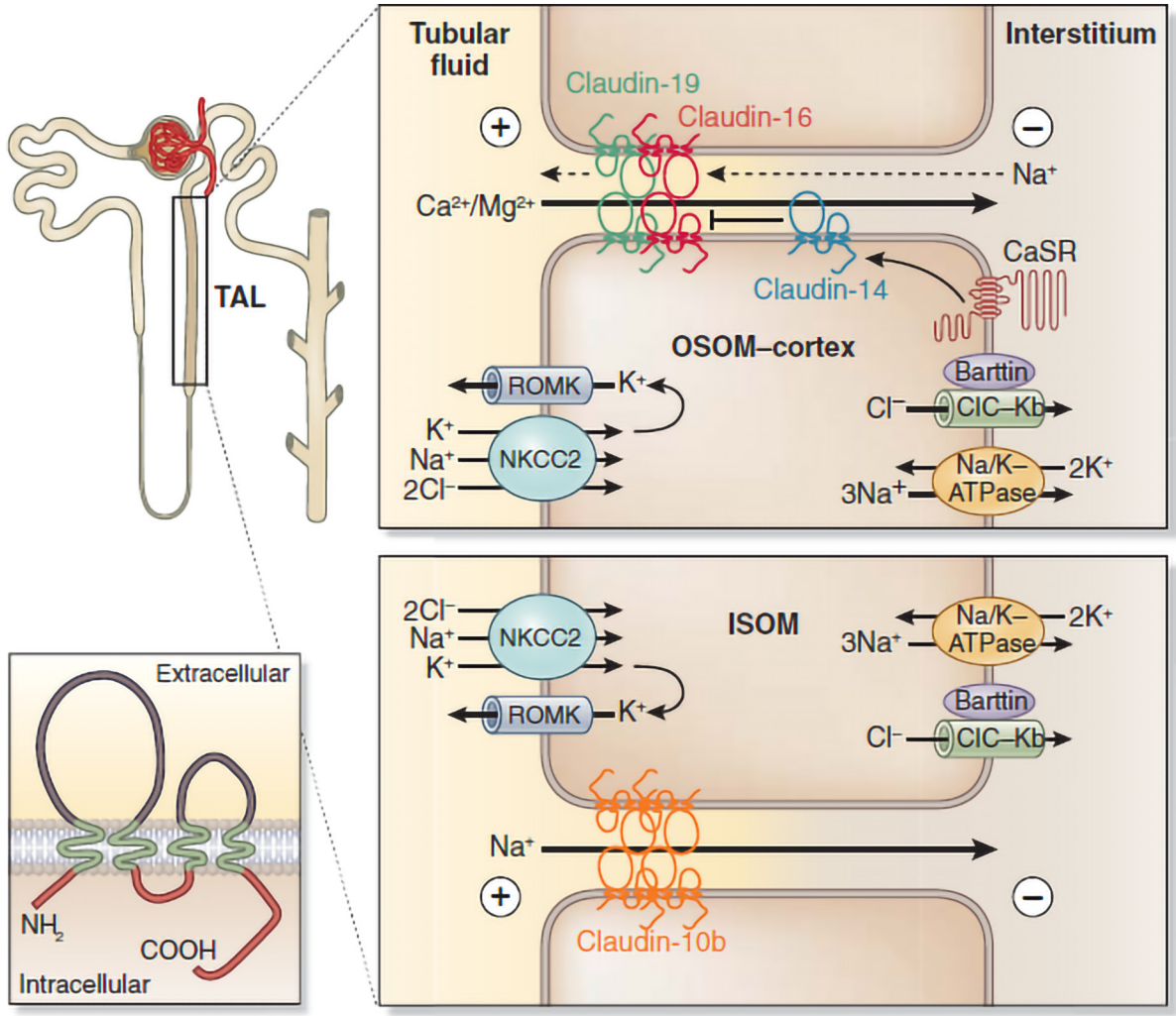


FIGURE 14. Expression and role of claudins in the TAL. Representation of the transcellular and paracellular transport pathways in the thick ascending limb (TAL) cells from the inner stripe of the outer medulla (ISOM) and the outer stripe of the outer medulla (OSOM) and the cortex. Most of K^+ entering the cell via NKCC2 is recycled through ROMK, leading to hyperpolarization of the apical membrane. Cl^- exiting via ClC-Kb is depolarizing the basolateral membrane. The difference in membrane potential constitutes a lumen-positive transepithelial potential that drives paracellular reabsorption of Ca^{2+}/Mg^{2+} and of Na^+. Recent studies have shown that the TAL expresses claudins in a mosaic pattern, with claudins 16/19 predominating in the tight junctions of the cortex and OSOM, whereas tight junctions exclusively made of claudin-10b predominate in the ISOM. This mosaic pattern results in a spatial separation of paracellular Na^+ transport and reabsorption of Ca^{2+} and Mg^{2+}. Tight junctions with claudin-10b favor Na^+ over Mg^{2+}, whereas tight junctions with claudins 16/19 prefer Mg^{2+} over Na^+. As a result, in ISOM TAL, tight junctions with exclusive claudin-10b mediate high paracellular Na^+ permeability, which adds to the transcellular uptake. Reabsorption of Na^+ without water in the ISOM leads to a hyposmotic luminal fluid in the cortical TAL, which may favor Na^+ diffusion from the interstitium into the lumen along its concentration gradient, through tight junctions rich in claudin-10b. *Inset*: general claudin protein and membrane-folding model: 4 transmembrane helical domains (green), 2 extracellular loops (blue), and 1 intracellular loop as well as a short NH_2-terminal and a long COOH-terminal cytoplasmic domain (red). ATPase, adenosine triphosphatase; CaSR, calcium sensing receptor; ClC-Kb, chloride channel Kb; ISOM, inner stripe of the outer medulla; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; OSOM, outer stripe of the outer medulla; ROMK, renal outer medullary K^+ channel. [Adapted from Milatz et al. (485) and Olinger et al. (544), with permission from Elsevier.]

proposed that misrouting of mutant FXYD2 will diminish the functionality of the Na^+-K^+-ATPase in DCT. Hence, reduced intracellular K^+ or increased intracellular Na^+ will lower the membrane potential at the apical membrane resulting in a diminished driving force for Mg^{2+} uptake and subsequent Mg^{2+} wasting.

A heterozygous mutation of the *FXYD2* gene in humans does not lead to hypomagnesemia, pointing towards a specific dominant-negative effect of the G41R mutation in patients with isolated hypomagnesemia (477). Another mechanism of action has been proposed by Sha and co-workers (486, 677), which measured large nonselec-

tive ion currents in FXYD2-expressing oocytes with different characteristics for the G41R mutant. It is, however, not known whether the protein forms an ion channel or indirectly affects other ionic currents. *Fxyd2* KO mice display no abnormalities in urinary Mg^{2+} excretion or serum Mg^{2+} levels (21, 356). Interestingly, they were suspected to have elevated Na^+-K^+-ATPase activity and showed hyperphosphorylation of NCC in kidney (22). This was anticipated to lead to Na^+ retention and hypertension, but the KO mice showed no abnormalities in their Na^+ balance and were normotensive (22). Of note, the mice exhibited a mild pancreatic phenotype with reduced blood glucose and elevated levels of circulating insulin. They showed enhanced glucose tolerance but no insulin resistance (21). Future investigation should unveil the mechanism responsible for these observations and assess these clinical parameters in patients harboring *FXYD2* mutations.

Identification of new causative genes for hypomagnesemia has also shed light on the *FXYD2* gene transcription in DCT. Mutations in the *HNF1B* gene encoding the transcription factor hepatocyte nuclear factor 1β (HNF1β) have been associated with an autosomal dominant disorder named renal cysts and diabetes syndrome (RCAD; MIM no. 137920). The disorder is characterized by maturity-onset diabetes of the young 5 (MODY5) and severe nondiabetic renal dysfunction (308, 525). In 2009, Adalat et al. (6) found that nearly half of the subjects carrying a *HNF1B* mutation present with hypomagnesemia due to renal Mg^{2+} wasting. The association of mutations in *HNF1B* with hypomagnesemia (and other tubular abnormalities) of renal origin has been confirmed in subsequent cohorts, which also evidenced the marked heterogeneity of the clinical presentation (196).

HNF1β is a homeodomain-containing transcription factor expressed in developing mouse ureters and collecting ducts, and postnatally observed in proximal and distal tubules (129, 394). HNF1β regulates the *FXYD2* gene expression (6, 206), at least in vitro, and that may explain its role in renal Mg^{2+} handling. In addition, it was recently identified as transcriptional activator of *KCNJ16*, which encodes the K^+ channel Kir5.1 (397). Mutations in *KCNJ16* are associated with SeSAME (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance) or EAST (epilepsy, ataxia, sensorineural deafness, and tubulopathy) syndrome, another Mg^{2+} wasting tubulopathy that will be discussed below. Kir5.1 likely plays an important role in Mg^{2+} transport in DCT, but the exact molecular mechanism remains to be elucidated. The study by Kompatscher et al. (397) implies that patients with *HNF1B* mutations have reduced Kir5.1 expression, which could explain the renal Mg^{2+} wasting.

Another recent study reported on three patients with homozygous mutations in the *PCBD1* gene, coding for pterin-4-alpha-carbinolamine dehydratase 1 (PCBD1), suffering from hypomagnesemia, renal Mg^{2+} wasting, and MODY5-like diabetes (205). Previously, recessive *PCBD1* mutations have been linked to transient neonatal hyperphenylalaninemia with primapterinuria and deficient tetrahydrobiopterin (BH4) (HPABH4D) (MIM no. 264070) (124, 743). In fact, PCBD1 acts as an enzyme to regenerate BH4, the cofactor for aromatic amino acid hydroxylases, and also acts as a binding partner of the HNF1 transcription factors (743). The finding that HNF1β forms heterotetrameric complexes with PCBD1 (208, 480) and the in vitro data demonstrated that the HNF1β-PCBD1 complex enhances the FXYD2 promoter provide a putative link between PCBD1 and Mg^{2+} reabsorption in DCT (205) **(FIGURE 13)**.

The latter findings strengthen the idea of the γ-subunit of the Na^+-K^+-ATPase regulating renal Mg^{2+} transport in DCT. They also point to a transcriptional level of regulation in the processes affecting renal Mg^{2+} handling, which needs further investigation.

4. Hypomagnesemia with secondary hypocalcemia

A) BRIEF CLINICAL DESCRIPTION. Initially described in 1968, familial hypomagnesemia with secondary hypocalcemia (HSH, also named hypomagnesemia 1, HOMG1; MIM no. 602014) is a rare recessive disorder that is characterized by severe electrolyte abnormalities shortly after birth (555). Patients suffer from severe hypomagnesemia (Mg^{2+} levels ~0.2 mM) and hypocalcemia, which causes neuromuscular symptoms including seizures and tetany, and they require life-long Mg^{2+} supplementation to overcome these complications. The hypomagnesemia is primarily caused by a defect in Mg^{2+} absorption in the intestine, but there is a renal Mg^{2+} leak as well (470, 658, 786). PTH levels were found to be inappropriately low, which is seen more often in cases of Mg^{2+} deficiency and thought to be the cause of hypocalcemia (217, 483, 628). The Ca^{2+} levels could be not be restored by administration of Ca^{2+} or vitamin D, but Mg^{2+} supplementation is needed (101, 679). Fast diagnosis and immediate treatment are essential to prevent permanent neurological damage or even cardiac arrest.

B) GENETICS. Mutations in the *TRPM6* gene (located on 9q21.13) were identified as the cause of HSH through a positional candidate gene approach (658, 786). *TRPM6* encodes the TRPM6 ion channel, which is a large protein (~2,000 amino acids) belonging to the melastatin subfamily of the transient receptor potential (TRP) family of ion channels (125). In the past decade, mainly NH_2-terminal splice site and frame-shift mutations have been described that lead to a truncated form of TRPM6. Additionally, several missense mutations were identified, which result in loss of channel function (763) **(FIGURE 13)**. Importantly, TRPM6 has a restricted expression pattern along the epithelia of the

kidney and intestine that actively transport Mg^{2+} (780). Together with the finding that it functions as a Mg^{2+}-permeable channel (780), it can explain the severe hypomagnesemia in HSH patients. Of interest, a recent meta-GWAS performed in 7 cohorts amounting to 9,099 individuals identified a common variant in the *TRPM6* locus associated with the urinary Mg^{2+} levels, substantiating the role of TRPM6 in Mg^{2+} homeostasis and metabolism (133).

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. A TRPM6 ion channel consists of four subunits, each containing six membrane-spanning domains and large intracellular NH_2 terminal and COOH termini (593, 651). In addition to its function as ion channel, the TRPM6 C-tail comprises a protein kinase domain, which led to the term *chanzyme* (channel and enzyme) (492). The functional link between ion channel and kinase domain is still not completely resolved, but the kinase domain seems to have a modulatory role in channel activity (155, 741, 764, 854). A recent study demonstrated one missense mutation, located in close proximity to the kinase domain (S1754D), which resulted in both loss of channel function and of kinase activity (410a, 764) **(FIGURE 13)**. Yeast two hybrid screens resulted in the identification of the TRPM6 kinase binding partners RACK1 (receptor for activated C kinase 1), REA (repressor of estrogen receptor activity), and MsrB1 (methionine sulfoxide reductase B1) that affect channel function (92–94). TRPM6 likely forms either homomeric complexes or heterotetramers with TRPM7, which influences channel characteristics (429, 854). Several intracellular components like pH, phosphatidylinositol 4,5-bisphosphate, ATP, and Mg^{2+} are also identified as channel regulators (428, 741, 780, 830).

Additional levels of channel regulation involve the transcription and cell surface expression. First, the renal TRPM6 mRNA level was shown to be upregulated in mice fed a Mg^{2+}-deficient diet to maximize renal Mg^{2+} conservation (265). Second, the magnesiotropic hormones EGF and estrogen are involved in the regulation of *TRPM6* mRNA expression (265, 266, 338, 339). Additionally, EGF can affect channel function by increasing the expression of TRPM6 at the plasma membrane through downstream signaling of the EGF receptor, involving the MAPK/extracellular signal-regulated kinase (ERK) pathway and signaling of PI3K and Rac1 (ras-related C3 botulinum toxin substrate 1) (740). Next, insulin was recently identified as the third hormone that plays a role in TRPM6 regulation (508). It can stimulate channel function via the PI3K and Rac1-mediated pathway that enhances cell surface expression of TRPM6 **(FIGURE 13)**. The authors examined two genetic variants in TRPM6 (I1393V and K1584E) that are associated with the total glycosylated hemoglobin level, a measure of insulin resistance, in pregnant women (508). Third, there is an increasing body of evidence for regulation of *TRPM6* mRNA expression in drug-induced hypomagnesemia involving the immunosuppressants cyclosporine A and tacrolimus, loop and thiazide-diuritics, proton pump inhibitors, and the anti-cancer drug cyclosporin (412).

The role of EGF in Mg^{2+} homeostasis has been further substantiated by the association of hypomagnesemia with a mutation in the *EGF* gene. In 1987, Geven et al. (240) reported two sisters with an autosomal recessive form of isolated renal Mg^{2+} loss. Their urinary Mg^{2+} excretion was in the normal range despite low serum Mg^{2+} values (0.53–0.66 mM) and they had no other biochemical abnormalities. Both sisters presented with psychomotor retardation and suffered from epileptic seizures (240). Genetic linkage analysis and subsequent candidate screening led to the identification of a homozygous mutation in *EGF* in this form of renal hypomagnesemia (HOMG4; MIM no. 611718) (266). *EGF* encodes a large membrane-anchored precursor protein, which can be cleaved into pro-EGF that in turn gives rise to the small peptide hormone EGF (39). Importantly, Groenestege et al. (266) demonstrated an overlapping expression of EGF and TRPM6 in DCT, and earlier studies (238, 635) have shown that the EGFR is present along the basolateral membrane of the TAL and DCT. The mutation identified in the two sisters with hypomagnesemia results in a proline to leucine substitution at position 1070 (P1070L) in the cytoplasmic tail of pro-EGF. This is thought to affect a basolateral sorting motif, thereby preventing pro-EGF trafficking and cleavage at the basolateral membrane (266, 290). Hence, the hypomagnesemia is likely caused by failed stimulation of the EGFR at the basolateral membrane due to insufficient secreted EGF. Together with the finding that EGF enhances TRPM6 channel activity, this led to the hypothesis that EGFR signaling plays a key role in renal Mg^{2+} reabsorption. This notion was further supported by clinical studies demonstrating that colorectal cancer patients develop hypomagnesemia due to anti-cancer treatment with the monoclonal EGFR antibody cetuximab (663, 735). Impaired EGF signaling is likely involved in other forms of hypomagnesemia as recent studies suggest that the chemotherapeutic drug cisplatin and the immunosuppressant cyclosporine inhibit renal Mg^{2+} reabsorption via downregulation of the TRPM6-EGF pathway (416, 417). The discovery of EGF as a magnesiotropic hormone has improved the understanding of the molecular mechanisms regulating systemic Mg^{2+} balance.

A mouse model with homozygous deletion of *Trpm6* was found to be embryonic lethal, pointing towards a developmental role of TRPM6 to maintain the Mg^{2+} balance (787, 818). The few *Trpm6* KO mice that were viable upon high-Mg^{2+} diet had defective brain and facial development (787). Additionally, both groups showed that the heterozygous *Trpm6* mice present a mild hypomagnesemia (787, 818). Chubanov et al. (122) recently developed a conditional *Trpm6* KO mouse model. Postnatal inactivation of *Trpm6* led to a shorter lifespan, growth retardation, im-

paired metabolism, and many characteristics that are generally a hallmark of "accelerated aging" (122). Importantly, the phenotype could be rescued by a high-Mg^{2+} diet. In addition to a global KO, Chubanov et al. (122) also generated kidney-specific and intestinal-specific *Trpm6* KO mice. While the conditional inactivation of TRPM6 in the kidney did not result in changes in serum Mg^{2+} levels, disruption of TRPM6 in the intestine led to hypomagnesemia (122). This suggest that TRPM6-mediated Mg^{2+} absorption in the colon is essential for the body's Mg^{2+} balance. Altogether, these investigations yielded crucial informations about the role of TRPM6 in Mg^{2+} homeostasis.

5. Autosomal dominant hypomagnesemia

A) BRIEF CLINICAL DESCRIPTION. In 2009, a new type of hypomagnesemia was identified in a large Brazilian family, with an autosomal dominant form of inheritance (245). The affected individuals present recurrent muscle cramps, tetany, tremor, and muscle weakness, detected from early childhood. Furthermore, a cerebral MRI demonstrated a slight atrophia of the cerebral vermis in one patient, and electromyographs of more affected family members indicated involuntary muscular movements called myokymia. Serum Mg^{2+} levels were low, while other electrolyte levels were in the normal range and there was no change urinary Mg^{2+} excretion indicative of a renal defect. Importantly, the proband also showed facial myokymia and intermittent tetanic contraction, which improved shortly after Mg^{2+} administration. Electromyographs of some affected family members showed myokymic discharge. A daily Mg^{2+} supplementation could improve the observed symptoms in the affected family members.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. A positional cloning approach led to the identification of a heterozygous mutation in the *KCNA1* gene (12p13.32), coding for the Shaker-related voltage-gated K^+ channel Kv1.1, in the affected family members (245). Kv1.1 functions as a tetrameric structure, and each subunit consists of six transmembrane segments (S1-S6), of which S4 acts as a voltage sensor and a pore region is formed by S5 and S6. The mutation results in an amino acid substitution (N255D) localized close to S3. Electrophysiological analysis demonstrated a dominant-negative effect of the mutation on wild-type Kv1.1 channel function (245). Recently, a second (de novo) *KCNA1* mutation was reported in a patient with tetany and hypomagnesemia. This L328V mutation also led to a dominant-negative loss of function of the encoded Kv1.1 channel (765). Immunohistochemistry showed Kv1.1 localization at the luminal membrane of DCT cells (97, 245), which suggests a potential link between Kv1.1-mediated K^+ efflux and Mg^{2+} reabsorption. The hypothesis arose that Kv1.1 is involved in the maintenance of the membrane potential across the apical membrane that functions as the driving force for Mg^{2+} uptake via TRPM6 **(FIGURE 13)**. Hence, the mutation may reduce this electrical gradient and therefore results in diminished Mg^{2+} transport and subsequent renal Mg^{2+} wasting.

Mutations in *KCNA1* had previously been associated with episodic ataxia type 1 (EA1) (MIM no. 160120), a dominant neurological disorder caused by defective Kv1.1 channels in the cerebellum (84, 260). Despite similar loss in Kv1.1 function, hypomagnesemia has not been reported in these cases, and it would, therefore, be of interest to investigate the plasma Mg^{2+} levels in this group of patients with *KCNA1* mutations. Next to this, *Kcna1* null mice (696) or *Kcna1* KI mice (85) that are currently studied to explain the epileptic seizures could be examined for Mg^{2+} wasting. It is generally known that a voltage-dependent K^+ secretion occurs along the distal tubule, which results in the lumen-positive membrane potential favoring Mg^{2+} uptake. However, it should be noted that other candidates than Kv1.1 have been proposed, including the ROMK and Maxi-K (or BK) channels (717). Future studies should reveal the exact components of K^+ secretion in DCT and its role in K^+ and Mg^{2+} homeostasis.

6. SeSAME/EAST syndrome

A) BRIEF CLINICAL DESCRIPTION. In 2009, two independent groups reported a new syndrome characterized by seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME) (62, 661). This association is also termed EAST syndrome (epilepsy, ataxia, sensorineural deafness, and a renal salt-losing tubulopathy) and has an autosomal recessive pattern of inheritance (MIM no. 612780). The patients presented with neurological symptoms from young age, including seizures, pronounced ataxia, and delayed psychomotor development. Some infants were unable to walk until the age of 3–9 yr. These neurological manifestations are the most invalidating aspect of the disease (1). Further laboratory analyses of the renal salt-losing tubulopathy showed hypokalemic metabolic alkalosis and hypomagnesemia, together with increased urinary excretion of K^+, Mg^{2+}, and Na^+. In addition, the levels of renin and aldosterone were increased without signs of hypertension. These features are similar to those associated with Gitelman syndrome. There is significant phenotypic heterogeneity and intrafamilial variability in the SeSAME/EAST syndrome (1). Patients receive salt, K^+, and Mg^{2+} supplementation to control their electrolyte levels (62, 661).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Whole-genome linkage analysis followed by candidate screening and sequencing revealed several missense mutations in *KCNJ10* (location 1q13.2) that encodes the K^+ channel Kir4.1 (62, 661). It belongs to the inward rectifier K^+ channel family and is expressed in the brain, inner ear, and kidney (12, 341, 731), which can explain the pleiotropic phenotype seen in patients. Kir4.1 localizes to the basolateral membranes of DCT and more distal nephron parts

(341). Here, heterotetrameric complexes of Kir4.1 and Kir5.1 likely represent the main K^+ channel functioning as a K^+ recycling mechanism needed for Na^+-K^+-ATPase activity (447, 851). The disease-causing mutations are shown to affect the function of both homomeric and heteromeric channels, either by mistrafficking or by altered channel characteristics (218, 550, 597, 634, 733, 811).

Studies performed in *Kcnj10* KO mice demonstrated an early lethality due to neurological complications such as seizures (516). Importantly, the renal phenotype in the neonates closely resembles that seen in SeSAME/EAST patients (62). In contrast, mice with deletion of *Kcnj16* (encoding Kir5.1) showed no difference in survival or growth compared with wild type, and the adult mice developed hypokalemic metabolic acidosis and hypercalciuria, contrasting with the SeSAME/EAST syndrome phenotype (554). Furthermore, Paulais et al. (554) demonstrated an increased basolateral K^+ conductance in DCT of *Kcnj16* KO mice, which suggests that homomeric Kir4.1 channels can maintain the transport function in DCT. In line with earlier studies (732, 832), these channels have an increased activity and a milder intracellular pH (pH_i) sensitivity compared with Kir4.1/Kir5.1 channels (554). This implies that variations in pH_i can produce significant changes in basolateral K^+ conductance and highlights the role of Kir5.1 in renal ion transport by Kir4.1 heteromerization. More recently, Cuevas et al. (139) generated an inducible kidney-specific *Kcnj10* KO line. These mice exhibited metabolic alkalosis and hypokalemia, combined with hypocalciuria and hypermagnesiuria. Further evidence for the role of Kir4.1 in sensing plasma K^+ levels came from the abrogated phosphorylation of NCC upon low dietary K^+ in these kidney-specific *Kcjn10* KO mice (139). As noted above, NCC expression and activity are highly sensitive to plasma K^+ levels, which can even dominate the effects of aldosterone or extracellular fluid volume on the DCT (736, 737). Terker et al. (737) demonstrated that NCC is regulated by the WNK/SPAK signaling pathway in response to changes in plasma K^+, through effects on membrane voltage in the DCT. The latter is controlled by Kir4.1, and likely Kir5.1, channels at the basolateral membrane, thereby demonstrating the molecular mechanism underlying the salt-wasting phenotype of SeSAME/EAST syndrome (804) **(FIGURE 11)**.

Yet, the exact mechanism that underlies decreased Mg^{2+} reabsorption (and hypermagnesiuria) in SeSAME is still not completely understood. Loss of Kir4.1 activity impedes Na^+-K^+-ATPase transport that in turn leads to depolarization of the basolateral membrane. The net effect is a diminished driving force for electrogenic transport via the putative Na^+/Mg^{2+} exchanger, thereby disturbing the Mg^{2+} transport gradient. However, it likely also diminishes the Cl^- efflux by Cl^- channels: a recent report by Zhang et al. postulated that subsequent activation of SPAK-dependent pathways plays an important role in the development of electrolyte disturbances (851). They demonstrated a reduced NCC expression in *Kcnj10* KO mice (851), which could lead to diminished TRPM6 expression as observed previously in *Slc12a3*-null mice and thiazide-treated rats (524, 665). Furthermore, analysis of dissected DCT tubules showed a depolarized membrane potential in *Kcnj10* KO (global and kidney-specific) animals compared with wild type, which would hamper TRPM6-mediated Mg^{2+} transport (139, 851). The hypokalemia and alkalosis result from increased salt delivery to the CNT and CCD, which increases Na^+ reabsorption by ENaC and K^+ and H^+ secretion. Overall, identification of Kir4.1 as the genetic factor of this multi-faceted syndrome has established a key role of basolateral K^+ transport in regulating distal tubular electrolyte transport.

7. Hypomagnesemia with seizures and mental retardation.

A) BRIEF CLINICAL DESCRIPTION AND GENETICS. Two unrelated families with a dominant form of renal hypomagnesemia (HOMG6) (MIM no. 613882) were screened for the causative gene of their Mg^{2+} wasting phenotype. Patients presented with muscle weakness, tremor, seizures, and headaches as a result of the low Mg^{2+} serum concentrations (0.3–0.5 mM), and had no other electrolyte disturbances detected (479, 716). Heterozygous mutations were identified in the *CNNM2* gene, which codes for the protein named cyclin and CBS domain divalent metal cation transport mediator 2 (CNNM2) (716). In addition to this finding, a recent report described five new families in which *CNNM2* mutations were linked to a distinct phenotype of hypomagnesemia with mental retardation and seizures (HOMGSMR1; MIM no. 616418) (19). Patients were diagnosed at early childhood and had a severe degree of psychomotor retardation. Mg^{2+} supplementation only moderately restored the serum Mg^{2+} levels, and seizures were suppressed by the use of anti-epileptic drugs. Of note, the brain phenotype and intellectual disability were most severe in patients carrying recessive mutations and could not be improved by Mg^{2+} supplementation (19).

B) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. CNNM2 was originally characterized as a member of the ancient conserved domain protein (ACDP) family, consisting of four members that share structural homology to cyclin proteins and have been listed as putative Mg^{2+} transporters (259, 791, 835). Additionally, common variants in the *CNNM2*, *CNNM3*, and *CNNM4* genes have been associated with serum Mg^{2+} concentrations in a GWAS study (482). CNNM2 has a ubiquitous expression pattern with highest abundance in kidney, brain, and lung (143, 791). Within the kidney, CNNM2 is mainly localized along the basolateral membrane of DCT, which raised the notion that it could be an unidentified Mg^{2+} extruder (143, 716). Further evidence for a role of CNNM2 in Mg^{2+} handling appeared from microarray

analysis of mouse DCT cells demonstrating Mg^{2+}-responsive gene regulation of the *CNNM2* gene (259). Interestingly, heterozygous and kidney-specific homozygous *Cnnm2* KO mice show hypomagnesemia, supporting a possible role of CNNM2 in renal Mg^{2+} handling (222).

However, the exact function of CNNM2 is still unclear. While Mg^{2+} currents could be evoked by overexpression in *Xenopus* oocytes (259), patch clamp and Mg^{2+} imaging experiments in mammalian cells did not demonstrate direct Mg^{2+} transport. Therefore, a regulatory role for CNNM2 in Mg^{2+} sensing was proposed (19, 716). Arjona et al. (19) showed an increased Mg^{2+} uptake upon overexpression of CNNM2, which was abrogated in the CNNM2 disease mutants. The examined mutants failed to reach the plasma membrane (19). In addition, knock-down of *cnnm2* in zebrafish decreased the body Mg^{2+} content, and it could be recovered by expressing the wild-type CNNM2, but not by a disease mutant of CNNM2 (19).

Structurally, CNNM2 contains five putative transmembrane segments and an extracellular COOH terminus, which holds two cystathionine β-synthase (CBS) domains that can form a dimer (716). Initial homology modeling of these CBS domains, based on the CorC protein, showed conservation of a potential Mg^{2+}-ATP binding site that encloses the disease-causing T568I mutation (143). This finding was recently confirmed by the resolved crystal structure that revealed conformational changes of the CBS dimer upon nucleotide binding (132). The CBS domains of CNNM2 indeed bind ATP, but not AMP, in a Mg^{2+}-dependent manner (300). Moreover, the T586I mutation was shown to hinder nucleotide binding and lock the CBS module, thereby rendering the protein in a nonfunctional state (132, 300). This failure may directly impair Mg^{2+} transport across the basolateral membrane, or indirectly by altering the regulation of other basolateral transporters in the DCT. A suggested mechanism of action is an incorrect sensing of the intracellular Mg-ATP levels.

Identification of mutations in *CNNM2* associated with hypomagnesemia shed light on the basolateral Mg^{2+} extrusion mechanism in the DCT. The recently resolved crystal structure will facilitate future studies to clarify the exact function of CNNM2 in DCT-regulated Mg^{2+} transport (132). In addition, CNNM2 should be considered an important factor in brain development, since the neurological phenotype observed in the patients with *CNNM2* mutations could not be attributed to Mg^{2+} status. Of note, genetic variants in *CNNM2* have been associated with schizophrenia in large population studies (269, 656).

IV. OUTLOOK AND PERSPECTIVES

Twenty-five years after the identification of the first gene involved in an inherited kidney tubular disease, NGS, multi-omics technologies, deep-phenotyping of model organisms combined with clinical studies and multicentric efforts to gather patient cohorts and to create registries and biobanks have yielded an unprecedented amount of informations that are directly relevant for our understanding of fundamental processes operating in health and disease. In turn, these insights proved valuable for refining disease ontology, improving diagnosis and follow-up, and providing new therapeutic targets in a number of rare kidney disorders (159).

The rare disorders discussed in this review illustrate the path between clinical description, gene discovery, mechanistic studies, and translational applications. These diseases involve various genetic mechanisms and modes of inheritance; they affect a large variety of cellular processes operating in distinct tubular segments of the kidney; most often, they have multi-systemic complications; they involve channels, transporters, receptors, enzymes, structural proteins, regulatory subunits, and transcription factors, all participating in transcellular and paracellular transport pathways **(TABLE 1, FIGURE 2)**. The genetic and mechanistic insights contributed to better understand the action, or side effects, of known drugs, but also to improve existing therapies or to develop new ones. They thus proved valuable in addressing the ultimate challenge— closing of the gap between genetic and mechanistic understanding and drug development for rare diseases.

These advances have left many open questions, which are currently investigated using increasingly efficient and affordable tools. The advent of NGS and multiplex testing, allowing the simultaneous investigation of all relevant genes for a given phenotype at reduced costs and turnaround times (24), will increase diagnosis efficiency for inherited kidney disorders. In turn, the newly identified cases will precise the genotype-phenotype correlations and the clinical manifestations, sometimes unsuspected or surprising, associated with a given syndrome, yielding new information about the role of the mutant protein in a given tissue (27, 56, 159, 167). The increasing availability of affordable whole exome or even whole genome sequencing should have broad consequences for our understanding of the genetic architecture of kidney disease. The number of unresolved cases should decrease, substantiating the genetic heterogeneity of some disorders (e.g., Dent disease) or clarifying the missing allele in some recessive disorders (e.g., Gitelman syndrome). These new genes, associated with multi-omics profiles (including transcriptomics, epigenomics, metabolomics, proteomics) and improved model organisms based on new genome editing technologies, induced pluripotent stem (iPS) cells, and human kidney organoids (279, 498, 565, 727, 728) or direct reprogramming (367), will drive multilevel analysis of cellular mechanisms and improve the ontology of disease. Another benefit of the sequencing technologies will be the discovery of common and rare genetic variants that could act as modifier genes,

helping to decipher the significant intrafamilial variability observed in many rare disorders, or explain the individual sensitivity to some drugs. These analyses should also substantiate the continuum of genetic kidney disease risk, with important genes involved from rare Mendelian disorders to common variation in the general population (163, 828). Information on the carrier state (for a recessive or *X*-linked disorder) will be important, not only for genetic counseling, but also for clinical implications and, more generally, selection mechanisms and evolutionary perspectives (159, 353, 387, 625).

Important physiological questions linked to the diseases discussed here include mechanisms and regulators of membrane trafficking, maintenance of epithelial cell differentiation, biogenesis of intracellular vesicular compartments, signaling pathways downstream of apical and basolateral receptors and cross-talk between membrane compartments, flow-mediated regulation of apical receptors and transport processes, functional segmentation and capacity of adaptation of specific tubular segments, and mechanisms of transcriptional regulation in tubular cells (160, 194, 544). Downstream of gene and mechanistic pathways, translational studies will have to address issues including the unexplained differences between human and mouse phenotypes (e.g., mouse models for Dent disease, Gitelman syndrome, claudin disorders), variable manifestations of tubular dysfunction in similar disorders (e.g., PT dysfunction and RFS), and the links between tubular dysfunction and the development of CKD.

Finally, the continuum between rare kidney diseases and more common disorders should be substantiated. For instance, some genes involved in the tubular handling of salt (*SLC12A3*, *KCNJ1*, *SLC12A1*, *UMOD*) are also relevant for blood pressure control as shown by analysis of the carrier state (353) or by GWAS for blood pressure in the population (547). Genes encoding the megalin (*LRP2*) and cubilin (*CUBN*) receptors, and the adaptor protein Dab-2 (*DAB2*), that mediate endocytosis of ultrafiltered LMW proteins in the proximal tubule and are defective in rare disorders were shown by GWAS to affect renal function and risk of CKD (74, 450, 553). The genes *SLC2A9* (GLUT9) and *SLC22A12* (URAT1), which are associated with hereditary renal hypouricemia, were also pointed in GWAS on serum urate concentration (395, 405). Genes involved in rare disorders of Ca^{2+} and Mg^{2+} handling (*CASR*, *TRPM6*, *CLDN14*, *CNNM2*) have also been associated with Ca^{2+} and Mg^{2+} homeostasis and metabolic traits in the general population (133, 134, 371, 482, 716). The characterization of the biological mechanisms sustaining the effect of rare and common variants in these genes or in additional genes identified by GWAS will undoubtedly provide further insights into the biological mechanisms sustaining kidney function.

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REFERENCES

1. Abdelhadi O, Iancu D, Stanescu H, Kleta R, Bockenhauer D. EAST syndrome: clinical, pathophysiological, and genetic aspects of mutations in KCNJ10. *Rare Dis* 4: e1195043, 2016. doi:10.1080/21675511.2016.1195043.

2. Abriel H, Loffing J, Rebhun JF, Pratt JH, Schild L, Horisberger JD, Rotin D, Staub O. Defective regulation of the epithelial Na+ channel by Nedd4 in Liddle's syndrome. *J Clin Invest* 103: 667–673, 1999. doi:10.1172/JCI5713.

3. Acuña R, Martínez-de-la-Maza L, Ponce-Coria J, Vázquez N, Ortal-Vite P, Pacheco-Alvarez D, Bobadilla NA, Gamba G. Rare mutations in SLC12A1 and SLC12A3 protect against hypertension by reducing the activity of renal salt cotransporters. *J Hypertens* 29: 475–483, 2011. doi:10.1097/HJH.0b013e328341d0fd.

4. Adachi M, Asakura Y, Sato Y, Tajima T, Nakajima T, Yamamoto T, Fujieda K. Novel SLC12A1 (NKCC2) mutations in two families with Bartter syndrome type 1. *Endocr J* 54: 1003–1007, 2007. doi:10.1507/endocrj.K06-204.

5. Adachi S, Uchida S, Ito H, Hata M, Hiroe M, Marumo F, Sasaki S. Two isoforms of a chloride channel predominantly expressed in thick ascending limb of Henle's loop and collecting ducts of rat kidney. *J Biol Chem* 269: 17677–17683, 1994.

6. Adalat S, Woolf AS, Johnstone KA, Wirsing A, Harries LW, Long DA, Hennekam RC, Ledermann SE, Rees L, van't Hoff W, Marks SD, Trompeter RS, Tullus K, Winyard PJ, Cansick J, Mushtaq I, Dhillon HK, Bingham C, Edghill EL, Shroff R, Stanescu H, Ryffel GU, Ellard S, Bockenhauer D. HNF1B mutations associate with hypomagnesemia and renal magnesium wasting. *J Am Soc Nephrol* 20: 1123–1131, 2009. doi:10.1681/ASN.2008060633.

7. Alexander RT, Cordat E, Chambrey R, Dimke H, Eladari D. Acidosis and Urinary Calcium Excretion: Insights from Genetic Disorders. *J Am Soc Nephrol* 27: 3511–3520, 2016. doi:10.1681/ASN.2016030305.

8. Amin N, Alvi NS, Barth JH, Field HP, Finlay E, Tyerman K, Frazer S, Savill G, Wright NP, Makaya T, Mushtaq T. Pseudohypoaldosteronism type 1: clinical features and management in infancy. *Endocrinol Diabetes Metab Case Rep* 2013: 130010, 2013. doi:10.1530/EDM-13-0010.

9. Amlal H, Legoff C, Vernimmen C, Paillard M, Bichara M. $Na(^{+})$-K^{+}-(NH_4^{+})-$2Cl^{-}$ cotransport in medullary thick ascending limb: control by PKA, PKC, and 20-HETE. *Am J Physiol Cell Physiol* 271: C455–C463, 1996. doi:10.1152/ajpcell.1996.271.2.C455.

11. Anderson TR, Slotkin TA. Maturation of the adrenal medulla–IV. Effects of morphine. *Biochem Pharmacol* 24: 1469–1474, 1975. doi:10.1016/0006-2952(75)90020-9.

12. Ando M, Takeuchi S. Immunological identification of an inward rectifier K^{+} channel (Kir4.1) in the intermediate cell (melanocyte) of the cochlear stria vascularis of gerbils and rats. *Cell Tissue Res* 298: 179–183, 1999. doi:10.1007/s004419900066.

13. Andrianesis V, Glykofridi S, Doupis J. The renal effects of SGLT2 inhibitors and a mini-review of the literature. *Ther Adv Endocrinol Metab* 7: 212–228, 2016. doi:10.1177/2042018816676239.

14. Andrini O, Keck M, Briones R, Lourdel S, Vargas-Poussou R, Teulon J. ClC-K chloride channels: emerging pathophysiology of Bartter syndrome type 3. *Am J Physiol Renal Physiol* 308: F1324–F1334, 2015. doi:10.1152/ajprenal.00004.2015.

15. Anzai N, Endou H. Urate transporters: an evolving field. *Semin Nephrol* 31: 400–409, 2011. doi:10.1016/j.semnephrol.2011.08.003.

16. Anzai N, Ichida K, Jutabha P, Kimura T, Babu E, Jin CJ, Srivastava S, Kitamura K, Hisatome I, Endou H, Sakurai H. Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATv1 (SLC2A9) in humans. *J Biol Chem* 283: 26834–26838, 2008. doi:10.1074/jbc.C800156200.

17. Anzai N, Jutabha P, Amonpatumrat-Takahashi S, Sakurai H. Recent advances in renal urate transport: characterization of candidate transporters indicated by genome-wide association studies. *Clin Exp Nephrol* 16: 89–95, 2012. doi:10.1007/s10157-011-0532-z.

18. Anzai N, Miyazaki H, Noshiro R, Khamdang S, Chairoungdua A, Shin H-J, Enomoto A, Sakamoto S, Hirata T, Tomita K, Kanai Y, Endou H. The multivalent PDZ domain-containing protein PDZK1 regulates transport activity of renal urate-anion exchanger URAT1 via its C terminus. *J Biol Chem* 279: 45942–45950, 2004. doi:10.1074/jbc.M406724200.

19. Arjona FJ, de Baaij JHF, Schlingmann KP, Lameris ALL, van Wijk E, Flik G, Regele S, Korenke GC, Neophytou B, Rust S, Reintjes N, Konrad M, Bindels RJM, Hoenderop JGJ. CNNM2 mutations cause impaired brain development and seizures in patients with hypomagnesemia. *PLoS Genet* 10: e1004267, 2014. doi:10.1371/journal.pgen.1004267.

20. Arteaga ME, Hunziker W, Teo ASM, Hillmer AM, Mutchinick OM. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: variable phenotypic expression in three affected sisters from Mexican ancestry. *Ren Fail* 37: 180–183, 2015. doi:10.3109/0886022X.2014.977141.

21. Arystarkhova E, Liu YB, Salazar C, Stanojevic V, Clifford RJ, Kaplan JH, Kidder GM, Sweadner KJ. Hyperplasia of pancreatic beta cells and improved glucose tolerance in mice deficient in the FXYD2 subunit of Na,K-ATPase. *J Biol Chem* 288: 7077–7085, 2013. doi:10.1074/jbc.M112.401190.

22. Arystarkhova E, Ralph DL, Liu YB, Bouley R, McDonough AA, Sweadner KJ. Paradoxical activation of the sodium chloride cotransporter (NCC) without hypertension in kidney deficient in a regulatory subunit of Na,K-ATPase, FXYD2. *Physiol Rep* 2: e12226, 2014. doi:10.14814/phy2.12226.

23. Arystarkhova E, Wetzel RK, Asinovski NK, Sweadner KJ. The gamma subunit modulates Na(+) and K(+) affinity of the renal Na,K-ATPase. *J Biol Chem* 274: 33183–33185, 1999. doi:10.1074/jbc.274.47.33183.

24. Ashton EJ, Legrand A, Benoit V, Roncelin I, Venisse A, Zennaro M-C, Jeunemaitre X, Iancu D, Van't Hoff WG, Walsh SB, Godefroid N, Rotthier A, Del Favero J, Devuyst O, Schaefer F, Jenkins LA, Kleta R, Dahan K, Vargas-Poussou R, Bockenhauer D. Simultaneous sequencing of 37 genes identified causative mutations in the majority of children with renal tubulopathies. *Kidney Int* 93: 961–967, 2018. doi:10.1016/j.kint.2017.10.016.

25. Attie MF, Gill JR Jr, Stock JL, Spiegel AM, Downs RW Jr, Levine MA, Marx SJ. Urinary calcium excretion in familial hypocalciuric hypercalcemia. Persistence of relative hypocalciuria after induction of hypoparathyroidism. *J Clin Invest* 72: 667–676, 1983. doi:10.1172/JCI111016.

26. Augustin R, Carayannopoulos MO, Dowd LO, Phay JE, Moley JF, Moley KH. Identification and characterization of human glucose transporter-like protein-9 (GLUT9): alternative splicing alters trafficking. *J Biol Chem* 279: 16229–16236, 2004. doi:10.1074/jbc.M312226200.

27. Aymé S, Bockenhauer D, Day S, Devuyst O, Guay-Woodford LM, Ingelfinger JR, Klein JB, Knoers NVAM, Perrone RD, Roberts J, Schaefer F, Torres VE, Cheung M, Wheeler DC, Winkelmayer WC, Angelis A, Antignac C, Bae K, Bergmann C, Bleyer AJ, Bos M, Budde K, Bull K, Chauveau D, Cnaan A, Cornel M, Cosyns E, de la Fosse J, Ding J, Gear S, Goodship THJ, Goodyer P, Gross O, Harr N, Harris PC, Harris T, Höfele J, Hogan MC, Hoorn E, Horie S, Kashtan CE, Kerecuk L, Kleta R, Konrad M, Langman CB, Mariz S, McKerracher G, Nieuwenhoven A, Odland D, Olinger E, Ortiz A, Pei Y, Pirson Y, Rayner BL, Remuzzi G, Renault D, Salomon R, Servais A, Smith RJ, Soliman NA, Stengel B, Storm M, Torra R, van't Hoff W, Vargas-Poussou R, Vroom E, Wanner C, Yap H-K; Conference Participants. Common Elements in Rare Kidney Diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. [Erratum in *Kidney Int* 92: 1558, 2017.] *Kidney Int* 92: 796–808, 2017. doi:10.1016/j.kint.2017.06.018.

28. Ba J, Brown D, Friedman PA. Calcium-sensing receptor regulation of PTH-inhibitable proximal tubule phosphate transport. *Am J Physiol Renal Physiol* 285: F1233–F1243, 2003. doi:10.1152/ajprenal.00249.2003.

29. Bahn A, Hagos Y, Reuter S, Balen D, Brzica H, Krick W, Burckhardt BC, Sabolic I, Burckhardt G. Identification of a new urate and high affinity nicotinate transporter, hOAT10 (SLC22A13). *J Biol Chem* 283: 16332–16341, 2008. doi:10.1074/jbc.M800737200.

30. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications. *Kidney Int* 75: 1272–1277, 2009. doi:10.1038/ki.2009.87.

31. Bankir L, Bichet DG, Morgenthaler NG. Vasopressin: physiology, assessment and osmosensation. *J Intern Med* 282: 284–297, 2017. doi:10.1111/joim.12645.

32. Barker DF, Hostikka SL, Zhou J, Chow LT, Oliphant AR, Gerken SC, Gregory MC, Skolnick MH, Atkin CL, Tryggvason K. Identification of mutations in the COL4A5 collagen gene in Alport syndrome. *Science* 248: 1224–1227, 1990. doi:10.1126/science.2349482.

33. Barker PA, Salehi A. The MAGE proteins: emerging roles in cell cycle progression, apoptosis, and neurogenetic disease. *J Neurosci Res* 67: 705–712, 2002. doi:10.1002/jnr.10160.

34. Barker PM, Nguyen MS, Gatzy JT, Grubb B, Norman H, Hummler E, Rossier B, Boucher RC, Koller B. Role of gammaENaC subunit in lung liquid clearance and electrolyte balance in newborn mice. Insights into perinatal adaptation and pseudohypoaldosteronism. *J Clin Invest* 102: 1634–1640, 1998. doi:10.1172/JCI3971.

35. Baron J, Winer KK, Yanovski JA, Cunningham AW, Laue L, Zimmerman D, Cutler GB Jr. Mutations in the Ca(2+)-sensing receptor gene cause autosomal dominant and sporadic hypoparathyroidism. *Hum Mol Genet* 5: 601–606, 1996. doi:10.1093/hmg/5.5.601.

36. Bartter FC, Pronove P, Gill JR Jr, MacCardle RC. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. A new syndrome. *Am J Med* 33: 811–828, 1962. doi:10.1016/0002-9343(62)90214-0.

37. Becker-Cohen R, Rinat C, Ben-Shalom E, Feinstein S, Ivgi H, Frishberg Y. Vitamin A deficiency associated with urinary retinol binding protein wasting in Dent's disease. *Pediatr Nephrol* 27: 1097–1102, 2012. doi:10.1007/s00467-012-2121-0.

38. Belge H, Gailly P, Schwaller B, Loffing J, Debaix H, Riveira-Munoz E, Beauwens R, Devogelaer J-P, Hoenderop JG, Bindels RJ, Devuyst O. Renal expression of parvalbumin is critical for NaCl handling and response to diuretics. *Proc Natl Acad Sci USA* 104: 14849–14854, 2007. doi:10.1073/pnas.0702810104.

39. Bell GI, Fong NM, Stempien MM, Wormsted MA, Caput D, Ku LL, Urdea MS, Rall LB, Sanchez-Pescador R. Human epidermal growth factor precursor: cDNA sequence, expression in vitro and gene organization. *Nucleic Acids Res* 14: 8427–8446, 1986. doi:10.1093/nar/14.21.8427.

40. Belot A, Ranchin B, Fichtner C, Pujo L, Rossier BC, Liutkus A, Morlat C, Nicolino M, Zennaro MC, Cochat P. Pseudohypoaldosteronisms, report on a 10-patient series. *Nephrol Dial Transplant* 23: 1636–1641, 2008. doi:10.1093/ndt/gfm862.

41. Berger S, Bleich M, Schmid W, Cole TJ, Peters J, Watanabe H, Kriz W, Warth R, Greger R, Schütz G. Mineralocorticoid receptor knockout mice: pathophysiology of Na^+ metabolism. *Proc Natl Acad Sci USA* 95: 9424–9429, 1998. doi:10.1073/pnas.95.16.9424.

42. Bertog M, Cuffe JE, Pradervand S, Hummler E, Hartner A, Porst M, Hilgers KF, Rossier BC, Korbmacher C. Aldosterone responsiveness of the epithelial sodium channel (ENaC) in colon is increased in a mouse model for Liddle's syndrome. *J Physiol* 586: 459–475, 2008. doi:10.1113/jphysiol.2007.140459.

43. Besouw MTP, Bienias M, Walsh P, Kleta R, Van't Hoff WG, Ashton E, Jenkins L, Bockenhauer D. Clinical and molecular aspects of distal renal tubular acidosis in children. [Erratum in *Pediatr Nephrol* 32: 1095, 2017.] *Pediatr Nephrol* 32: 987–996, 2017. doi:10.1007/s00467-016-3573-4.

44. Bettinelli A, Bianchetti MG, Girardin E, Caringella A, Cecconi M, Appiani AC, Pavanello L, Gastaldi R, Isimbaldi C, Lama G, Marchesoni C, Matteucci C, Patriarca P, Natale BD, Setzu C, Vitucci P. Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. *J Pediatr* 120: 38–43, 1992. doi:10.1016/S0022-3476(05)80594-3.

45. Bettinelli A, Borsa N, Bellantuono R, Syrèn ML, Calabrese R, Edefonti A, Komninos J, Santostefano M, Beccaria L, Pela I, Bianchetti MG, Tedeschi S. Patients with biallelic mutations in the chloride channel gene CLCNKB: long-term management and outcome. *Am J Kidney Dis* 49: 91–98, 2007. doi:10.1053/j.ajkd.2006.10.001.

46. Bettinelli A, Ciarmatori S, Cesareo L, Tedeschi S, Ruffa G, Appiani AC, Rosini A, Grumieri G, Mercuri B, Sacco M, Leozappa G, Binda S, Cecconi M, Navone C, Curcio C, Syren ML, Casari G. Phenotypic variability in Bartter syndrome type I. *Pediatr Nephrol* 14: 940–945, 2000. doi:10.1007/PL00013418.

47. Bettinelli A, Tosetto C, Colussi G, Tommasini G, Edefonti A, Bianchetti MG. Electrocardiogram with prolonged QT interval in Gitelman disease. *Kidney Int* 62: 580–584, 2002. doi:10.1046/j.1523-1755.2002.00467.x.

48. Béguin P, Crambert G, Guennoun S, Garty H, Horisberger JD, Geering K. CHIF, a member of the FXYD protein family, is a regulator of Na,K-ATPase distinct from the gamma-subunit. *EMBO J* 20: 3993–4002, 2001. doi:10.1093/emboj/20.15.3993.

49. Béguin P, Wang X, Firsov D, Puoti A, Claeys D, Horisberger JD, Geering K. The gamma subunit is a specific component of the Na,K-ATPase and modulates its transport function. *EMBO J* 16: 4250–4260, 1997. doi:10.1093/emboj/16.14.4250.

50. Bhalla V, Daidié D, Li H, Pao AC, LaGrange LP, Wang J, Vandewalle A, Stockand JD, Staub O, Pearce D. Serum- and glucocorticoid-regulated kinase 1 regulates ubiquitin ligase neural precursor cell-expressed, developmentally down-regulated protein 4-2 by inducing interaction with 14-3-3. *Mol Endocrinol* 19: 3073–3084, 2005. doi:10.1210/me.2005-0193.

51. Bibee KP, Augustin R, Gazit V, Moley KH. The apical sorting signal for human GLUT9b resides in the N-terminus. *Mol Cell Biochem* 376: 163–173, 2013. doi:10.1007/s11010-013-1564-3.

52. Biber J, Hernando N, Forster I. Phosphate transporters and their function. *Annu Rev Physiol* 75: 535–550, 2013. doi:10.1146/annurev-physiol-030212-183748.

53. Biemesderfer D, Pizzonia J, Abu-Alfa A, Exner M, Reilly R, Igarashi P, Aronson PS. NHE3: a Na^+/H^+ exchanger isoform of renal brush border. *Am J Physiol Renal Fluid Electrolyte Physiol* 265: F736–F742, 1993. doi:10.1152/ajprenal.1993.265.5.F736.

54. Bingham C, Ellard S, Nicholls AJ, Pennock CA, Allen J, James AJ, Satchell SC, Salzmann MB, Hattersley AT. The generalized aminoaciduria seen in patients with hepatocyte nuclear factor-1alpha mutations is a feature of all patients with diabetes and is associated with glucosuria. *Diabetes* 50: 2047–2052, 2001. doi:10.2337/diabetes.50.9.2047.

55. Birkenhäger R, Otto E, Schürmann MJ, Vollmer M, Ruf EM, Maier-Lutz I, Beekmann F, Fekete A, Omran H, Feldmann D, Milford DV, Jeck N, Konrad M, Landau D, Knoers NV, Antignac C, Sudbrak R, Kispert A, Hildebrandt F. Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. *Nat Genet* 29: 310–314, 2001. doi:10.1038/ng752.

56. Blanchard A, Bockenhauer D, Bolignano D, Calò LA, Cosyns E, Devuyst O, Ellison DH, Karet Frankl FE, Knoers NVAM, Konrad M, Lin S-H, Vargas-Poussou R. Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 91: 24–33, 2017. doi:10.1016/j.kint.2016.09.046.

57. Blanchard A, Curis E, Guyon-Roger T, Kahila D, Treard C, Baudouin V, Bérard E, Champion G, Cochat P, Dubourg J, de la Faille R, Devuyst O, Deschenes G, Fischbach M, Harambat J, Houillier P, Karras A, Knebelmann B, Lavocat MP, Loirat C, Merieau E, Niaudet P, Nobili F, Novo R, Salomon R, Ulinski T, Jeunemaître X, Vargas-Poussou R. Observations of a large Dent disease cohort. *Kidney Int* 90: 430–439, 2016. doi:10.1016/j.kint.2016.04.022.

58. Blanchard A, Vargas-Poussou R, Vallet M, Caumont-Prim A, Allard J, Desport E, Dubourg L, Monge M, Bergerot D, Baron S, Essig M, Bridoux F, Tack I, Azizi M. Indomethacin, amiloride, or eplerenone for treating hypokalemia in Gitelman syndrome. *J Am Soc Nephrol* 26: 468–475, 2015. doi:10.1681/ASN.2014030293.

59. Blau JE, Collins MT. The PTH-Vitamin D-FGF23 axis. *Rev Endocr Metab Disord* 16: 165–174, 2015. doi:10.1007/s11154-015-9318-z.

60. Bobulescu IA, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. *Adv Chronic Kidney Dis* 19: 358–371, 2012. doi:10.1053/j.ackd.2012.07.009.

61. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nat Rev Nephrol* 11: 576–588, 2015. doi:10.1038/nrneph.2015.89.

62. Bockenhauer D, Feather S, Stanescu HC, Bandulik S, Zdebik AA, Reichold M, Tobin J, Lieberer E, Sterner C, Landoure G, Arora R, Sirimanna T, Thompson D, Cross JH, van't Hoff W, Al Masri O, Tullus K, Yeung S, Anikster Y, Klootwijk E, Hubank M, Dillon MJ, Heitzmann D, Arcos-Burgos M, Knepper MA, Dobbie A, Gahl WA, Warth R, Sheridan E, Kleta R. Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. *N Engl J Med* 360: 1960–1970, 2009. doi:10.1056/NEJMoa0810276.

63. Boettger T, Hübner CA, Maier H, Rust MB, Beck FX, Jentsch TJ. Deafness and renal tubular acidosis in mice lacking the K-Cl co-transporter Kcc4. *Nature* 416: 874–878, 2002. doi:10.1038/416874a.

64. Bomsztyk K, Calalb MB. Bicarbonate absorption stimulates active calcium absorption in the rat proximal tubule. *J Clin Invest* 81: 1455–1461, 1988. doi:10.1172/JCI113476.

65. Bongers EMHF, Shelton LM, Milatz S, Verkaart S, Bech AP, Schoots J, Cornelissen EAM, Bleich M, Hoenderop JGJ, Wetzels JFM, Lugtenberg D, Nijenhuis T. A Novel Hypokalemic-Alkalotic Salt-Losing Tubulopathy in Patients with *CLDN10* Mutations. *J Am Soc Nephrol* 28: 3118–3128, 2017. doi:10.1681/ASN.2016080881.

66. Bonventre JV. Dedifferentiation and proliferation of surviving epithelial cells in acute renal failure. *J Am Soc Nephrol* 14, Suppl 1: 55S–61S, 2003. doi:10.1097/01.ASN.0000067652.51441.21.

67. Boscardin E, Perrier R, Sergi C, Maillard M, Loffing J, Loffing-Cueni D, Koesters R, Rossier BC, Hummler E. Severe hyperkalemia is rescued by low-potassium diet in renal βENaC-deficient mice. *Pflugers Arch* 469: 1387–1399, 2017. doi:10.1007/s00424-017-1990-2.

68. Boscardin E, Perrier R, Sergi C, Maillard MP, Loffing J, Loffing-Cueni D, Koesters R, Rossier BC, Hummler E. Plasma Potassium Determines NCC Abundance in Adult Kidney-Specific γENaC Knockout. *J Am Soc Nephrol* 29: 977–990, 2018. doi:10.1681/ASN.2017030345.

69. Bosson D, Kuhnle U, Mees N, Ramet J, Vamos E, Vertongen F, Wolter R, Armanini D. Generalized unresponsiveness to mineralocorticoid hormones: familial recessive pseudohypoaldosteronism due to aldosterone-receptor deficiency. *Acta Endocrinol Suppl (Copenh)* 279, 4_Suppl: S376–S380, 1986. doi:10.1530/acta.0.112S376.

70. Botero-Velez M, Curtis JJ, Warnock DG. Brief report: Liddle's syndrome revisited--a disorder of sodium reabsorption in the distal tubule. *N Engl J Med* 330: 178–181, 1994. doi:10.1056/NEJM199401203300305.

71. Bourcier T, Blain P, Massin P, Grünfeld JP, Gaudric A. Sclerochoroidal calcification associated with Gitelman syndrome. *Am J Ophthalmol* 128: 767–768, 1999. doi:10.1016/S0002-9394(99)00277-9.

72. Boute N, Gribouval O, Roselli S, Benessy F, Lee H, Fuchshuber A, Dahan K, Gubler MC, Niaudet P, Antignac C. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. *Nat Genet* 24: 349–354, 2000. doi:10.1038/74166.

73. Boyden LM, Choi M, Choate KA, Nelson-Williams CJ, Farhi A, Toka HR, Tikhonova IR, Bjornson R, Mane SM, Colussi G, Lebel M, Gordon RD, Semmekrot BA, Poujol A, Välimäki MJ, De Ferrari ME, Sanjad SA, Gutkin M, Karet FE, Tucci JR, Stockigt JR, Keppler-Noreuil KM, Porter CC, Anand SK, Whiteford ML, Davis ID, Dewar SB, Bettinelli A, Fadrowski JJ, Belsha CW, Hunley TE, Nelson RD, Trachtman H, Cole TRP, Pinsk M, Bockenhauer D, Shenoy M, Vaidyanathan P, Foreman JW, Rasoulpour M, Thameem F, Al-Shahrouri HZ, Radhakrishnan J, Gharavi AG, Goilav B, Lifton RP. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature* 482: 98–102, 2012. doi:10.1038/nature10814.

74. Böger CA, Chen M-H, Tin A, Olden M, Köttgen A, de Boer IH, Fuchsberger C, O'Seaghdha CM, Pattaro C, Teumer A, Liu C-T, Glazer NL, Li M, O'Connell JR, Tanaka T, Peralta CA, Kutalik Z, Luan J, Zhao JH, Hwang S-J, Akylbekova E, Kramer H, van der Harst P, Smith AV, Lohman K, de Andrade M, Hayward C, Kollerits B, Tönjes A, Aspelund T, Ingelsson E, Eiriksdottir G, Launer LJ, Harris TB, Shuldiner AR, Mitchell BD, Arking DE, Franceschini N, Boerwinkle E, Egan J, Hernandez D, Reilly M, Townsend RR, Lumley T, Siscovick DS, Psaty BM, Kestenbaum B, Haritunians T, Bergmann S, Vollenweider P, Waeber G, Mooser V, Waterworth D, Johnson AD, Florez JC, Meigs JB, Lu X, Turner ST, Atkinson EJ, Leak TS, Aasarød K, Skorpen F, Syvänen A-C, Illig T, Baumert J, Koenig W, Krämer BK, Devuyst O, Mychaleckyj JC, Minelli C, Bakker SJL, Kedenko L, Paulweber B, Coassin S, Endlich K, Kroemer HK, Biffar R, Stracke S, Völzke H, Stumvoll M, Mägi R, Campbell H, Vitart V, Hastie ND, Gudnason V, Kardia SLR, Liu Y, Polašek O, Curhan G, Kronenberg F, Prokopenko I, Rudan I, Arnlöv J, Hallan S, Navis G, Parsa A, Ferrucci L, Coresh J, Shlipak MG, Bull SB, Paterson NJ, Wichmann H-E, Wareham NJ, Loos RJF, Rotter JI, Pramstaller PP, Cupples LA, Beckmann JS, Yang Q, Heid IM, Rettig R, Dreisbach AW, Bochud M, Fox CS, Kao WHL; CKDGen Consortium. CUBN is a gene locus for albuminuria. *J Am Soc Nephrol* 22: 555–570, 2011. doi:10.1681/ASN.2010060598.

75. Böger CA, Heid IM. Chronic kidney disease: novel insights from genome-wide association studies. *Kidney Blood Press Res* 34: 225–234, 2011. doi:10.1159/000326901.

76. Bökenkamp A, Böckenhauer D, Cheong HI, Hoppe B, Tasic V, Unwin R, Ludwig M. Dent-2 disease: a mild variant of Lowe syndrome. *J Pediatr* 155: 94–99, 2009. doi:10.1016/j.jpeds.2009.01.049.

77. Bökenkamp A, Ludwig M. Disorders of the renal proximal tubule. *Nephron Physiol* 118: 1–6, 2011. doi:10.1159/000320880.

78. Breiderhoff T, Himmerkus N, Drewell H, Plain A, Günzel D, Mutig K, Willnow TE, Müller D, Bleich M. Deletion of claudin-10 rescues claudin-16-deficient mice from hypomagnesemia and hypercalciuria. *Kidney Int* 93: 580–588, 2018. doi:10.1016/j.kint.2017.08.029.

79. Breiderhoff T, Himmerkus N, Stuiver M, Mutig K, Will C, Meij IC, Bachmann S, Bleich M, Willnow TE, Müller D. Deletion of claudin-10 (Cldn10) in the thick ascending limb impairs paracellular sodium permeability and leads to hypermagnesemia and nephrocalcinosis. [Correction in *Proc Natl Acad Sci USA* 109: 15072, 2012.] *Proc Natl Acad Sci USA* 109: 14241–14246, 2012. doi:10.1073/pnas.1203834109.

80. Brochard K, Boyer O, Blanchard A, Loirat C, Niaudet P, Macher M-A, Deschenes G, Bensman A, Decramer S, Cochat P, Morin D, Broux F, Caillez M, Guyot C, Novo R, Jeunemaître X, Vargas-Poussou R. Phenotype-genotype correlation in antenatal and neonatal variants of Bartter syndrome. *Nephrol Dial Transplant* 24: 1455–1464, 2009. doi:10.1093/ndt/gfn689.

81. Brodin-Sartorius A, Tête M-J, Niaudet P, Antignac C, Guest G, Ottolenghi C, Charbit M, Moyse D, Legendre C, Lesavre P, Cochat P, Servais A. Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. *Kidney Int* 81: 179–189, 2012. doi:10.1038/ki.2011.277.

82. Brown EM, Gamba G, Riccardi D, Lombardi M, Butters R, Kifor O, Sun A, Hediger MA, Lytton J, Hebert SC. Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. *Nature* 366: 575–580, 1993. doi:10.1038/366575a0.

83. Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. *Physiol Rev* 81: 239–297, 2001. doi:10.1152/physrev.2001.81.1.239.

84. Browne DL, Gancher ST, Nutt JG, Brunt ER, Smith EA, Kramer P, Litt M. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. *Nat Genet* 8: 136–140, 1994. doi:10.1038/ng1094-136.

85. Brunetti O, Imbrici P, Botti FM, Pettorossi VE, D'Adamo MC, Valentino M, Zammit C, Mora M, Gibertini S, Di Giovanni G, Muscat R, Pessia M. Kv1.1 knock-in ataxic mice exhibit spontaneous myokymic activity exacerbated by fatigue, ischemia and low temperature. *Neurobiol Dis* 47: 310–321, 2012. doi:10.1016/j.nbd.2012.05.002.

86. Cairo ER, Friedrich T, Swarts HGP, Knoers NV, Bindels RJM, Monnens LA, Willems PHGM, De Pont JJHHM, Koenderink JB. Impaired routing of wild type FXYD2 after oligomerisation with FXYD2-G41R might explain the dominant nature of renal hypomagnesemia. *Biochim Biophys Acta* 1778: 398–404, 2008. doi:10.1016/j.bbamem.2007.10.009.

87. Calado J, Loeffler J, Sakallioglu O, Gok F, Lhotta K, Barata J, Rueff J. Familial renal glucosuria: SLC5A2 mutation analysis and evidence of salt-wasting. *Kidney Int* 69: 852–855, 2006. doi:10.1038/sj.ki.5000194.

88. Calado J, Santer R, Rueff J. Effect of kidney disease on glucose handling (including genetic defects). *Kidney Int Suppl* 79: S7–S13, 2011. doi:10.1038/ki.2010.510.

89. Calado J, Soto K, Clemente C, Correia P, Rueff J. Novel compound heterozygous mutations in SLC5A2 are responsible for autosomal recessive renal glucosuria. *Hum Genet* 114: 314–316, 2004. doi:10.1007/s00439-003-1054-x.

90. Calado J, Sznajer Y, Metzger D, Rita A, Hogan MC, Kattamis A, Scharf M, Tasic V, Greil J, Brinkert F, Kemper MJ, Santer R. Twenty-one additional cases of familial renal glucosuria: absence of genetic heterogeneity, high prevalence of private mutations and further evidence of volume depletion. *Nephrol Dial Transplant* 23: 3874–3879, 2008. doi:10.1093/ndt/gfn386.

91. Canessa CM, Schild L, Buell G, Thorens B, Gautschi I, Horisberger JD, Rossier BC. Amiloride-sensitive epithelial Na+ channel is made of three homologous subunits. *Nature* 367: 463–467, 1994. doi:10.1038/367463a0.

92. Cao G, Lee KP, van der Wijst J, de Graaf M, van der Kemp A, Bindels RJM, Hoenderop JGJ. Methionine sulfoxide reductase B1 (MsrB1) recovers TRPM6 channel activity during oxidative stress. *J Biol Chem* 285: 26081–26087, 2010. doi:10.1074/jbc.M110.103655.

93. Cao G, Thébault S, van der Wijst J, van der Kemp A, Lasonder E, Bindels RJ, Hoenderop JG. RACK1 inhibits TRPM6 activity via phosphorylation of the fused alpha-kinase domain. *Curr Biol* 18: 168–176, 2008. doi:10.1016/j.cub.2007.12.058.

94. Cao G, van der Wijst J, van der Kemp A, van Zeeland F, Bindels RJ, Hoenderop JG. Regulation of the epithelial Mg^{2+} channel TRPM6 by estrogen and the associated repressor protein of estrogen receptor activity (REA). *J Biol Chem* 284: 14788–14795, 2009. doi:10.1074/jbc.M808752200.

95. Capasso G, Geibel PJ, Damiano S, Jaeger P, Richards WG, Geibel JP. The calcium sensing receptor modulates fluid reabsorption and acid secretion in the proximal tubule. *Kidney Int* 84: 277–284, 2013. doi:10.1038/ki.2013.137.

96. Carling T, Udelsman R. Parathyroid surgery in familial hyperparathyroid disorders. *J Intern Med* 257: 27–37, 2005. doi:10.1111/j.1365-2796.2004.01428.x.

97. Carrisoza-Gaytán R, Salvador C, Diaz-Bello B, Escobar LI. Differential expression of the Kv1 voltage-gated potassium channel family in the rat nephron. *J Mol Histol* 45: 583–597, 2014. doi:10.1007/s10735-014-9581-4.

98. Castañeda-Bueno M, Cervantes-Pérez LG, Vázquez N, Uribe N, Kantesaria S, Morla L, Bobadilla NA, Doucet A, Alessi DR, Gamba G. Activation of the renal Na+:Cl- cotransporter by angiotensin II is a WNK4-dependent process. *Proc Natl Acad Sci USA* 109: 7929–7934, 2012. doi:10.1073/pnas.1200947109.

99. Caulfield MJ, Munroe PB, O'Neill D, Witkowska K, Charchar FJ, Doblado M, Evans S, Eyheramendy S, Onipinla A, Howard P, Shaw-Hawkins S, Dobson RJ, Wallace C, Newhouse SJ, Brown M, Connell JM, Dominiczak A, Farrall M, Lathrop GM, Samani NJ, Kumari M, Marmot M, Brunner E, Chambers J, Elliott P, Kooner J, Laan M, Org E, Veldre G, Viigimaa M, Cappuccio FP, Ji C, Iacone R, Strazzullo P, Moley KH, Cheeseman C. SLC2A9 is a high-capacity urate transporter in humans. *PLoS Med* 5: e197, 2008. doi:10.1371/journal.pmed.0050197.

100. Cha S-K, Huang C, Ding Y, Qi X, Huang C-L, Miller RT. Calcium-sensing receptor decreases cell surface expression of the inwardly rectifying K^+ channel Kir4.1. *J Biol Chem* 286: 1828–1835, 2011. doi:10.1074/jbc.M110.160390.

101. Challa A, Papaefstathiou I, Lapatsanis D, Tsolas O. Primary idiopathic hypomagnesemia in two female siblings. *Acta Paediatr* 84: 1075–1078, 1995. doi:10.1111/j.1651-2227.1995.tb13830.x.

102. Chambers JC, Zhang W, Lord GM, van der Harst P, Lawlor DA, Sehmi JS, Gale DP, Wass MN, Ahmadi KR, Bakker SJL, Beckmann J, Bilo HJG, Bochud M, Brown MJ, Caulfield MJ, Connell JMC, Cook HT, Cotlarciuc I, Davey Smith G, de Silva R, Deng G, Devuyst O, Dikkeschei LD, Dimkovic N, Dockrell M, Dominiczak A, Ebrahim S, Eggermann T, Farrall M, Ferrucci L, Floege J, Forouhi NG, Gansevoort RT, Han X, Hedblad B, Homan van der Heide JJ, Hepkema BG, Hernandez-Fuentes M, Hypponen E, Johnson T, de Jong PE, Kleefstra N, Lagou V, Lapsley M, Li Y, Loos RJF, Luan J, Luttropp K, Maréchal C, Melander O, Munroe PB, Nordfors L, Parsa A, Peltonen L, Penninx BW, Perucha E, Pouta A, Prokopenko I, Roderick PJ, Ruokonen A, Samani NJ, Sanna S, Schalling M, Schlessinger D, Schlieper G, Seelen MAJ, Shuldiner AR, Sjögren M, Smit JH, Snieder H, Soranzo N, Spector TD, Stenvinkel P, Sternberg MJE, Swaminathan R, Tanaka T, Ubink-Veltmaat LJ, Uda M, Vollenweider P, Wallace C, Waterworth D, Zerres K, Waeber G, Wareham NJ, Maxwell PH, McCarthy MI, Jarvelin M-R, Mooser V, Abecasis GR, Lightstone L, Scott J, Navis G, Elliott P, Kooner JS. Genetic loci influencing kidney function and chronic kidney disease. *Nat Genet* 42: 373–375, 2010. doi:10.1038/ng.566.

103. Chang SS, Grunder S, Hanukoglu A, Rösler A, Mathew PM, Hanukoglu I, Schild L, Lu Y, Shimkets RA, Nelson-Williams C, Rossier BC, Lifton RP. Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. *Nat Genet* 12: 248–253, 1996. doi:10.1038/ng0396-248.

104. Chang W, Tu C, Chen T-H, Bikle D, Shoback D. The extracellular calcium-sensing receptor (CaSR) is a critical modulator of skeletal development. *Sci Signal* 1: ra1, 2008. doi:10.1126/scisignal.1159945.

105. Chasis H, Jolliffe N, Smith HW. The action of phlorizin on the excretion of glucose, xylose, sucrose, creatinine and urea by man. *J Clin Invest* 12: 1083–1090, 1933. doi:10.1172/JCI100559.

106. Chen C-J, Tseng C-C, Yen J-H, Chang J-G, Chou W-C, Chu H-W, Chang S-J, Liao W-T. ABCG2 contributes to the development of gout and hyperuricemia in a genome-wide association study. *Sci Rep* 8: 3137, 2018. doi:10.1038/s41598-018-21425-7.

107. Chen LH, Leung PS. Inhibition of the sodium glucose co-transporter-2: its beneficial action and potential combination therapy for type 2 diabetes mellitus. *Diabetes Obes Metab* 15: 392–402, 2013. doi:10.1111/dom.12064.

108. Chen SY, Bhargava A, Mastroberardino L, Meijer OC, Wang J, Buse P, Firestone GL, Verrey F, Pearce D. Epithelial sodium channel regulated by aldosterone-induced protein sgk. *Proc Natl Acad Sci USA* 96: 2514–2519, 1999. doi:10.1073/pnas.96.5.2514.

109. Cheong HI, Kang JH, Lee JH, Ha IS, Kim S, Komoda F, Sekine T, Igarashi T, Choi Y. Mutational analysis of idiopathic renal hypouricemia in Korea. *Pediatr Nephrol* 20: 886–890, 2005. doi:10.1007/s00467-005-1863-3.

110. Cherqui S, Courtoy PJ. The renal Fanconi syndrome in cystinosis: pathogenic insights and therapeutic perspectives. *Nat Rev Nephrol* 13: 115–131, 2017. doi:10.1038/nrneph.2016.182.

111. Cherqui S, Kalatzis V, Trugnan G, Antignac C. The targeting of cystinosin to the lysosomal membrane requires a tyrosine-based signal and a novel sorting motif. *J Biol Chem* 276: 13314–13321, 2001. doi:10.1074/jbc.M010562200.

112. Chiga M, Rafiqi FH, Alessi DR, Sohara E, Ohta A, Rai T, Sasaki S, Uchida S. Phenotypes of pseudohypoaldosteronism type II caused by the WNK4 D561A missense mutation are dependent on the WNK-OSR1/SPAK kinase cascade. *J Cell Sci* 124: 1391–1395, 2011. doi:10.1242/jcs.084111.

113. Chin E, Zhou J, Bondy C. Anatomical and developmental patterns of facilitative glucose transporter gene expression in the rat kidney. *J Clin Invest* 91: 1810–1815, 1993. doi:10.1172/JCI116392.

114. Choate KA, Kahle KT, Wilson FH, Nelson-Williams C, Lifton RP. WNK1, a kinase mutated in inherited hypertension with hyperkalemia, localizes to diverse Cl^--transporting epithelia. *Proc Natl Acad Sci USA* 100: 663–668, 2003. doi:10.1073/pnas.242728499.

115. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am J Med* 120: 442–447, 2007. doi:10.1016/j.amjmed.2006.06.040.

116. Chong JX, Buckingham KJ, Jhangiani SN, Boehm C, Sobreira N, Smith JD, Harrell TM, McMillin MJ, Wiszniewski W, Gambin T, Coban Akdemir ZH, Doheny K, Scott AF, Avramopoulos D, Chakravarti A, Hoover-Fong J, Mathews D, Witmer PD, Ling H, Hetrick K, Watkins L, Patterson KE, Reinier F, Blue E, Muzny D, Kircher M, Bilguvar K, López-Giráldez F, Sutton VR, Tabor HK, Leal SM, Gunel M, Mane S, Gibbs RA, Boerwinkle E, Hamosh A, Shendure J, Lupski JR, Lifton RP, Valle D, Nickerson DA, Bamshad MJ; Centers for Mendelian Genomics. The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities. *Am J Hum Genet* 97: 199–215, 2015. doi:10.1016/j.ajhg.2015.06.009.

117. Christ A, Herzog K, Willnow TE. LRP2, an auxiliary receptor that controls sonic hedgehog signaling in development and disease. *Dev Dyn* 245: 569–579, 2016. doi:10.1002/dvdy.24394.

118. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. *Physiol Rev* 96: 365–408, 2016. doi:10.1152/physrev.00014.2015.

119. Christensen BM, Perrier R, Wang Q, Zuber AM, Maillard M, Mordasini D, Malsure S, Ronzaud C, Stehle J-C, Rossier BC, Hummler E. Sodium and potassium balance depends on αENaC expression in connecting tubule. *J Am Soc Nephrol* 21: 1942–1951, 2010. doi:10.1681/ASN.2009101077.

120. Christensen EI, Birn H. Megalin and cubilin: multifunctional endocytic receptors. *Nat Rev Mol Cell Biol* 3: 258–266, 2002. doi:10.1038/nrm778.

121. Christensen EI, Devuyst O, Dom G, Nielsen R, Van der Smissen P, Verroust P, Leruth M, Guggino WB, Courtoy PJ. Loss of chloride channel ClC-5 impairs endocytosis by defective trafficking of megalin and cubilin in kidney proximal tubules. *Proc Natl Acad Sci USA* 100: 8472–8477, 2003. doi:10.1073/pnas.1432873100.

122. Chubanov V, Ferioli S, Wisnowsky A, Simmons DG, Leitzinger C, Einer C, Jonas W, Shymkiv Y, Bartsch H, Braun A, Akdogan B, Mittermeier L, Sytik L, Torben F, Jurinovic V, van der Vorst EP, Weber C, Yildirim ÖA, Sotlar K, Schürmann A, Zierler S, Zischka H, Ryazanov AG, Gudermann T. Epithelial magnesium transport by TRPM6 is essential for prenatal development and adult survival. *eLife* 5: e20914, 2016. doi:10.7554/eLife.20914.

123. Ciampolillo F, McCoy DE, Green RB, Karlson KH, Dagenais A, Molday RS, Stanton BA. Cell-specific expression of amiloride-sensitive, Na^+-conducting ion channels in the kidney. *Am J Physiol Cell Physiol* 271: C1303–C1315, 1996. doi:10.1152/ajpcell.1996.271.4.C1303.

124. Citron BA, Kaufman S, Milstien S, Naylor EW, Greene CL, Davis MD. Mutation in the 4a-carbinolamine dehydratase gene leads to mild hyperphenylalaninemia with defective cofactor metabolism. *Am J Hum Genet* 53: 768–774, 1993.

125. Clapham DE, Runnels LW, Strübing C. The TRP ion channel family. *Nat Rev Neurosci* 2: 387–396, 2001. doi:10.1038/35077544.

126. Clark WF, Devuyst O, Roussel R. The vasopressin system: new insights for patients with kidney diseases: Epidemiological evidence and therapeutic perspectives. *J Intern Med* 282: 310–321, 2017. doi:10.1111/joim.12654.

127. Claverie-Martin F, Trujillo-Suarez J, Gonzalez-Acosta H, Aparicio C, Justa Roldan ML, Stiburkova B, Ichida K, Martín-Gomez MA, Herrero Goñi M, Carrasco Hidalgo-Barquero M, Iñigo V, Enriquez R, Cordoba-Lanus E, Garcia-Nieto VM; RenalTube Group. URAT1 and GLUT9 mutations in Spanish patients with renal hypouricemia. *Clin Chim Acta* 481: 83–89, 2018. doi:10.1016/j.cca.2018.02.030.

128. Coady MJ, El Tarazi A, Santer R, Bissonnette P, Sasseville LJ, Calado J, Lussier Y, Dumayne C, Bichet DG, Lapointe J-Y. MAP17 Is a Necessary Activator of Renal Na^+/Glucose Cotransporter SGLT2. *J Am Soc Nephrol* 28: 85–93, 2017. doi:10.1681/ASN.2015111282.

129. Coffinier C, Barra J, Babinet C, Yaniv M. Expression of the vHNF1/HNF1beta homeoprotein gene during mouse organogenesis. *Mech Dev* 89: 211–213, 1999. doi:10.1016/S0925-4773(99)00221-X.

130. Colussi G, Rombolà G, De Ferrari ME, Macaluso M, Minetti L. Correction of hypokalemia with antialdosterone therapy in Gitelman's syndrome. *Am J Nephrol* 14: 127–135, 1994. doi:10.1159/000168701.

131. Cope G, Murthy M, Golbang AP, Hamad A, Liu C-H, Cuthbert AW, O'Shaughnessy KM. WNK1 affects surface expression of the ROMK potassium channel independent of WNK4. *J Am Soc Nephrol* 17: 1867–1874, 2006. doi:10.1681/ASN.2005111224.

132. Corral-Rodríguez MÁ, Stuiver M, Abascal-Palacios G, Diercks T, Oyenarte I, Ereño-Orbea J, de Opakua AI, Blanco FJ, Encinar JA, Spiwok V, Terashima H, Accardi A, Müller D, Martínez-Cruz LA. Nucleotide binding triggers a conformational change of the CBS module of the magnesium transporter CNNM2 from a twisted towards a flat structure. *Biochem J* 464: 23–34, 2014. doi:10.1042/BJ20140409.

133. Corre T, Arjona FJ, Hayward C, Youhanna S, de Baaij JHF, Belge H, Nägele N, Debaix H, Blanchard MG, Traglia M, Harris SE, Ulivi S, Rueedi R, Lamparter D, Macé A, Sala C, Lenarduzzi S, Ponte B, Pruijm M, Ackermann D, Ehret G, Baptista D, Polašek O, Rudan I, Hurd TW, Hastie ND, Vitart V, Waeber G, Kutalik Z, Bergmann S, Vargas-Poussou R, Konrad M, Gasparini P, Deary IJ, Starr JM, Toniolo D, Vollenweider P, Hoenderop JGJ, Bindels RJM, Bochud M, Devuyst O. Genome-Wide Meta-Analysis Unravels Interactions Between Magnesium Homeostasis and Metabolic Phenotypes. *J Am Soc Nephrol* 29: 335–348, 2018. doi:10.1681/ASN.2017030267.

134. Corre T, Olinger E, Harris SE, Traglia M, Ulivi S, Lenarduzzi S, Belge H, Youhanna S, Tokonami N, Bonny O, Houillier P, Polašek O, Deary IJ, Starr JM, Toniolo D, Gasparini P, Vollenweider P, Hayward C, Bochud M, Devuyst O. Common variants in CLDN14 are associated with differential excretion of magnesium over calcium in urine. *Pflugers Arch* 469: 91–103, 2017. doi:10.1007/s00424-016-1913-7.

135. Costanzo LS. Comparison of calcium and sodium transport in early and late rat distal tubules: effect of amiloride. *Am J Physiol Renal Fluid Electrolyte Physiol* 246: F937–F945, 1984. doi:10.1152/ajprenal.1984.246.6.F937.

136. Coudroy G, Gburek J, Kozyraki R, Madsen M, Trugnan G, Moestrup SK, Verroust PJ, Maurice M. Contribution of cubilin and amnionless to processing and membrane targeting of cubilin-amnionless complex. *J Am Soc Nephrol* 16: 2330–2337, 2005. doi:10.1681/ASN.2004110925.

137. Couette B, Jalaguier S, Hellal-Levy C, Lupo B, Fagart J, Auzou G, Rafestin-Oblin ME. Folding requirements of the ligand-binding domain of the human mineralocorticoid receptor. *Mol Endocrinol* 12: 855–863, 1998. doi:10.1210/mend.12.6.0119.

138. Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB; Yale Gitelman's and Bartter's Syndrome Collaborative Study Group. Gitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. *Kidney Int* 59: 710–717, 2001. doi:10.1046/j.1523-1755.2001.059002710.x.

139. Cuevas CA, Su X-T, Wang M-X, Terker AS, Lin D-H, McCormick JA, Yang C-L, Ellison DH, Wang W-H. Potassium Sensing by Renal Distal Tubules Requires Kir4.1. *J Am Soc Nephrol* 28: 1814–1825, 2017. doi:10.1681/ASN.2016090935.

140. Dai LJ, Ritchie G, Kerstan D, Kang HS, Cole DE, Quamme GA. Magnesium transport in the renal distal convoluted tubule. *Physiol Rev* 81: 51–84, 2001. doi:10.1152/physrev.2001.81.1.51.

141. Davies M, Adams PH, Lumb GA, Berry JL, Loveridge N. Familial hypocalciuric hypercalcaemia: evidence for continued enhanced renal tubular reabsorption of calcium following total parathyroidectomy. *Acta Endocrinol (Copenh)* 106: 499–504, 1984. doi:10.1530/acta.0.1060499.

142. De Baaij JHF, Dorresteijn EM, Hennekam EAM, Kamsteeg E-J, Meijer R, Dahan K, Muller M, van den Dorpel MA, Bindels RJM, Hoenderop JGJ, Devuyst O, Knoers NVAM. Recurrent FXYD2 p.Gly41Arg mutation in patients with isolated dominant hypomagnesaemia. *Nephrol Dial Transplant* 30: 952–957, 2015. doi:10.1093/ndt/gfv014.

143. De Baaij JHF, Stuiver M, Meij IC, Lainez S, Kopplin K, Venselaar H, Müller D, Bindels RJM, Hoenderop JGJ. Membrane topology and intracellular processing of cyclin M2 (CNNM2). *J Biol Chem* 287: 13644–13655, 2012. doi:10.1074/jbc.M112.342204.

144. De Jong JC, Van Der Vliet WA, Van Den Heuvel LPWJ, Willems PHGM, Knoers NVAM, Bindels RJM. Functional expression of mutations in the human NaCl cotransporter: evidence for impaired routing mechanisms in Gitelman's syndrome. *J Am Soc Nephrol* 13: 1442–1448, 2002. doi:10.1097/01.ASN.0000017904.77985.03.

145. De Jong JC, Willems PHGM, Mooren FJM, van den Heuvel LPWJ, Knoers NVAM, Bindels RJM. The structural unit of the thiazide-sensitive NaCl cotransporter is a homodimer. *J Biol Chem* 278: 24302–24307, 2003. doi:10.1074/jbc.M303101200.

146. De Leo MG, Staiano L, Vicinanza M, Luciani A, Carissimo A, Mutarelli M, Di Campli A, Polishchuk E, Di Tullio G, Morra V, Levtchenko E, Oltrabella F, Starborg T, Santoro M, Di Bernardo D, Devuyst O, Lowe M, Medina DL, Ballabio A, De Matteis MA. Autophagosome-lysosome fusion triggers a lysosomal response mediated by TLR9 and controlled by OCRL. *Nat Cell Biol* 18: 839–850, 2016. doi:10.1038/ncb3386.

147. De Marchi S, Cecchin E, Basile A, Proto G, Donadon W, Schinella D, Lengo A, De Paoli P, Jus A, Villalta D, . Is renal glycosuria a benign condition? *Proc Eur Dial Transplant Assoc* 20: 681–685, 1983.

148. De Matteis MA, Staiano L, Emma F, Devuyst O. The 5-phosphatase OCRL in Lowe syndrome and Dent disease 2. *Nat Rev Nephrol* 13: 455–470, 2017. doi:10.1038/nrneph.2017.83.

149. De Paoli P, Battistin S, Jus A, Reitano M, Villalta D, De Marchi S, Cecchin E, Basile A, Santini G. Immunological characterization of renal glycosuria patients. *Clin Exp Immunol* 56: 289–294, 1984.

150. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. *Nat Rev Nephrol* 13: 11–26, 2017. doi:10.1038/nrneph.2016.170.

151. Dehghan A, Köttgen A, Yang Q, Hwang S-J, Kao WL, Rivadeneira F, Boerwinkle E, Levy D, Hofman A, Astor BC, Benjamin EJ, van Duijn CM, Witteman JC, Coresh J, Fox CS. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. *Lancet* 372: 1953–1961, 2008. doi:10.1016/S0140-6736(08)61343-4.

152. Dekkers CCJ, Gansevoort RT, Heerspink HJL. New Diabetes Therapies and Diabetic Kidney Disease Progression: the Role of SGLT-2 Inhibitors. *Curr Diab Rep* 18: 27, 2018. doi:10.1007/s11892-018-0992-6.

153. Delaloy C, Elvira-Matelot E, Clemessy M, Zhou X-O, Imbert-Teboul M, Houot A-M, Jeunemaitre X, Hadchouel J. Deletion of WNK1 first intron results in misregulation of both isoforms in renal and extrarenal tissues. *Hypertension* 52: 1149–1154, 2008. doi:10.1161/HYPERTENSIONAHA.108.120899.

154. Delaloy C, Lu J, Houot A-M, Disse-Nicodeme S, Gasc J-M, Corvol P, Jeunemaitre X. Multiple promoters in the WNK1 gene: one controls expression of a kidney-specific kinase-defective isoform. *Mol Cell Biol* 23: 9208–9221, 2003. doi:10.1128/MCB.23.24.9208-9221.2003.

155. Demeuse P, Penner R, Fleig A. TRPM7 channel is regulated by magnesium nucleotides via its kinase domain. *J Gen Physiol* 127: 421–434, 2006. doi:10.1085/jgp.200509410.

156. Dent CE, Friedman M. Hypercalcuric rickets associated with renal tubular damage. *Arch Dis Child* 39: 240–249, 1964. doi:10.1136/adc.39.205.240.

157. Deschênes G, Burguet A, Guyot C, Hubert P, Garabédian M, Dechaux M, Loirat C, Broyer M. [Antenatal form of Bartter's syndrome]. *Ann Pediatr (Paris)* 40: 95–101, 1993.

158. Devuyst O, Christie PT, Courtoy PJ, Beauwens R, Thakker RV. Intra-renal and subcellular distribution of the human chloride channel, CLC-5, reveals a pathophysiological basis for Dent's disease. *Hum Mol Genet* 8: 247–257, 1999. doi:10.1093/hmg/8.2.247.

159. Devuyst O, Knoers NVAM, Remuzzi G, Schaefer F; Board of the Working Group for Inherited Kidney Diseases of the European Renal Association and European Dialysis and Transplant Association. Rare inherited kidney diseases: challenges, opportunities, and perspectives. *Lancet* 383: 1844–1859, 2014. doi:10.1016/S0140-6736(14)60659-0.

160. Devuyst O, Luciani A. Chloride transporters and receptor-mediated endocytosis in the renal proximal tubule. *J Physiol* 593: 4151–4164, 2015. doi:10.1113/JP270087.

161. Devuyst O, Meij I, Jeunemaitre X, Ronco P, Antignac C, Christensen EI, Knoers NV, Levtchenko EN, Deen PM, Müller D, Wagner CA, Rampoldi L, van't Hoff WG; EUNEFRON Consortium. EUNEFRON, the European Network for the Study of Orphan Nephropathies. *Nephrol Dial Transplant* 24: 2011–2015, 2009. doi:10.1093/ndt/gfp095.

162. Devuyst O, Olinger E, Rampoldi L. Uromodulin: from physiology to rare and complex kidney disorders. *Nat Rev Nephrol* 13: 525–544, 2017. doi:10.1038/nrneph.2017.101.

163. Devuyst O, Pattaro C. The *UMOD* Locus: Insights into the Pathogenesis and Prognosis of Kidney Disease. *J Am Soc Nephrol* 29: 713–726, 2018. doi:10.1681/ASN.2017070716.

164. Devuyst O, Pirson Y. Genetics of hypercalciuric stone forming diseases. *Kidney Int* 72: 1065–1072, 2007. doi:10.1038/sj.ki.5002441.

165. Devuyst O, Thakker RV. Dent's disease. *Orphanet J Rare Dis* 5: 28, 2010. doi:10.1186/1750-1172-5-28.

166. Devuyst O. Salt wasting and blood pressure. *Nat Genet* 40: 495–496, 2008. doi:10.1038/ng0508-495.

167. Devuyst O. Genetics of kidney diseases in 2017: unveiling the genetic architecture of kidney disease. *Nat Rev Nephrol* 14: 80–82, 2018. doi:10.1038/nrneph.2017.177.

168. Di Stefano A, Wittner M, Nitschke R, Braitsch R, Greger R, Bailly C, Amiel C, Roinel N, de Rouffignac C. Effects of parathyroid hormone and calcitonin on Na^+, Cl^-, K^+, Mg^{2+} and Ca^{2+} transport in cortical and medullary thick ascending limbs of mouse kidney. *Pflugers Arch* 417: 161–167, 1990. doi:10.1007/BF00370694.

169. Diamond HS, Paolino JS. Evidence for a postsecretory reabsorptive site for uric acid in man. *J Clin Invest* 52: 1491–1499, 1973. doi:10.1172/JCI107323.

170. Diepens RJW, den Dekker E, Bens M, Weidema AF, Vandewalle A, Bindels RJM, Hoenderop JGJ. Characterization of a murine renal distal convoluted tubule cell line for the study of transcellular calcium transport. *Am J Physiol Renal Physiol* 286: F483–F489, 2004. doi:10.1152/ajprenal.00231.2003.

171. Dinour D, Bahn A, Ganon L, Ron R, Geifman-Holtzman O, Knecht A, Gafter U, Rachamimnov R, Sela B-A, Burckhardt G, Holtzman EJ. URAT1 mutations cause renal hypouricemia type 1 in Iraqi Jews. *Nephrol Dial Transplant* 26: 2175–2181, 2011. doi:10.1093/ndt/gfq722.

172. Dinour D, Gray NK, Campbell S, Shu X, Sawyer L, Richardson W, Rechavi G, Amariglio N, Ganon L, Sela B-A, Bahat H, Goldman M, Weissgarten J, Millar MR, Wright AF, Holtzman EJ. Homozygous SLC2A9 mutations cause severe renal hypouricemia. *J Am Soc Nephrol* 21: 64–72, 2010. doi:10.1681/ASN.2009040406.

173. Dinour D, Gray NK, Ganon L, Knox AJS, Shalev H, Sela B-A, Campbell S, Sawyer L, Shu X, Valsamidou E, Landau D, Wright AF, Holtzman EJ. Two novel homozygous SLC2A9 mutations cause renal hypouricemia type 2. *Nephrol Dial Transplant* 27: 1035–1041, 2012. doi:10.1093/ndt/gfr419.

174. Dirks JH. The kidney and magnesium regulation. *Kidney Int* 23: 771–777, 1983. doi:10.1038/ki.1983.93.

175. Dirlewanger M, Huser D, Zennaro M-C, Girardin E, Schild L, Schwitzgebel VM. A homozygous missense mutation in SCNN1A is responsible for a transient neonatal form of pseudohypoaldosteronism type 1. *Am J Physiol Endocrinol Metab* 301: E467–E473, 2011. doi:10.1152/ajpendo.00066.2011.

176. Disse-Nicodème S, Achard JM, Desitter I, Houot AM, Fournier A, Corvol P, Jeunemaitre X. A new locus on chromosome 12p13.3 for pseudohypoaldosteronism type II, an autosomal dominant form of hypertension. *Am J Hum Genet* 67: 302–310, 2000. doi:10.1086/303020.

177. Disse-Nicodème S, Desitter I, Fiquet-Kempf B, Houot AM, Stern N, Delahousse M, Potier J, Ader JL, Jeunemaitre X. Genetic heterogeneity of familial hyperkalaemic hypertension. *J Hypertens* 19: 1957–1964, 2001. doi:10.1097/00004872-200111000-00005.

178. Dizin E, Hasler U, Nlandu-Khodo S, Fila M, Roth I, Ernandez T, Doucet A, Martin P-Y, Feraille E, de Seigneux S. Albuminuria induces a proinflammatory and profibrotic response in cortical collecting ducts via the 24p3 receptor. *Am J Physiol Renal Physiol* 305: F1053–F1063, 2013. doi:10.1152/ajprenal.00006.2013.

179. Dong Z, Zhou J, Xu X, Jiang S, Li Y, Zhao D, Yang C, Ma Y, Wang Y, He H, Ji H, Zhang J, Yuan Z, Yang Y, Wang X, Pang Y, Jin L, Zou H, Wang J. Genetic variants in two pathways influence serum urate levels and gout risk: a systematic pathway analysis. *Sci Rep* 8: 3848, 2018. doi:10.1038/s41598-018-21858-0.

180. Doucet A, Katz AI, Morel F. Determination of Na-K-ATPase activity in single segments of the mammalian nephron. *Am J Physiol Renal Fluid Electrolyte Physiol* 237: F105–F113, 1979. doi:10.1152/ajprenal.1979.237.2.F105.

181. Doyle LA, Yang W, Abruzzo LV, Krogmann T, Gao Y, Rishi AK, Ross DD. A multidrug resistance transporter from human MCF-7 breast cancer cells. *Proc Natl Acad Sci USA* 95: 15665–15670, 1998. doi:10.1073/pnas.95.26.15665.

182. Döring A, Gieger C, Mehta D, Gohlke H, Prokisch H, Coassin S, Fischer G, Henke K, Klopp N, Kronenberg F, Paulweber B, Pfeufer A, Rosskopf D, Völzke H, Illig T, Meitinger T, Wichmann H-E, Meisinger C. SLC2A9 influences uric acid concentrations with pronounced sex-specific effects. *Nat Genet* 40: 430–436, 2008. doi:10.1038/ng.107.

183. Dutzler R, Campbell EB, Cadene M, Chait BT, MacKinnon R. X-ray structure of a ClC chloride channel at 3.0 A reveals the molecular basis of anion selectivity. *Nature* 415: 287–294, 2002. doi:10.1038/415287a.

184. Eckardt K-U, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, Levin A. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet* 382: 158–169, 2013. doi:10.1016/S0140-6736(13)60439-0.

185. Edelheit O, Hanukoglu I, Shriki Y, Tfilin M, Dascal N, Gillis D, Hanukoglu A. Truncated beta epithelial sodium channel (ENaC) subunits responsible for multi-system pseudohypoaldosteronism support partial activity of ENaC. *J Steroid Biochem Mol Biol* 119: 84–88, 2010. doi:10.1016/j.jsbmb.2010.01.002.

185a. El Karoui K, Viau A, Dellis O, Bagattin A, Nguyen C, Baron W, Burtin M, Broueilh M, Heidet L, Mollet G, Druilhe A, Antignac C, Knebelmann B, Friedlander G, Bienaimé F, Gallazzini M, Terzi F. Endoplasmic reticulum stress drives proteinuria-induced kidney lesions via Lipocalin 2. *Nat Commun* 7: 10330, 2016. doi:10.1038/ncomms10330.

186. Elin RJ. Magnesium: the fifth but forgotten electrolyte. *Am J Clin Pathol* 102: 616–622, 1994. doi:10.1093/ajcp/102.5.616.

187. Ellison DH, Velázquez H, Wright FS. Thiazide-sensitive sodium chloride cotransport in early distal tubule. *Am J Physiol Renal Fluid Electrolyte Physiol* 253: F546–F554, 1987. doi:10.1152/ajprenal.1987.253.3.F546.

188. Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E. Cystinosis: a review. *Orphanet J Rare Dis* 11: 47, 2016. doi:10.1186/s13023-016-0426-y.

189. Emma F, Montini G, Parikh SM, Salviati L. Mitochondrial dysfunction in inherited renal disease and acute kidney injury. *Nat Rev Nephrol* 12: 267–280, 2016. doi:10.1038/nrneph.2015.214.

190. Enomoto A, Endou H. Roles of organic anion transporters (OATs) and a urate transporter (URAT1) in the pathophysiology of human disease. *Clin Exp Nephrol* 9: 195–205, 2005. doi:10.1007/s10157-005-0368-5.

191. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, Hosoyamada M, Takeda M, Sekine T, Igarashi T, Matsuo H, Kikuchi Y, Oda T, Ichida K, Hosoya T, Shimokata K, Niwa T, Kanai Y, Endou H. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature* 417: 447–452, 2002. doi:10.1038/nature742.

192. Eraly SA, Vallon V, Rieg T, Gangoiti JA, Wikoff WR, Siuzdak G, Barshop BA, Nigam SK. Multiple organic anion transporters contribute to net renal excretion of uric acid. *Physiol Genomics* 33: 180–192, 2008. doi:10.1152/physiolgenomics.00207.2007.

193. Erdmann KS, Mao Y, McCrea HJ, Zoncu R, Lee S, Paradise S, Modregger J, Biemesderfer D, Toomre D, De Camilli P. A role of the Lowe syndrome protein OCRL in early steps of the endocytic pathway. *Dev Cell* 13: 377–390, 2007. doi:10.1016/j.devcel.2007.08.004.

194. Eshbach ML, Weisz OA. Receptor-Mediated Endocytosis in the Proximal Tubule. *Annu Rev Physiol* 79: 425–448, 2017. doi:10.1146/annurev-physiol-022516-034234.

195. Estévez R, Boettger T, Stein V, Birkenhäger R, Otto E, Hildebrandt F, Jentsch TJ. Barttin is a Cl^- channel beta-subunit crucial for renal Cl^- reabsorption and inner ear K^+ secretion. *Nature* 414: 558–561, 2001. doi:10.1038/35107099.

196. Faguer S, Decramer S, Chassaing N, Bellanné-Chantelot C, Calvas P, Beaufils S, Bessenay L, Lengelé J-P, Dahan K, Ronco P, Devuyst O, Chauveau D. Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. *Kidney Int* 80: 768–776, 2011. doi:10.1038/ki.2011.225.

197. Fanconi G.. Die nicht diabetischen Glykosurien und Hyperglykaemien des aelteren Kindes. *Jahrbuch fuer Kinderheilkunde* 133: 257–300, 1931.

198. Faulhaber-Walter R, Chen L, Oppermann M, Kim SM, Huang Y, Hiramatsu N, Mizel D, Kajiyama H, Zerfas P, Briggs JP, Kopp JB, Schnermann J. Lack of A1 adenosine receptors augments diabetic hyperfiltration and glomerular injury. *J Am Soc Nephrol* 19: 722–730, 2008. doi:10.1681/ASN.2007060721.

199. Faundez V, Hartzell HC. Intracellular chloride channels: determinants of function in the endosomal pathway. *Sci STKE* 2004: re8, 2004. doi:10.1126/stke.2332004re8.

200. Feig DI, Kang D-H, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 359: 1811–1821, 2008. doi:10.1056/NEJMra0800885.

201. Feng L, Campbell EB, Hsiung Y, MacKinnon R. Structure of a eukaryotic CLC transporter defines an intermediate state in the transport cycle. *Science* 330: 635–641, 2010. doi:10.1126/science.1195230.

202. Fernandes-Rosa FL, Hubert E-L, Fagart J, Tchitchek N, Gomes D, Jouanno E, Benecke A, Rafestin-Oblin M-E, Jeunemaitre X, Antonini SR, Zennaro M-C. Mineralocorticoid

receptor mutations differentially affect individual gene expression profiles in pseudohypoaldosteronism type 1. *J Clin Endocrinol Metab* 96: E519–E527, 2011. doi:10.1210/jc.2010-1486.

203. Fernández-Llama P, Ecelbarger CA, Ware JA, Andrews P, Lee AJ, Turner R, Nielsen S, Knepper MA. Cyclooxygenase inhibitors increase Na-K-2Cl cotransporter abundance in thick ascending limb of Henle's loop. *Am J Physiol Renal Physiol* 277: F219–F226, 1999. doi:10.1152/ajprenal.1999.277.2.F219.

204. Ferrannini E. Sodium-Glucose Co-transporters and Their Inhibition: Clinical Physiology. *Cell Metab* 26: 27–38, 2017. doi:10.1016/j.cmet.2017.04.011.

205. Ferrè S, de Baaij JHF, Ferreira P, Germann R, de Klerk JBC, Lavrijsen M, van Zeeland F, Venselaar H, Kluijtmans LAJ, Hoenderop JGJ, Bindels RJM. Mutations in PCBD1 cause hypomagnesemia and renal magnesium wasting. *J Am Soc Nephrol* 25: 574–586, 2014. doi:10.1681/ASN.2013040337.

206. Ferrè S, Veenstra GJC, Bouwmeester R, Hoenderop JGJ, Bindels RJM. HNF-1B specifically regulates the transcription of the γa-subunit of the Na^+/K^+-ATPase. *Biochem Biophys Res Commun* 404: 284–290, 2011. doi:10.1016/j.bbrc.2010.11.108.

207. Festa BP, Chen Z, Berquez M, Debaix H, Tokonami N, Prange JA, Hoek GV, Alessio C, Raimondi A, Nevo N, Giles RH, Devuyst O, Luciani A. Impaired autophagy bridges lysosomal storage disease and epithelial dysfunction in the kidney. *Nat Commun* 9: 161, 2018. doi:10.1038/s41467-017-02536-7.

208. Ficner R, Sauer UH, Stier G, Suck D. Three-dimensional structure of the bifunctional protein PCD/DCoH, a cytoplasmic enzyme interacting with transcription factor HNF1. *EMBO J* 14: 2034–2042, 1995. doi:10.1002/j.1460-2075.1995.tb07195.x.

209. Finegold DN, Armitage MM, Galiani M, Matise TC, Pandian MR, Perry YM, Deka R, Ferrell RE. Preliminary localization of a gene for autosomal dominant hypoparathyroidism to chromosome 3q13. *Pediatr Res* 36: 414–417, 1994. doi:10.1203/00006450-199409000-00024.

210. Finer G, Shalev H, Birk OS, Galron D, Jeck N, Sinai-Treiman L, Landau D. Transient neonatal hyperkalemia in the antenatal (ROMK defective) Bartter syndrome. *J Pediatr* 142: 318–323, 2003. doi:10.1067/mpd.2003.100.

211. Firsov D, Schild L, Gautschi I, Mérillat AM, Schneeberger E, Rossier BC. Cell surface expression of the epithelial Na channel and a mutant causing Liddle syndrome: a quantitative approach. *Proc Natl Acad Sci USA* 93: 15370–15375, 1996. doi:10.1073/pnas.93.26.15370.

212. Flatman PW. Magnesium transport across cell membranes. *J Membr Biol* 80: 1–14, 1984. doi:10.1007/BF01868686.

213. Foglia PEG, Bettinelli A, Tosetto C, Cortesi C, Crosazzo L, Edefonti A, Bianchetti MG. Cardiac work up in primary renal hypokalaemia-hypomagnesaemia (Gitelman syndrome). *Nephrol Dial Transplant* 19: 1398–1402, 2004. doi:10.1093/ndt/gfh204.

214. Foley TP Jr, Harrison HC, Arnaud CD, Harrison HE. Familial benign hypercalcemia. *J Pediatr* 81: 1060–1067, 1972. doi:10.1016/S0022-3476(72)80232-4.

215. Fougeray S, Pallet N. Mechanisms and biological functions of autophagy in diseased and ageing kidneys. *Nat Rev Nephrol* 11: 34–45, 2015. doi:10.1038/nrneph.2014.201.

216. Francis J, Zhang J, Farhi A, Carey H, Geller DS. A novel SGLT2 mutation in a patient with autosomal recessive renal glucosuria. *Nephrol Dial Transplant* 19: 2893–2895, 2004. doi:10.1093/ndt/gfh426.

217. Freitag JJ, Martin KJ, Conrades MB, Bellorin-Font E, Teitelbaum S, Klahr S, Slatopolsky E. Evidence for skeletal resistance to parathyroid hormone in magnesium deficiency. Studies in isolated perfused bone. *J Clin Invest* 64: 1238–1244, 1979. doi:10.1172/JCI109578.

218. Freudenthal B, Kulaveerasingam D, Lingappa L, Shah MA, Brueton L, Wassmer E, Ognjanovic M, Dorison N, Reichold M, Bockenhauer D, Kleta R, Zdebik AA. KCNJ10 mutations disrupt function in patients with EAST syndrome. *Nephron, Physiol* 119: 40–48, 2011. doi:10.1159/000330250.

219. Frindt G, Palmer LG. Apical potassium channels in the rat connecting tubule. *Am J Physiol Renal Physiol* 287: F1030–F1037, 2004. doi:10.1152/ajprenal.00169.2004.

220. Frishberg Y, Dinour D, Belostotsky R, Becker-Cohen R, Rinat C, Feinstein S, Navon-Elkan P, Ben-Shalom E. Dent's disease manifesting as focal glomerulosclerosis: Is it the tip of the iceberg? *Pediatr Nephrol* 24: 2369–2373, 2009. doi:10.1007/s00467-009-1299-2.

221. Fuller CM, Awayda MS, Arrate MP, Bradford AL, Morris RG, Canessa CM, Rossier BC, Benos DJ. Cloning of a bovine renal epithelial Na^+ channel subunit. *Am J Physiol Cell Physiol* 269: C641–C654, 1995. doi:10.1152/ajpcell.1995.269.3.C641.

222. Funato Y, Yamazaki D, Miki H. Renal function of cyclin M2 Mg^{2+} transporter maintains blood pressure. *J Hypertens* 35: 585–592, 2017. doi:10.1097/HJH.0000000000001211.

223. Furuse M, Sasaki H, Tsukita S. Manner of interaction of heterogeneous claudin species within and between tight junction strands. *J Cell Biol* 147: 891–903, 1999. doi:10.1083/jcb.147.4.891.

224. Fyfe JC, Madsen M, Højrup P, Christensen EI, Tanner SM, de la Chapelle A, He Q, Moestrup SK. The functional cobalamin (vitamin B12)-intrinsic factor receptor is a novel complex of cubilin and amnionless. *Blood* 103: 1573–1579, 2004. doi:10.1182/blood-2003-08-2852.

225. Gabriel SS, Belge H, Gassama A, Debaix H, Luciani A, Fehr T, Devuyst O. Bone marrow transplantation improves proximal tubule dysfunction in a mouse model of Dent disease. *Kidney Int* 91: 842–855, 2017. doi:10.1016/j.kint.2016.11.016.

226. Gabrikova D, Bernasovska J, Sokolova J, Stiburkova B. High frequency of SLC22A12 variants causing renal hypouricemia 1 in the Czech and Slovak Roma population; simple and rapid detection method by allele-specific polymerase chain reaction. *Urolithiasis* 43: 441–445, 2015. doi:10.1007/s00240-015-0790-4.

227. Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med* 347: 111–121, 2002. doi:10.1056/NEJMra020552.

228. Gaide Chevronnay HP, Janssens V, Van Der Smissen P, N'Kuli F, Nevo N, Guiot Y, Levtchenko E, Marbaix E, Pierreux CE, Cherqui S, Antignac C, Courtoy PJ. Time course of pathogenic and adaptation mechanisms in cystinotic mouse kidneys. *J Am Soc Nephrol* 25: 1256–1269, 2014. doi:10.1681/ASN.2013060598.

229. Gailly P, Jouret F, Martin D, Debaix H, Parreira KS, Nishita T, Blanchard A, Antignac C, Willnow TE, Courtoy PJ, Scheinman SJ, Christensen EI, Devuyst O. A novel renal carbonic anhydrase type III plays a role in proximal tubule dysfunction. *Kidney Int* 74: 52–61, 2008. doi:10.1038/sj.ki.5002794.

230. Gamba G, Miyanoshita A, Lombardi M, Lytton J, Lee WS, Hediger MA, Hebert SC. Molecular cloning, primary structure, and characterization of two members of the mammalian electroneutral sodium-(potassium)-chloride cotransporter family expressed in kidney. *J Biol Chem* 269: 17713–17722, 1994.

231. Gamba G, Saltzberg SN, Lombardi M, Miyanoshita A, Lytton J, Hediger MA, Brenner BM, Hebert SC. Primary structure and functional expression of a cDNA encoding the thiazide-sensitive, electroneutral sodium-chloride cotransporter. *Proc Natl Acad Sci USA* 90: 2749–2753, 1993. doi:10.1073/pnas.90.7.2749.

232. Gannon AW, Monk HM, Levine MA. Cinacalcet monotherapy in neonatal severe hyperparathyroidism: a case study and review. *J Clin Endocrinol Metab* 99: 7–11, 2014. doi:10.1210/jc.2013-2834.

233. Garrett JE, Capuano IV, Hammerland LG, Hung BC, Brown EM, Hebert SC, Nemeth EF, Fuller F. Molecular cloning and functional expression of human parathyroid calcium receptor cDNAs. *J Biol Chem* 270: 12919–12925, 1995. doi:10.1074/jbc.270.21.12919.

234. Garty H, Palmer LG. Epithelial sodium channels: function, structure, and regulation. *Physiol Rev* 77: 359–396, 1997. doi:10.1152/physrev.1997.77.2.359.

235. Gaudelus J, Dandine M, Nathanson M, Perelman R, Hassan M. Rib case deformity in neonatal hyperparathyroidism. *Am J Dis Child* 137: 408–409, 1983.

236. Geller DS, Rodriguez-Soriano J, Boado AV, Schifter S, Bayer M, Chang SS, Lifton RP. Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism type I. *Nat Genet* 19: 279–281, 1998. doi:10.1038/966.

237. Geller DS, Zhang J, Zennaro M-C, Vallo-Boado A, Rodriguez-Soriano J, Furu L, Haws R, Metzger D, Botelho B, Karaviti L, Haqq AM, Corey H, Janssens S, Corvol P, Lifton RP. Autosomal dominant pseudohypoaldosteronism type 1: mechanisms, evidence for neonatal lethality, and phenotypic expression in adults. *J Am Soc Nephrol* 17: 1429–1436, 2006. doi:10.1681/ASN.2005111188.

238. Gesualdo L, Di Paolo S, Calabró A, Milani S, Maiorano E, Ranieri E, Pannarale G, Schena FP. Expression of epidermal growth factor and its receptor in normal and diseased human kidney: an immunohistochemical and in situ hybridization study. *Kidney Int* 49: 656–665, 1996. doi:10.1038/ki.1996.94.

239. Geven WB, Monnens LA, Willems HL, Buijs WC, ter Haar BG. Renal magnesium wasting in two families with autosomal dominant inheritance. *Kidney Int* 31: 1140–1144, 1987. doi:10.1038/ki.1987.120.

240. Geven WB, Monnens LA, Willems JL, Buijs W, Hamel CJ. Isolated autosomal recessive renal magnesium loss in two sisters. *Clin Genet* 32: 398–402, 1987. doi:10.1111/j.1399-0004.1987.tb03157.x.

241. Gewin LS. Renal fibrosis: primacy of the proximal tubule. *Matrix Biol* 68-69: 248–262, 2018. doi:10.1016/j.matbio.2018.02.006.

242. Gilbert RE. Sodium-glucose linked transporter-2 inhibitors: potential for renoprotection beyond blood glucose lowering? *Kidney Int* 86: 693–700, 2014. doi:10.1038/ki.2013.451.

243. Gillen CM, Brill S, Payne JA, Forbush B III. Molecular cloning and functional expression of the K-Cl cotransporter from rabbit, rat, and human. A new member of the cation-chloride cotransporter family. *J Biol Chem* 271: 16237–16244, 1996. doi:10.1074/jbc.271.27.16237.

244. Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. *Trans Assoc Am Physicians* 79: 221–235, 1966.

245. Glaudemans B, van der Wijst J, Scola RH, Lorenzoni PJ, Heister A, van der Kemp AW, Knoers NV, Hoenderop JG, Bindels RJ. A missense mutation in the Kv1.1 voltage-gated potassium channel-encoding gene KCNA1 is linked to human autosomal dominant hypomagnesemia. *J Clin Invest* 119: 936–942, 2009. doi:10.1172/JCI36948.

246. Glaudemans B, Yntema HG, San-Cristobal P, Schoots J, Pfundt R, Kamsteeg E-J, Bindels RJ, Knoers NVAM, Hoenderop JG, Hoefsloot LH. Novel NCC mutants and functional analysis in a new cohort of patients with Gitelman syndrome. *Eur J Hum Genet* 20: 263–270, 2012. doi:10.1038/ejhg.2011.189.

247. Godefroid N, Riveira-Munoz E, Saint-Martin C, Nassogne M-C, Dahan K, Devuyst O. A novel splicing mutation in SLC12A3 associated with Gitelman syndrome and idiopathic intracranial hypertension. *Am J Kidney Dis* 48: e73–e79, 2006. doi:10.1053/j.ajkd.2006.08.005.

248. Gong Y, Himmerkus N, Plain A, Bleich M, Hou J. Epigenetic regulation of microRNAs controlling CLDN14 expression as a mechanism for renal calcium handling. *J Am Soc Nephrol* 26: 663–676, 2015. doi:10.1681/ASN.2014020129.

249. Gong Y, Hou J. Claudin-14 underlies Ca^{++}-sensing receptor-mediated Ca^{++} metabolism via NFAT-microRNA-based mechanisms. *J Am Soc Nephrol* 25: 745–760, 2014. doi:10.1681/ASN.2013050553.

250. Gong Y, Hou J. Claudins in barrier and transport function-the kidney. *Pflugers Arch* 469: 105–113, 2017. doi:10.1007/s00424-016-1906-6.

251. Gong Y, Renigunta V, Himmerkus N, Zhang J, Renigunta A, Bleich M, Hou J. Claudin-14 regulates renal Ca^{++} transport in response to CaSR signalling via a novel microRNA pathway. *EMBO J* 31: 1999–2012, 2012. doi:10.1038/emboj.2012.49.

252. Gonzalez-Vicente A, Saez F, Monzon CM, Asirwatham J, Garvin JL. Thick Ascending Limb Sodium Transport in the Pathogenesis of Hypertension. *Physiol Rev* 99: 235–309, 2019. doi:10.1152/physrev.00055.2017.

253. Gopal E, Fei Y-J, Sugawara M, Miyauchi S, Zhuang L, Martin P, Smith SB, Prasad PD, Ganapathy V. Expression of slc5a8 in kidney and its role in Na(+)-coupled transport of lactate. *J Biol Chem* 279: 44522–44532, 2004. doi:10.1074/jbc.M405365200.

254. Gopal E, Umapathy NS, Martin PM, Ananth S, Gnana-Prakasam JP, Becker H, Wagner CA, Ganapathy V, Prasad PD. Cloning and functional characterization of human SMCT2 (SLC5A12) and expression pattern of the transporter in kidney. *Biochim Biophys Acta* 1768: 2690–2697, 2007. doi:10.1016/j.bbamem.2007.06.031.

255. Gordon RD, Geddesj RA, Pawsey CG, O'Halloran MW. Hypertension and severe hyperkalaemia associated with suppression of renin and aldosterone and completely reversed by dietary sodium restriction. *Australas Ann Med* 19: 287–294, 1970. doi:10.1111/imj.1970.19.4.287.

256. Gordon RD. *Heterogeneous Hypertension*. London: Nature, 1995.

257. Gorvin CM, Wilmer MJ, Piret SE, Harding B, van den Heuvel LP, Wrong O, Jat PS, Lippiat JD, Levtchenko EN, Thakker RV. Receptor-mediated endocytosis and endosomal acidification is impaired in proximal tubule epithelial cells of Dent disease patients. *Proc Natl Acad Sci USA* 110: 7014–7019, 2013. doi:10.1073/pnas.1302063110.

258. Gotzsche O. Renal glucosuria and aminoaciduria. *Acta Med Scand* 202: 65–67, 1977. doi:10.1111/j.0954-6820.1977.tb16785.x.

259. Goytain A, Quamme GA. Functional characterization of ACDP2 (ancient conserved domain protein), a divalent metal transporter. *Physiol Genomics* 22: 382–389, 2005. doi:10.1152/physiolgenomics.00058.2005.

260. Graves TD, Cha Y-H, Hahn AF, Barohn R, Salajegheh MK, Griggs RC, Bundy BN, Jen JC, Baloh RW, Hanna MG; CINCH Investigators. Episodic ataxia type 1: clinical characterization, quality of life and genotype-phenotype correlation. *Brain* 137: 1009–1018, 2014. doi:10.1093/brain/awu012.

261. Greene ML, Marcus R, Aurbach GD, Kazam ES, Seegmiller JE. Hypouricemia due to isolated renal tubular defect. Dalmatian dog mutation in man. *Am J Med* 53: 361–367, 1972. doi:10.1016/0002-9343(72)90181-7.

262. Greger R, Schlatter E. Properties of the basolateral membrane of the cortical thick ascending limb of Henle's loop of rabbit kidney. A model for secondary active chloride transport. *Pflugers Arch* 396: 325–334, 1983. doi:10.1007/BF01063938.

263. Greger R. Chloride reabsorption in the rabbit cortical thick ascending limb of the loop of Henle. A sodium dependent process. *Pflugers Arch* 390: 38–43, 1981. doi:10.1007/BF00582708.

264. Greger R. Ion transport mechanisms in thick ascending limb of Henle's loop of mammalian nephron. *Physiol Rev* 65: 760–797, 1985. doi:10.1152/physrev.1985.65.3.760.

265. Groenestege WMT, Hoenderop JG, van den Heuvel L, Knoers N, Bindels RJ. The epithelial Mg^{2+} channel transient receptor potential melastatin 6 is regulated by dietary Mg^{2+} content and estrogens. *J Am Soc Nephrol* 17: 1035–1043, 2006. doi:10.1681/ASN.2005070700.

266. Groenestege WMT, Thébault S, van der Wijst J, van den Berg D, Janssen R, Tejpar S, van den Heuvel LP, van Cutsem E, Hoenderop JG, Knoers NV, Bindels RJ. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. *J Clin Invest* 117: 2260–2267, 2007. doi:10.1172/JCI31680.

267. Gründer S, Firsov D, Chang SS, Jaeger NF, Gautschi I, Schild L, Lifton RP, Rossier BC. A mutation causing pseudohypoaldosteronism type 1 identifies a conserved glycine that is involved in the gating of the epithelial sodium channel. *EMBO J* 16: 899–907, 1997. doi:10.1093/emboj/16.5.899.

268. Gründer S, Jaeger NF, Gautschi I, Schild L, Rossier BC. Identification of a highly conserved sequence at the N-terminus of the epithelial Na^+ channel alpha subunit involved in gating. *Pflugers Arch* 438: 709–715, 1999. doi:10.1007/s004249900119.

269. Guan F, Zhang T, Li L, Fu D, Lin H, Chen G, Chen T. Two-stage replication of previous genome-wide association studies of AS3MT-CNNM2-NT5C2 gene cluster region in a large schizophrenia case-control sample from Han Chinese population. *Schizophr Res* 176: 125–130, 2016. doi:10.1016/j.schres.2016.07.004.

270. Guay-Woodford LM. Bartter syndrome: unraveling the pathophysiologic enigma. *Am J Med* 105: 151–161, 1998. doi:10.1016/S0002-9343(98)00196-X.

271. Günther W, Lüchow A, Cluzeaud F, Vandewalle A, Jentsch TJ. ClC-5, the chloride channel mutated in Dent's disease, colocalizes with the proton pump in endocytotically active kidney cells. *Proc Natl Acad Sci USA* 95: 8075–8080, 1998. doi:10.1073/pnas.95.14.8075.

272. Günther W, Piwon N, Jentsch TJ. The ClC-5 chloride channel knock-out mouse–an animal model for Dent's disease. *Pflugers Arch* 445: 456–462, 2003. doi:10.1007/s00424-002-0950-6.

273. Günzel D. Claudins: vital partners in transcellular and paracellular transport coupling. *Pflugers Arch* 469: 35–44, 2017. doi:10.1007/s00424-016-1909-3.

274. Hadchouel J, Ellison DH, Gamba G. Regulation of Renal Electrolyte Transport by WNK and SPAK-OSR1 Kinases. *Annu Rev Physiol* 78: 367–389, 2016. doi:10.1146/annurev-physiol-021115-105431.

275. Hadchouel J, Jeunemaitre X. Life and death of the distal nephron: WNK4 and NCC as major players. *Cell Metab* 4: 335–337, 2006. doi:10.1016/j.cmet.2006.10.007.

276. Hadchouel J, Soukaseum C, Büsst C, Zhou X-O, Baudrie V, Zürrer T, Cambillau M, Elghozi J-L, Lifton RP, Loffing J, Jeunemaitre X. Decreased ENaC expression compensates the increased NCC activity following inactivation of the kidney-specific isoform of WNK1 and prevents hypertension. *Proc Natl Acad Sci USA* 107: 18109–18114, 2010. doi:10.1073/pnas.1006128107.

277. Hadj-Rabia S, Brideau G, Al-Sarraj Y, Maroun RC, Figueres M-L, Leclerc-Mercier S, Olinger E, Baron S, Chaussain C, Nochy D, Taha RZ, Knebelmann B, Joshi V, Curmi PA, Kambouris M, Vargas-Poussou R, Bodemer C, Devuyst O, Houillier P, El-Shanti H. Multiplex epithelium dysfunction due to CLDN10 mutation: the HELIX syndrome. *Genet Med* 20: 190–201, 2018. doi:10.1038/gim.2017.71.

278. Hagos Y, Stein D, Ugele B, Burckhardt G, Bahn A. Human renal organic anion transporter 4 operates as an asymmetric urate transporter. *J Am Soc Nephrol* 18: 430–439, 2007. doi:10.1681/ASN.2006040415.

279. Hale LJ, Howden SE, Phipson B, Lonsdale A, Er PX, Ghobrial I, Hosawi S, Wilson S, Lawlor KT, Khan S, Oshlack A, Quinlan C, Lennon R, Little MH. 3D organoid-derived human glomeruli for personalised podocyte disease modelling and drug screening. *Nat Commun* 9: 5167, 2018. doi:10.1038/s41467-018-07594-z.

280. Hallow KM, Gebremichael Y, Helmlinger G, Vallon V. Primary proximal tubule hyperreabsorption and impaired tubular transport counterregulation determine glomerular hyperfiltration in diabetes: a modeling analysis. *Am J Physiol Renal Physiol* 312: F819–F835, 2017. doi:10.1152/ajprenal.00497.2016.

281. Hamm LL, Feng Z, Hering-Smith KS. Regulation of sodium transport by ENaC in the kidney. *Curr Opin Nephrol Hypertens* 19: 98–105, 2010. doi:10.1097/MNH.0b013e328332bda4.

282. Hannan FM, Babinsky VN, Thakker RV. Disorders of the calcium-sensing receptor and partner proteins: insights into the molecular basis of calcium homeostasis. *J Mol Endocrinol* 57: R127–R142, 2016. doi:10.1530/JME-16-0124.

283. Hannan FM, Howles SA, Rogers A, Cranston T, Gorvin CM, Babinsky VN, Reed AA, Thakker CE, Bockenhauer D, Brown RS, Connell JM, Cook J, Darzy K, Ehtisham S, Graham U, Hulse T, Hunter SJ, Izatt L, Kumar D, McKenna MJ, McKnight JA, Morrison PJ, Mughal MZ, O'Halloran D, Pearce SH, Porteous ME, Rahman M, Richardson T, Robinson R, Scheers I, Siddique H, Van't Hoff WG, Wang T, Whyte MP, Nesbit MA, Thakker RV. Adaptor protein-2 sigma subunit mutations causing familial hypocalciuric hypercalcaemia type 3 (FHH3) demonstrate genotype-phenotype correlations, codon bias and dominant-negative effects. *Hum Mol Genet* 24: 5079–5092, 2015. doi:10.1093/hmg/ddv226.

284. Hannan FM, Nesbit MA, Zhang C, Cranston T, Curley AJ, Harding B, Fratter C, Rust N, Christie PT, Turner JJO, Lemos MC, Bowl MR, Bouillon R, Brain C, Bridges N, Burren C, Connell JM, Jung H, Marks E, McCredie D, Mughal Z, Rodda C, Tollefsen S, Brown EM, Yang JJ, Thakker RV. Identification of 70 calcium-sensing receptor mutations in hyper- and hypo-calcaemic patients: evidence for clustering of extracellular domain mutations at calcium-binding sites. *Hum Mol Genet* 21: 2768–2778, 2012. doi:10.1093/hmg/dds105.

285. Hansson JH, Nelson-Williams C, Suzuki H, Schild L, Shimkets R, Lu Y, Canessa C, Iwasaki T, Rossier B, Lifton RP. Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. *Nat Genet* 11: 76–82, 1995. doi:10.1038/ng0995-76.

286. Hanukoglu A, Edelheit O, Shriki Y, Gizewska M, Dascal N, Hanukoglu I. Renin-aldosterone response, urinary Na/K ratio and growth in pseudohypoaldosteronism patients with mutations in epithelial sodium channel (ENaC) subunit genes. *J Steroid Biochem Mol Biol* 111: 268–274, 2008. doi:10.1016/j.jsbmb.2008.06.013.

287. Hanukoglu A, Hanukoglu I. Clinical improvement in patients with autosomal recessive pseudohypoaldosteronism and the necessity for salt supplementation. *Clin Exp Nephrol* 14: 518–519, 2010. doi:10.1007/s10157-010-0326-8.

288. Hanukoglu A. Type I pseudohypoaldosteronism includes two clinically and genetically distinct entities with either renal or multiple target organ defects. *J Clin Endocrinol Metab* 73: 936–944, 1991. doi:10.1210/jcem-73-5-936.

289. Hayama A, Rai T, Sasaki S, Uchida S. Molecular mechanisms of Bartter syndrome caused by mutations in the BSND gene. *Histochem Cell Biol* 119: 485–493, 2003. doi:10.1007/s00418-003-0535-2.

290. He C, Hobert M, Friend L, Carlin C. The epidermal growth factor receptor juxtamembrane domain has multiple basolateral plasma membrane localization determinants, including a dominant signal with a polyproline core. *J Biol Chem* 277: 38284–38293, 2002. doi:10.1074/jbc.M104646200.

291. Heath H III. Familial benign (hypocalciuric) hypercalcemia. A troublesome mimic of mild primary hyperparathyroidism. *Endocrinol Metab Clin North Am* 18: 723–740, 1989. doi:10.1016/S0889-8529(18)30362-1.

292. Hebert SC, Mount DB, Gamba G. Molecular physiology of cation-coupled Cl^- cotransport: the SLC12 family. *Pflugers Arch* 447: 580–593, 2004. doi:10.1007/s00424-003-1066-3.

293. Hebert SC. Extracellular calcium-sensing receptor: implications for calcium and magnesium handling in the kidney. *Kidney Int* 50: 2129–2139, 1996. doi:10.1038/ki.1996.539.

294. Hebert SC. Bartter syndrome. *Curr Opin Nephrol Hypertens* 12: 527–532, 2003. doi:10.1097/00041552-200309000-00008.

295. Hediger MA, Rhoads DB. Molecular physiology of sodium-glucose cotransporters. *Physiol Rev* 74: 993–1026, 1994. doi:10.1152/physrev.1994.74.4.993.

296. Heise CJ, Xu B-E, Deaton SL, Cha S-K, Cheng C-J, Earnest S, Sengupta S, Juang Y-C, Stippec S, Xu Y, Zhao Y, Huang C-L, Cobb MH. Serum and glucocorticoid-induced kinase (SGK) 1 and the epithelial sodium channel are regulated by multiple with no lysine (WNK) family members. *J Biol Chem* 285: 25161–25167, 2010. doi:10.1074/jbc.M110.103432.

297. Hennings JC, Andrini O, Picard N, Paulais M, Huebner AK, Cayuqueo IKL, Bignon Y, Keck M, Cornière N, Böhm D, Jentsch TJ, Chambrey R, Teulon J, Hübner CA, Eladari D. The ClC-K2 Chloride Channel Is Critical for Salt Handling in the Distal Nephron. *J Am Soc Nephrol* 28: 209–217, 2017. doi:10.1681/ASN.2016010085.

298. Hichri H, Rendu J, Monnier N, Coutton C, Dorseuil O, Poussou RV, Baujat G, Blanchard A, Nobili F, Ranchin B, Remesy M, Salomon R, Satre V, Lunardi J. From Lowe syndrome to Dent disease: correlations between mutations of the OCRL1 gene and clinical and biochemical phenotypes. *Hum Mutat* 32: 379–388, 2011. doi:10.1002/humu.21391.

299. Hillman DA, Scriver CR, Pedvis S, Shragovitch I. Neonatal familial primary hyperparathyroidism. *N Engl J Med* 270: 483–490, 1964. doi:10.1056/NEJM196403052701001.

300. Hirata Y, Funato Y, Takano Y, Miki H. Mg^{2+}-dependent interactions of ATP with the cystathionine-β-synthase (CBS) domains of a magnesium transporter. *J Biol Chem* 289: 14731–14739, 2014. doi:10.1074/jbc.M114.551176.

301. Hjärne U. A Study of Orthoglycaemic Glycosuria with Particular Reference to its Hereditability. *Acta Med Scand* 67: 422–494, 1927.

302. Ho C, Conner DA, Pollak MR, Ladd DJ, Kifor O, Warren HB, Brown EM, Seidman JG, Seidman CE. A mouse model of human familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. *Nat Genet* 11: 389–394, 1995. doi:10.1038/ng1295-389.

303. Hoenderop JGJ, Nilius B, Bindels RJM. Calcium absorption across epithelia. *Physiol Rev* 85: 373–422, 2005. doi:10.1152/physrev.00003.2004.

304. Hoenderop JGJ, van Leeuwen JPTM, van der Eerden BCJ, Kersten FFJ, van der Kemp AWCM, Mérillat A-M, Waarsing JH, Rossier BC, Vallon V, Hummler E, Bindels RJM. Renal Ca^{2+} wasting, hyperabsorption, and reduced bone thickness in mice lacking TRPV5. *J Clin Invest* 112: 1906–1914, 2003. doi:10.1172/JCI200319826.

305. Hofer AM, Brown EM. Extracellular calcium sensing and signalling. *Nat Rev Mol Cell Biol* 4: 530–538, 2003. doi:10.1038/nrm1154.

306. Hoopes RR Jr, Shrimpton AE, Knohl SJ, Hueber P, Hoppe B, Matyus J, Simckes A, Tasic V, Toenshoff B, Suchy SF, Nussbaum RL, Scheinman SJ. Dent Disease with mutations in OCRL1. *Am J Hum Genet* 76: 260–267, 2005. doi:10.1086/427887.

307. Hoover RS, Poch E, Monroy A, Vázquez N, Nishio T, Gamba G, Hebert SC. *N*-Glycosylation at two sites critically alters thiazide binding and activity of the rat thiazide-sensitive Na^+:Cl^- cotransporter. *J Am Soc Nephrol* 14: 271–282, 2003. doi:10.1097/01.ASN.0000043903.93452.D0.

308. Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, Lindner T, Yamagata K, Ogata M, Tomonaga O, Kuroki H, Kasahara T, Iwamoto Y, Bell GI. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet* 17: 384–385, 1997. doi:10.1038/ng1297-384.

309. Hosoyamada M, Ichida K, Enomoto A, Hosoya T, Endou H. Function and localization of urate transporter 1 in mouse kidney. *J Am Soc Nephrol* 15: 261–268, 2004. doi:10.1097/01.ASN.0000107560.80107.19.

310. Hosoyamada M, Takiue Y, Morisaki H, Cheng J, Ikawa M, Okabe M, Morisaki T, Ichida K, Hosoya T, Shibasaki T. Establishment and analysis of SLC22A12 (URAT1) knockout mouse. *Nucleosides Nucleotides Nucleic Acids* 29: 314–320, 2010. doi:10.1080/15257771003738634.

311. Hosoyamada M, Tsurumi Y, Hirano H, Tomioka NH, Sekine Y, Morisaki T, Uchida S. Urat1-Uox double knockout mice are experimental animal models of renal hypouricemia and exercise-induced acute kidney injury. *Nucleosides Nucleotides Nucleic Acids* 35: 543–549, 2016. doi:10.1080/15257770.2016.1143559.

312. Hossain Khan MZ, Sohara E, Ohta A, Chiga M, Inoue Y, Isobe K, Wakabayashi M, Oi K, Rai T, Sasaki S, Uchida S. Phosphorylation of Na-Cl cotransporter by OSR1 and SPAK kinases regulates its ubiquitination. *Biochem Biophys Res Commun* 425: 456–461, 2012. doi:10.1016/j.bbrc.2012.07.124.

313. Hou J, Paul DL, Goodenough DA. Paracellin-1 and the modulation of ion selectivity of tight junctions. *J Cell Sci* 118: 5109–5118, 2005. doi:10.1242/jcs.02631.

314. Hou J, Rajagopal M, Yu ASL. Claudins and the kidney. *Annu Rev Physiol* 75: 479–501, 2013. doi:10.1146/annurev-physiol-030212-183705.

315. Hou J, Renigunta A, Gomes AS, Hou M, Paul DL, Waldegger S, Goodenough DA. Claudin-16 and claudin-19 interaction is required for their assembly into tight junctions and for renal reabsorption of magnesium. *Proc Natl Acad Sci USA* 106: 15350–15355, 2009. doi:10.1073/pnas.0907724106.

316. Hou J, Renigunta A, Konrad M, Gomes AS, Schneeberger EE, Paul DL, Waldegger S, Goodenough DA. Claudin-16 and claudin-19 interact and form a cation-selective tight junction complex. *J Clin Invest* 118: 619–628, 2008. doi:10.1172/JCI33970.

317. Hou J, Shan Q, Wang T, Gomes AS, Yan Q, Paul DL, Bleich M, Goodenough DA. Transgenic RNAi depletion of claudin-16 and the renal handling of magnesium. *J Biol Chem* 282: 17114–17122, 2007. doi:10.1074/jbc.M700632200.

318. Hou J. Regulation of paracellular transport in the distal nephron. *Curr Opin Nephrol Hypertens* 21: 547–551, 2012. doi:10.1097/MNH.0b013e328355cb47.

319. Hu J, Mora S, Weber G, Zamproni I, Proverbio MC, Spiegel AM. Autosomal dominant hypocalcemia in monozygotic twins caused by a de novo germline mutation near the amino-terminus of the human calcium receptor. *J Bone Miner Res* 19: 578–586, 2004. doi:10.1359/JBMR.040106.

320. Hu J, Reyes-Cruz G, Chen W, Jacobson KA, Spiegel AM. Identification of acidic residues in the extracellular loops of the seven-transmembrane domain of the human Ca^{2+} receptor critical for response to Ca^{2+} and a positive allosteric modulator. *J Biol Chem* 277: 46622–46631, 2002. doi:10.1074/jbc.M207100200.

321. Hu M-C, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. *Annu Rev Physiol* 75: 503–533, 2013. doi:10.1146/annurev-physiol-030212-183727.

322. Huang C, Sindic A, Hill CE, Hujer KM, Chan KW, Sassen M, Wu Z, Kurachi Y, Nielsen S, Romero MF, Miller RT. Interaction of the Ca^{2+}-sensing receptor with the inwardly rectifying potassium channels Kir4.1 and Kir4.2 results in inhibition of channel function. *Am J Physiol Renal Physiol* 292: F1073–F1081, 2007. doi:10.1152/ajprenal.00269.2006.

323. Huang Y, Zhou Y, Castiblanco A, Yang W, Brown EM, Yang JJ. Multiple Ca(2+)-binding sites in the extracellular domain of the Ca(2+)-sensing receptor corresponding to cooperative Ca(2+) response. *Biochemistry* 48: 388–398, 2009. doi:10.1021/bi8014604.

324. Huang Y, Zhou Y, Yang W, Butters R, Lee H-W, Li S, Castiblanco A, Brown EM, Yang JJ. Identification and dissection of Ca(2+)-binding sites in the extracellular domain of Ca(2+)-sensing receptor. *J Biol Chem* 282: 19000–19010, 2007. doi:10.1074/jbc.M701096200.

325. Hui JY, Choi JWJ, Mount DB, Zhu Y, Zhang Y, Choi HK. The independent association between parathyroid hormone levels and hyperuricemia: a national population study. *Arthritis Res Ther* 14: R56, 2012. doi:10.1186/ar3769.

326. Hummler E, Barker P, Gatzy J, Beermann F, Verdumo C, Schmidt A, Boucher R, Rossier BC. Early death due to defective neonatal lung liquid clearance in alpha-ENaC-deficient mice. *Nat Genet* 12: 325–328, 1996. doi:10.1038/ng0396-325.

327. Hunter DJ, De Lange M, Snieder H, MacGregor AJ, Swaminathan R, Thakker RV, Spector TD. Genetic contribution to renal function and electrolyte balance: a twin study. *Clin Sci (Lond)* 103: 259–265, 2002. doi:10.1042/cs1030259.

328. Hurtado-Lorenzo A, Skinner M, El Annan J, Futai M, Sun-Wada G-H, Bourgoin S, Casanova J, Wildeman A, Bechoua S, Ausiello DA, Brown D, Marshansky V. V-ATPase interacts with ARNO and Arf6 in early endosomes and regulates the protein degradative pathway. *Nat Cell Biol* 8: 124–136, 2006. doi:10.1038/ncb1348.

329. Iacobone M, Carnaille B, Palazzo FF, Vriens M. Hereditary hyperparathyroidism--a consensus report of the European Society of Endocrine Surgeons (ESES). *Langenbecks Arch Surg* 400: 867–886, 2015. doi:10.1007/s00423-015-1342-7.

330. Ichida K, Hosoyamada M, Hisatome I, Enomoto A, Hikita M, Endou H, Hosoya T. Clinical and molecular analysis of patients with renal hypouricemia in Japan-influence of URAT1 gene on urinary urate excretion. *J Am Soc Nephrol* 15: 164–173, 2004. doi:10.1097/01.ASN.0000105320.04395.D0.

331. Ichida K, Hosoyamada M, Kamatani N, Kamitsuji S, Hisatome I, Shibasaki T, Hosoya T. Age and origin of the G774A mutation in SLC22A12 causing renal hypouricemia in Japanese. *Clin Genet* 74: 243–251, 2008. doi:10.1111/j.1399-0004.2008.01021.x.

332. Ichida K, Matsuo H, Takada T, Nakayama A, Murakami K, Shimizu T, Yamanashi Y, Kasuga H, Nakashima H, Nakamura T, Takada Y, Kawamura Y, Inoue H, Okada C, Utsumi Y, Ikebuchi Y, Ito K, Nakamura M, Shinohara Y, Hosoyamada M, Sakurai Y, Shinomiya N, Hosoya T, Suzuki H. Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun* 3: 764, 2012. doi:10.1038/ncomms1756.

333. Ichida K. What lies behind serum urate concentration? Insights from genetic and genomic studies. *Genome Med* 1: 118, 2009. doi:10.1186/gm118.

334. Idris I, Donnelly R. Sodium-glucose co-transporter-2 inhibitors: an emerging new class of oral antidiabetic drug. *Diabetes Obes Metab* 11: 79–88, 2009. doi:10.1111/j.1463-1326.2008.00982.x.

335. Iglesias J, Abernethy VE, Wang Z, Lieberthal W, Koh JS, Levine JS. Albumin is a major serum survival factor for renal tubular cells and macrophages through scavenging of ROS. *Am J Physiol Renal Physiol* 277: F711–F722, 1999. doi:10.1152/ajprenal.1999.277.5.F711.

336. Iharada M, Miyaji T, Fujimoto T, Hiasa M, Anzai N, Omote H, Moriyama Y. Type 1 sodium-dependent phosphate transporter (SLC17A1 Protein) is a Cl(-)-dependent urate exporter. *J Biol Chem* 285: 26107–26113, 2010. doi:10.1074/jbc.M110.122721.

337. Ikari A, Matsumoto S, Harada H, Takagi K, Hayashi H, Suzuki Y, Degawa M, Miwa M. Phosphorylation of paracellin-1 at Ser217 by protein kinase A is essential for localization in tight junctions. *J Cell Sci* 119: 1781–1789, 2006. doi:10.1242/jcs.02901.

338. Ikari A, Okude C, Sawada H, Yamazaki Y, Sugatani J, Miwa M. TRPM6 expression and cell proliferation are up-regulated by phosphorylation of ERK1/2 in renal epithelial cells. *Biochem Biophys Res Commun* 369: 1129–1133, 2008. doi:10.1016/j.bbrc.2008.03.002.

339. Ikari A, Sanada A, Okude C, Sawada H, Yamazaki Y, Sugatani J, Miwa M. Up-regulation of TRPM6 transcriptional activity by AP-1 in renal epithelial cells. *J Cell Physiol* 222: 481–487, 2010. doi:10.1002/jcp.21988.

339a. International Collaborative Study Group for Bartter-like Syndromes. Mutations in the gene encoding the inwardly-rectifying renal potassium channel, ROMK, cause the antenatal variant of Bartter syndrome: evidence for genetic heterogeneity. *Hum Mol Genet* 6: 17–26, 1997.

340. Isaka Y, Kimura T, Takabatake Y. The protective role of autophagy against aging and acute ischemic injury in kidney proximal tubular cells. *Autophagy* 7: 1085–1087, 2011. doi:10.4161/auto.7.9.16465.

341. Ito M, Inanobe A, Horio Y, Hibino H, Isomoto S, Ito H, Mori K, Tonosaki A, Tomoike H, Kurachi Y. Immunolocalization of an inwardly rectifying K^+ channel, K(AB)-2 (Kir4.1), in the basolateral membrane of renal distal tubular epithelia. *FEBS Lett* 388: 11–15, 1996. doi:10.1016/0014-5793(96)00502-9.

342. Iwai N, Mino Y, Hosoyamada M, Tago N, Kokubo Y, Endou H. A high prevalence of renal hypouricemia caused by inactive SLC22A12 in Japanese. *Kidney Int* 66: 935–944, 2004. doi:10.1111/j.1523-1755.2004.00839.x.

343. Janssen AGH, Scholl U, Domeyer C, Nothmann D, Leinenweber A, Fahlke C. Disease-causing dysfunctions of barttin in Bartter syndrome type IV. *J Am Soc Nephrol* 20: 145–153, 2009. doi:10.1681/ASN.2008010102.

344. Jeannin G, Chiarelli N, Gaggiotti M, Ritelli M, Maiorca P, Quinzani S, Verzeletti F, Possenti S, Colombi M, Cancarini G. Recurrent exercise-induced acute renal failure in a young Pakistani man with severe renal hypouricemia and SLC2A9 compound heterozygosity. *BMC Med Genet* 15: 3, 2014. doi:10.1186/1471-2350-15-3.

345. Jeck N, Konrad M, Peters M, Weber S, Bonzel KE, Seyberth HW. Mutations in the chloride channel gene, CLCNKB, leading to a mixed Bartter-Gitelman phenotype. *Pediatr Res* 48: 754–758, 2000. doi:10.1203/00006450-200012000-00009.

346. Jeck N, Reinalter SC, Henne T, Marg W, Mallmann R, Pasel K, Vollmer M, Klaus G, Leonhardt A, Seyberth HW, Konrad M. Hypokalemic salt-losing tubulopathy with chronic renal failure and sensorineural deafness. *Pediatrics* 108: e5, 2001. doi:10.1542/peds.108.1.e5.

347. Jeck N, Schlingmann KP, Reinalter SC, Kömhoff M, Peters M, Waldegger S, Seyberth HW. Salt handling in the distal nephron: lessons learned from inherited human disorders. *Am J Physiol Regul Integr Comp Physiol* 288: R782–R795, 2005. doi:10.1152/ajpregu.00600.2004.

348. Jentsch TJ, Neagoe I, Scheel O. CLC chloride channels and transporters. *Curr Opin Neurobiol* 15: 319–325, 2005. doi:10.1016/j.conb.2005.05.002.

349. Jentsch TJ. CLC chloride channels and transporters: from genes to protein structure, pathology and physiology. *Crit Rev Biochem Mol Biol* 43: 3–36, 2008. doi:10.1080/10409230701829110.

350. Jentsch TJ. Discovery of CLC transport proteins: cloning, structure, function and pathophysiology. *J Physiol* 593: 4091–4109, 2015. doi:10.1113/JP270043.

351. Jeunemaitre X, Bassilana F, Persu A, Dumont C, Champigny G, Lazdunski M, Corvol P, Barbry P. Genotype-phenotype analysis of a newly discovered family with Liddle's syndrome. *J Hypertens* 15: 1091–1100, 1997. doi:10.1097/00004872-199715100-00007.

352. Jézégou A, Llinares E, Anne C, Kieffer-Jaquinod S, O'Regan S, Aupetit J, Chabli A, Sagné C, Debacker C, Chadefaux-Vekemans B, Journet A, André B, Gasnier B. Heptahelical protein PQLC2 is a lysosomal cationic amino acid exporter underlying the action of cysteamine in cystinosis therapy. [Correction in *Proc Natl Acad Sci USA* 110: 3197, 2013.] *Proc Natl Acad Sci USA* 109: E3434–E3443, 2012. doi:10.1073/pnas.1211198109.

353. Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, Newton-Cheh C, State MW, Levy D, Lifton RP. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 40: 592–599, 2008. doi:10.1038/ng.118.

354. Johnson RJ, Bakris GL, Borghi C, Chonchol MB, Feldman D, Lanaspa MA, Merriman TR, Moe OW, Mount DB, Sanchez Lozada LG, Stahl E, Weiner DE, Chertow GM. Hyperuricemia, Acute and Chronic Kidney Disease, Hypertension, and Cardiovascular Disease: Report of a Scientific Workshop Organized by the National Kidney Foundation. *Am J Kidney Dis* 71: 851–865, 2018. doi:10.1053/j.ajkd.2017.12.009.

355. Johnson RJ, Nakagawa T, Jalal D, Sánchez-Lozada LG, Kang D-H, Ritz E. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant* 28: 2221–2228, 2013. doi:10.1093/ndt/gft029.

356. Jones DH, Li TY, Arystarkhova E, Barr KJ, Wetzel RK, Peng J, Markham K, Sweadner KJ, Fong G-H, Kidder GM. Na,K-ATPase from mice lacking the gamma subunit (FXYD2) exhibits altered Na^+ affinity and decreased thermal stability. *J Biol Chem* 280: 19003–19011, 2005. doi:10.1074/jbc.M500697200.

357. Jouret F, Bernard A, Hermans C, Dom G, Terryn S, Leal T, Lebecque P, Cassiman J-J, Scholte BJ, de Jonge HR, Courtoy PJ, Devuyst O. Cystic fibrosis is associated with a defect in apical receptor-mediated endocytosis in mouse and human kidney. *J Am Soc Nephrol* 18: 707–718, 2007. doi:10.1681/ASN.2006030269.

358. Jouret F, Wu J, Hull M, Rajendran V, Mayr B, Schöfl C, Geibel J, Caplan MJ. Activation of the Ca^{2+}-sensing receptor induces deposition of tight junction components to the epithelial cell plasma membrane. *J Cell Sci* 126: 5132–5142, 2013. doi:10.1242/jcs.127555.

359. Jutabha P, Anzai N, Kitamura K, Taniguchi A, Kaneko S, Yan K, Yamada H, Shimada H, Kimura T, Katada T, Fukutomi T, Tomita K, Urano W, Yamanaka H, Seki G, Fujita T, Moriyama Y, Yamada A, Uchida S, Wempe MF, Endou H, Sakurai H. Human sodium phosphate transporter 4 (hNPT4/SLC17A3) as a common renal secretory pathway for drugs and urate. *J Biol Chem* 285: 35123–35132, 2010. doi:10.1074/jbc.M110.121301.

360. Jutabha P, Kanai Y, Hosoyamada M, Chairoungdua A, Kim DK, Iribe Y, Babu E, Kim JY, Anzai N, Chatsudthipong V, Endou H. Identification of a novel voltage-driven organic anion transporter present at apical membrane of renal proximal tubule. *J Biol Chem* 278: 27930–27938, 2003. doi:10.1074/jbc.M303210200.

361. Kahle KT, Macgregor GG, Wilson FH, Van Hoek AN, Brown D, Ardito T, Kashgarian M, Giebisch G, Hebert SC, Boulpaep EL, Lifton RP. Paracellular Cl^- permeability is regulated by WNK4 kinase: insight into normal physiology and hypertension. *Proc Natl Acad Sci USA* 101: 14877–14882, 2004. doi:10.1073/pnas.0406172101.

362. Kahle KT, Ring AM, Lifton RP. Molecular physiology of the WNK kinases. *Annu Rev Physiol* 70: 329–355, 2008. doi:10.1146/annurev.physiol.70.113006.100651.

363. Kahle KT, Wilson FH, Leng Q, Lalioti MD, O'Connell AD, Dong K, Rapson AK, MacGregor GG, Giebisch G, Hebert SC, Lifton RP. WNK4 regulates the balance between renal NaCl reabsorption and K^+ secretion. *Nat Genet* 35: 372–376, 2003. doi:10.1038/ng1271.

364. Kalatzis V, Cherqui S, Antignac C, Gasnier B. Cystinosin, the protein defective in cystinosis, is a H(+)-driven lysosomal cystine transporter. *EMBO J* 20: 5940–5949, 2001. doi:10.1093/emboj/20.21.5940.

365. Kalatzis V, Nevo N, Cherqui S, Gasnier B, Antignac C. Molecular pathogenesis of cystinosis: effect of CTNS mutations on the transport activity and subcellular localization of cystinosin. *Hum Mol Genet* 13: 1361–1371, 2004. doi:10.1093/hmg/ddh152.

366. Kamatani Y, Matsuda K, Okada Y, Kubo M, Hosono N, Daigo Y, Nakamura Y, Kamatani N. Genome-wide association study of hematological and biochemical traits in a Japanese population. *Nat Genet* 42: 210–215, 2010. doi:10.1038/ng.531.

367. Kaminski MM, Tosic J, Kresbach C, Engel H, Klockenbusch J, Müller A-L, Pichler R, Grahammer F, Kretz O, Huber TB, Walz G, Arnold SJ, Lienkamp SS. Direct reprogramming of fibroblasts into renal tubular epithelial cells by defined transcription factors. *Nat Cell Biol* 18: 1269–1280, 2016. doi:10.1038/ncb3437.

368. Kanai Y, Lee WS, You G, Brown D, Hediger MA. The human kidney low affinity Na^+/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose. *J Clin Invest* 93: 397–404, 1994. doi:10.1172/JCI116972.

369. Kantarci S, Al-Gazali L, Hill RS, Donnai D, Black GCM, Bieth E, Chassaing N, Lacombe D, Devriendt K, Teebi A, Loscertales M, Robson C, Liu T, MacLaughlin DT, Noonan KM, Russell MK, Walsh CA, Donahoe PK, Pober BR. Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico-renal syndromes. *Nat Genet* 39: 957–959, 2007. doi:10.1038/ng2063.

370. Kantham L, Quinn SJ, Egbuna OI, Baxi K, Butters R, Pang JL, Pollak MR, Goltzman D, Brown EM. The calcium-sensing receptor (CaSR) defends against hypercalcemia independently of its regulation of parathyroid hormone secretion. *Am J Physiol Endocrinol Metab* 297: E915–E923, 2009. doi:10.1152/ajpendo.00315.2009.

371. Kapur K, Johnson T, Beckmann ND, Sehmi J, Tanaka T, Kutalik Z, Styrkarsdottir U, Zhang W, Marek D, Gudbjartsson DF, Milaneschi Y, Holm H, Diiorio A, Waterworth D, Li Y, Singleton AB, Bjornsdottir US, Sigurdsson G, Hernandez DG, Desilva R, Elliott P, Eyjolfsson GI, Guralnik JM, Scott J, Thorsteinsdottir U, Bandinelli S, Chambers J, Stefansson K, Waeber G, Ferrucci L, Kooner JS, Mooser V, Vollenweider P, Beckmann JS, Bochud M, Bergmann S. Genome-wide meta-analysis for serum calcium identifies significantly associated SNPs near the calcium-sensing receptor (CASR) gene. *PLoS Genet* 6: e1001035, 2010. doi:10.1371/journal.pgen.1001035.

373. Katz AI, Doucet A, Morel F. Na-K-ATPase activity along the rabbit, rat, and mouse nephron. *Am J Physiol Renal Fluid Electrolyte Physiol* 237: F114–F120, 1979. doi:10.1152/ajprenal.1979.237.2.F114.

374. Kausalya PJ, Amasheh S, Günzel D, Wurps H, Müller D, Fromm M, Hunziker W. Disease-associated mutations affect intracellular traffic and paracellular Mg^{2+} transport function of Claudin-16. *J Clin Invest* 116: 878–891, 2006. doi:10.1172/JCI26323.

375. Keck M, Andrini O, Lahuna O, Burgos J, Cid LP, Sepúlveda FV, L'hoste S, Blanchard A, Vargas-Poussou R, Lourdel S, Teulon J. Novel CLCNKB mutations causing Bartter syndrome affect channel surface expression. *Hum Mutat* 34: 1269–1278, 2013. doi:10.1002/humu.22361.

376. Kellenberger S, Gautschi I, Schild L. A single point mutation in the pore region of the epithelial Na^+ channel changes ion selectivity by modifying molecular sieving. *Proc Natl Acad Sci USA* 96: 4170–4175, 1999. doi:10.1073/pnas.96.7.4170.

377. Kellenberger S, Hoffmann-Pochon N, Gautschi I, Schneeberger E, Schild L. On the molecular basis of ion permeation in the epithelial Na^+ channel. *J Gen Physiol* 114: 13–30, 1999. doi:10.1085/jgp.114.1.13.

378. Kerem E, Bistritzer T, Hanukoglu A, Hofmann T, Zhou Z, Bennett W, MacLaughlin E, Barker P, Nash M, Quittell L, Boucher R, Homolya V, Keenan B, Knowles MR. Pulmonary epithelial sodium-channel dysfunction and excess airway liquid in pseudohypoaldosteronism. *N Engl J Med* 341: 156–162, 1999. doi:10.1056/NEJM199907153410304.

379. Kim G-H. Renal effects of prostaglandins and cyclooxygenase-2 inhibitors. *Electrolyte Blood Press* 6: 35–41, 2008. doi:10.5049/EBP.2008.6.1.35.

380. Kim KM, Kwon SK, Kim H-Y. A Case of Isolated Glycosuria Mediated by an *SLC5A2* Gene Mutation and Characterized by Postprandial Heavy Glycosuria Without Salt Wasting. *Electrolyte Blood Press* 14: 35–37, 2016. doi:10.5049/EBP.2016.14.2.35.

381. Kim SW, Kim JW, Choi KC, Ma SK, Oh Y, Jung J-Y, Kim J, Lee J. Indomethacin enhances shuttling of aquaporin-2 despite decreased abundance in rat kidney. *J Am Soc Nephrol* 15: 2998–3005, 2004. doi:10.1097/01.ASN.0000145877.28811.82.

382. Kim YH, Kwon T-H, Frische S, Kim J, Tisher CC, Madsen KM, Nielsen S. Immunocytochemical localization of pendrin in intercalated cell subtypes in rat and mouse kidney. *Am J Physiol Renal Physiol* 283: F744–F754, 2002. doi:10.1152/ajprenal.00037.2002.

383. Kimura T, Amonpatumrat S, Tsukada A, Fukutomi T, Jutabha P, Thammapratip T, Lee EJ, Ichida K, Anzai N, Sakurai H. Increased expression of SLC2A9 decreases urate excretion from the kidney. *Nucleosides Nucleotides Nucleic Acids* 30: 1295–1301, 2011. doi:10.1080/15257770.2011.628354.

384. Kimura T, Takahashi M, Yan K, Sakurai H. Expression of SLC2A9 isoforms in the kidney and their localization in polarized epithelial cells. *PLoS One* 9: e84996, 2014. doi:10.1371/journal.pone.0084996.

385. Kiuchi-Saishin Y, Gotoh S, Furuse M, Takasuga A, Tano Y, Tsukita S. Differential expression patterns of claudins, tight junction membrane proteins, in mouse nephron segments. *J Am Soc Nephrol* 13: 875–886, 2002.

386. Klar J, Piontek J, Milatz S, Tariq M, Jameel M, Breiderhoff T, Schuster J, Fatima A, Asif M, Sher M, Mäbert K, Fromm A, Baig SM, Günzel D, Dahl N. Altered paracellular cation permeability due to a rare CLDN10B variant causes anhidrosis and kidney damage. *PLoS Genet* 13: e1006897, 2017. doi:10.1371/journal.pgen.1006897.

387. Kleta R, Bockenhauer D. Salt-Losing Tubulopathies in Children: What's New, What's Controversial? *J Am Soc Nephrol* 29: 727–739, 2018. doi:10.1681/ASN.2017060600.

388. Kleta R, Stuart C, Gill FA, Gahl WA. Renal glucosuria due to SGLT2 mutations. *Mol Genet Metab* 82: 56–58, 2004. doi:10.1016/j.ymgme.2004.01.018.

389. Klootwijk ED, Reichold M, Unwin RJ, Kleta R, Warth R, Bockenhauer D. Renal Fanconi syndrome: taking a proximal look at the nephron. *Nephrol Dial Transplant* 30: 1456–1460, 2015. doi:10.1093/ndt/gfu377.

390. Knoers NVAM, Levtchenko EN. Gitelman syndrome. *Orphanet J Rare Dis* 3: 22, 2008. doi:10.1186/1750-1172-3-22.

391. Ko B, Kamsteeg E-J, Cooke LL, Moddes LN, Deen PMT, Hoover RS. RasGRP1 stimulation enhances ubiquitination and endocytosis of the sodium-chloride cotransporter. *Am J Physiol Renal Physiol* 299: F300–F309, 2010. doi:10.1152/ajprenal.00441.2009.

392. Kocher O, Cheresh P, Brown LF, Lee SW. Identification of a novel gene, selectively up-regulated in human carcinomas, using the differential display technique. *Clin Cancer Res* 1: 1209–1215, 1995.

393. Kohda Y, Ding W, Phan E, Housini I, Wang J, Star RA, Huang CL. Localization of the ROMK potassium channel to the apical membrane of distal nephron in rat kidney. *Kidney Int* 54: 1214–1223, 1998. doi:10.1046/j.1523-1755.1998.00120.x.

394. Kolatsi-Joannou M, Bingham C, Ellard S, Bulman MP, Allen LI, Hattersley AT, Woolf AS. Hepatocyte nuclear factor-1beta: a new kindred with renal cysts and diabetes and gene expression in normal human development. *J Am Soc Nephrol* 12: 2175–2180, 2001.

395. Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, Perola M, Mangino M, Albrecht E, Wallace C, Farrall M, Johansson A, Nyholt DR, Aulchenko Y, Beckmann JS, Bergmann S, Bochud M, Brown M, Campbell H, Connell J, Dominiczak A, Homuth G, Lamina C, McCarthy MI, Meitinger T, Mooser V, Munroe P, Nauck M, Peden J, Prokisch H, Salo P, Salomaa V, Samani NJ, Schlessinger D, Uda M, Völker U, Waeber G, Waterworth D, Wang-Sattler R, Wright AF, Adamski J, Whitfield JB, Gyllensten U, Wilson JF, Rudan I, Pramstaller P, Watkins H, Doering A, Wichmann HE, Spector TD, Peltonen L, Völzke H, Nagaraja R, Vollenweider P, Caulfield M, Illig T, Gieger C; EUROSPAN Consortium; ENGAGE Consortium; PROCARDIS Consortium; KORA Study; WTCCC. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet* 5: e1000504, 2009. doi:10.1371/journal.pgen.1000504.

396. Komoda F, Sekine T, Inatomi J, Enomoto A, Endou H, Ota T, Matsuyama T, Ogata T, Ikeda M, Awazu M, Muroya K, Kamimaki I, Igarashi T. The W258X mutation in SLC22A12 is the predominant cause of Japanese renal hypouricemia. *Pediatr Nephrol* 19: 728–733, 2004. doi:10.1007/s00467-004-1424-1.

397. Kompatscher A, de Baaij JHF, Aboudehen K, Hoefnagels APWM, Igarashi P, Bindels RJM, Veenstra GJC, Hoenderop JGJ. Loss of transcriptional activation of the potassium channel Kir5.1 by HNF1β drives autosomal dominant tubulointerstitial kidney disease. *Kidney Int* 92: 1145–1156, 2017. doi:10.1016/j.kint.2017.03.034.

398. Konrad M, Hou J, Weber S, Dötsch J, Kari JA, Seeman T, Kuwertz-Bröking E, Peco-Antic A, Tasic V, Dittrich K, Alshaya HO, von Vigier RO, Gallati S, Goodenough DA, Schaller A. CLDN16 genotype predicts renal decline in familial hypomagnesemia with hypercalciuria and nephrocalcinosis. *J Am Soc Nephrol* 19: 171–181, 2008. doi:10.1681/ASN.2007060709.

399. Konrad M, Schaller A, Seelow D, Pandey AV, Waldegger S, Lesslauer A, Vitzthum H, Suzuki Y, Luk JM, Becker C, Schlingmann KP, Schmid M, Rodriguez-Soriano J, Ariceta G, Cano F, Enriquez R, Juppner H, Bakkaloglu SA, Hediger MA, Gallati S, Neuhauss SCF, Nurnberg P, Weber S. Mutations in the tight-junction gene claudin 19 (CLDN19) are associated with renal magnesium wasting, renal failure, and severe ocular involvement. *Am J Hum Genet* 79: 949–957, 2006. doi:10.1086/508617.

400. Konrad M, Vollmer M, Lemmink HH, van den Heuvel LP, Jeck N, Vargas-Poussou R, Lakings A, Ruf R, Deschênes G, Antignac C, Guay-Woodford L, Knoers NV, Seyberth HW, Feldmann D, Hildebrandt F. Mutations in the chloride channel gene CLCNKB as a cause of classic Bartter syndrome. *J Am Soc Nephrol* 11: 1449–1459, 2000.

401. Konrad M, Weber S. Recent advances in molecular genetics of hereditary magnesium-losing disorders. *J Am Soc Nephrol* 14: 249–260, 2003. doi:10.1097/01.ASN.0000049161.60740.CE.

402. Kos CH, Karaplis AC, Peng J-B, Hediger MA, Goltzman D, Mohammad KS, Guise TA, Pollak MR. The calcium-sensing receptor is required for normal calcium homeostasis independent of parathyroid hormone. *J Clin Invest* 111: 1021–1028, 2003. doi:10.1172/JCI17416.

403. Koshimizu T-A, Nakamura K, Egashira N, Hiroyama M, Nonoguchi H, Tanoue A. Vasopressin V1a and V1b receptors: from molecules to physiological systems. *Physiol Rev* 92: 1813–1864, 2012. doi:10.1152/physrev.00035.2011.

404. Köckerling A, Reinalter SC, Seyberth HW. Impaired response to furosemide in hyperprostaglandin E syndrome: evidence for a tubular defect in the loop of Henle. *J Pediatr* 129: 519–528, 1996. doi:10.1016/S0022-3476(96)70116-6.

405. Köttgen A, Albrecht E, Teumer A, Vitart V, Krumsiek J, Hundertmark C, Pistis G, Ruggiero D, O'Seaghdha CM, Haller T, Yang Q, Tanaka T, Johnson AD, Kutalik Z, Smith AV, Shi J, Struchalin M, Middelberg RPS, Brown MJ, Gaffo AL, Pirastu N, Li G, Hayward C, Zemunik T, Huffman J, Yengo L, Zhao JH, Demirkan A, Feitosa MF, Liu X, Malerba G, Lopez LM, van der Harst P, Li X, Kleber ME, Hicks AA, Nolte IM, Johansson A, Murgia F, Wild SH, Bakker SJL, Peden JF, Dehghan A, Steri M, Tenesa A, Lagou V, Salo P, Mangino M, Rose LM, Lehtimäki T, Woodward OM, Okada Y, Tin A, Müller C, Oldmeadow C, Putku M, Czamara D, Kraft P, Frogheri L, Thun GA, Grotevendt A, Gislason GK, Harris TB, Launer LJ, McArdle P, Shuldiner AR, Boerwinkle E, Coresh J, Schmidt H, Schallert M, Martin NG, Montgomery GW, Kubo M, Nakamura Y, Tanaka T, Munroe PB, Samani NJ, Jacobs DR Jr, Liu K, D'Adamo P, Ulivi S, Rotter JI, Psaty BM, Vollenweider P, Waeber G, Campbell S, Devuyst O, Navarro P, Kolcic I, Hastie N, Balkau B, Froguel P, Esko T, Salumets A, Khaw KT, Langenberg C, Wareham NJ, Isaacs A, Kraja A, Zhang Q, Wild PS, Scott RJ, Holliday EG, Org E, Viigimaa M, Bandinelli S, Metter JE, Lupo A, Trabetti E, Sorice R, Döring A, Lattka E, Strauch K, Theis F, Waldenberger M, Wichmann H-E, Davies G, Gow AJ, Bruinenberg M, Stolk RP, Kooner JS, Zhang W, Winkelmann BR, Boehm BO, Lucae S, Penninx BW, Smit JH, Curhan G, Mudgal P, Plenge RM, Portas L, Persico I, Kirin M, Wilson JF, Mateo Leach I, van Gilst WH, Goel A, Ongen H, Hofman A, Rivadeneira F, Uitterlinden AG, Imboden M, von Eckardstein A, Cucca F, Nagaraja R, Piras MG, Nauck M, Schurmann C, Budde K, Ernst F, Farrington SM, Theodoratou E, Prokopenko I, Stumvoll M, Jula A, Perola M, Salomaa V, Shin S-Y, Spector TD, Sala C, Ridker PM, Kähönen M, Viikari J, Hengstenberg C, Nelson CP, Meschia JF, Nalls MA, Sharma P, Singleton AB, Kamatani N, Zeller T, Burnier M, Attia J, Laan M, Klopp N, Hillege HL, Kloiber S, Choi H, Pirastu M, Tore S, Probst-Hensch NM, Völzke H, Gudnason V, Parsa A, Schmidt R, Whitfield JB, Fornage M, Gasparini P, Siscovick DS, Polašek O, Campbell H, Rudan I, Bouatia-Naji N, Metspalu A, Loos RJF, van Duijn CM, Borecki IB, Ferrucci L, Gambaro G, Deary IJ, Wolffenbuttel BHR, Chambers JC, März W, Pramstaller PP, Snieder H, Gyllensten U, Wright AF, Navis G, Watkins H, Witteman JCM, Sanna S, Schipf S, Dunlop MG, Tönjes A, Ripatti S, Soranzo N, Toniolo D, Chasman DI, Raitakari O, Kao WHL, Ciullo M, Fox CS, Caulfield M, Bochud M, Gieger C; LifeLines Cohort StudyCARDIoGRAM ConsortiumDIAGRAM ConsortiumICBP Consortium; MAGIC Consortium. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat Genet* 45: 145–154, 2013. doi:10.1038/ng.2500.

406. Köttgen A, Pattaro C, Böger CA, Fuchsberger C, Olden M, Glazer NL, Parsa A, Gao X, Yang Q, Smith AV, O'Connell JR, Li M, Schmidt H, Tanaka T, Isaacs A, Ketkar S, Hwang S-J, Johnson AD, Dehghan A, Teumer A, Paré G, Atkinson EJ, Zeller T, Lohman K, Cornelis MC, Probst-Hensch NM, Kronenberg F, Tönjes A, Hayward C, Aspelund T, Eiriksdottir G, Launer LJ, Harris TB, Rampersaud E, Mitchell BD, Arking DE, Boerwinkle E, Struchalin M, Cavalieri M, Singleton A, Giallauria F, Metter J, de Boer IH, Haritunians T, Lumley T, Siscovick D, Psaty BM, Zillikens MC, Oostra BA, Feitosa M, Province M, de Andrade M, Turner ST, Schillert A, Ziegler A, Wild PS, Schnabel RB, Wilde S, Munzel TF, Leak TS, Illig T, Klopp N, Meisinger C, Wichmann H-E, Koenig W, Zgaga L, Zemunik T, Kolcic I, Minelli C, Hu FB, Johansson A, Igl W, Zaboli G, Wild SH, Wright AF, Campbell H, Ellinghaus D, Schreiber S, Aulchenko YS, Felix JF, Rivadeneira F, Uitterlinden AG, Hofman A, Imboden M, Nitsch D, Brandstätter A, Kollerits B, Kedenko L, Mägi R, Stumvoll M, Kovacs P, Boban M, Campbell S, Endlich K, Völzke H, Kroemer HK, Nauck M, Völker U, Polašek O, Vitart V, Badola S, Parker AN, Ridker PM, Kardia SLR, Blankenberg S, Liu Y, Curhan GC, Franke A, Rochat T, Paulweber B, Prokopenko I, Wang W, Gudnason V, Shuldiner AR, Coresh J, Schmidt R, Ferrucci L, Shlipak MG, van Duijn CM, Borecki I, Krämer BK, Rudan I, Gyllensten U, Wilson JF, Witteman JC, Pramstaller PP, Rettig R, Hastie N, Chasman DI, Kao WH, Heid IM, Fox CS. New loci associated with kidney function and chronic kidney disease. *Nat Genet* 42: 376–384, 2010. doi:10.1038/ng.568.

407. Köttgen A. Genome-wide association studies in nephrology research. *Am J Kidney Dis* 56: 743–758, 2010. doi:10.1053/j.ajkd.2010.05.018.

408. Kriz W, Kaissling B. Structural organization of the mammalian kidney. In: *The Kidney: Physiology and Pathophysiology*, edited by Seldin DW, Giebisch G. New York: Raven, 1992, p. 707–777.

409. Krug SM, Günzel D, Conrad MP, Rosenthal R, Fromm A, Amasheh S, Schulzke JD, Fromm M. Claudin-17 forms tight junction channels with distinct anion selectivity. *Cell Mol Life Sci* 69: 2765–2778, 2012. doi:10.1007/s00018-012-0949-x.

410. Laghmani K, Beck BB, Yang S-S, Seaayfan E, Wenzel A, Reusch B, Vitzthum H, Priem D, Demaretz S, Bergmann K, Duin LK, Göbel H, Mache C, Thiele H, Bartram MP, Dombret C, Altmüller J, Nürnberg P, Benzing T, Levtchenko E, Seyberth HW, Klaus G, Yigit G, Lin S-H, Timmer A, de Koning TJ, Scherjon SA, Schlingmann KP, Bertrand MJM, Rinschen MM, de Backer O, Konrad M, Kömhoff M. Polyhydramnios, Transient Antenatal Bartter's Syndrome, and MAGED2 Mutations. *N Engl J Med* 374: 1853–1863, 2016. doi:10.1056/NEJMoa1507629.

410a. Lainez S, Schlingmann KP, van der Wijst J, Dworniczak B, van Zeeland F, Konrad M, Bindels RJ, Hoenderop JG. New TRPM6 missense mutations linked to hypomagnesemia with secondary hypocalcemia. *Eur J Hum Genet* 22: 497–504, 2014. doi:10.1038/ejhg.2013.178.

411. Lalioti MD, Zhang J, Volkman HM, Kahle KT, Hoffmann KE, Toka HR, Nelson-Williams C, Ellison DH, Flavell R, Booth CJ, Lu Y, Geller DS, Lifton RP. Wnk4 controls blood pressure and potassium homeostasis via regulation of mass and activity of the distal convoluted tubule. *Nat Genet* 38: 1124–1132, 2006. doi:10.1038/ng1877.

412. Lameris AL, Monnens LA, Bindels RJ, Hoenderop JGJ. Drug-induced alterations in Mg^{2+} homoeostasis. *Clin Sci (Lond)* 123: 1–14, 2012. doi:10.1042/CS20120045.

413. Landau D, Shalev H, Ohaly M, Carmi R. Infantile variant of Bartter syndrome and sensorineural deafness: a new autosomal recessive disorder. *Am J Med Genet* 59: 454–459, 1995. doi:10.1002/ajmg.1320590411.

414. Langman CB, Barshop BA, Deschênes G, Emma F, Goodyer P, Lipkin G, Midgley JP, Ottolenghi C, Servais A, Soliman NA, Thoene JG, Levtchenko EN, Amon O, Ariceta G, Basurto M, Belmont-Martínez L, Bertholet-Thomas A, Bos M, Brown T, Cherqui S, Cornelissen EAM, Del Monte M, Ding J, Dohil R, Doyle M, Elenberg E, Gahl WA, Gomez V, Greco M, Greeley C, Greenbaum LA, Grimm P, Hohenfellner K, Holm T, Hotz V, Janssen MC, Kaskel F, Magriço R, Nesterova G, Newsholme P, Niaudet P, Rioux P, Sarwal MM, Schneider J, Topaloglu R, Trauner DA, Vaisbich MH, van den Heuvel LP, Van't Hoff W; Conference Participants. Controversies and research agenda in nephropathic cystinosis: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int* 89: 1192–1203, 2016. doi:10.1016/j.kint.2016.01.033.

415. Leach K, Wen A, Davey AE, Sexton PM, Conigrave AD, Christopoulos A. Identification of molecular phenotypes and biased signaling induced by naturally occurring mutations of the human calcium-sensing receptor. *Endocrinology* 153: 4304–4316, 2012. doi:10.1210/en.2012-1449.

416. Ledeganck KJ, Boulet GA, Bogers JJ, Verpooten GA, De Winter BY. The TRPM6/EGF pathway is downregulated in a rat model of cisplatin nephrotoxicity. *PLoS One* 8: e57016, 2013. doi:10.1371/journal.pone.0057016.

417. Ledeganck KJ, De Winter BY, Van den Driessche A, Jürgens A, Bosmans J-L, Couttenye MM, Verpooten GA. Magnesium loss in cyclosporine-treated patients is related to renal epidermal growth factor downregulation. *Nephrol Dial Transplant* 29: 1097–1102, 2014. doi:10.1093/ndt/gft498.

418. Lee H, Han KH, Park HW, Shin JI, Kim CJ, Namgung MK, Kim KH, Koo JW, Chung WY, Lee D-Y, Kim S-Y, Cheong HI. Familial renal glucosuria: a clinicogenetic study of 23 additional cases. *Pediatr Nephrol* 27: 1091–1095, 2012. doi:10.1007/s00467-012-2109-9.

419. Lee MR, Ball SG, Thomas TH, Morgan DB. Hypertension and hyperkalaemia responding to bendrofluazide. *Q J Med* 48: 245–258, 1979.

420. Lee WS, Hebert SC. ROMK inwardly rectifying ATP-sensitive K^+ channel. I. Expression in rat distal nephron segments. *Am J Physiol Renal Physiol* 268: F1124–F1131, 1995. doi:10.1152/ajprenal.1995.268.6.F1124.

421. Lee WS, Kanai Y, Wells RG, Hediger MA. The high affinity Na^+/glucose cotransporter. Re-evaluation of function and distribution of expression. *J Biol Chem* 269: 12032–12039, 1994.

422. Legrand A, Treard C, Roncelin I, Dreux S, Bertholet-Thomas A, Broux F, Bruno D, Decramer S, Deschenes G, Djeddi D, Guigonis V, Jay N, Khalifeh T, Llanas B, Morin D, Morin G, Nobili F, Pietrement C, Ryckewaert A, Salomon R, Vrillon I, Blanchard A, Vargas-Poussou R. Prevalence of Novel *MAGED2* Mutations in Antenatal Bartter Syndrome. *Clin J Am Soc Nephrol* 13: 242–250, 2018. doi:10.2215/CJN.05670517.

423. Lemmink HH, Knoers NV, Károlyi L, van Dijk H, Niaudet P, Antignac C, Guay-Woodford LM, Goodyer PR, Carel JC, Hermes A, Seyberth HW, Monnens LA, van den Heuvel LP. Novel mutations in the thiazide-sensitive NaCl cotransporter gene in patients with Gitelman syndrome with predominant localization to the C-terminal domain. *Kidney Int* 54: 720–730, 1998. doi:10.1046/j.1523-1755.1998.00070.x.

424. Lemmink HH, van den Heuvel LP, van Dijk HA, Merkx GF, Smilde TJ, Taschner PE, Monnens LA, Hebert SC, Knoers NV. Linkage of Gitelman syndrome to the thiazide-sensitive sodium-chloride cotransporter gene with identification of mutations in Dutch families. *Pediatr Nephrol* 10: 403–407, 1996. doi:10.1007/s004670050129.

425. Letz S, Rus R, Haag C, Dörr H-G, Schnabel D, Möhlig M, Schulze E, Frank-Raue K, Raue F, Mayr B, Schöfl C. Novel activating mutations of the calcium-sensing receptor: the calcilytic NPS-2143 mitigates excessive signal transduction of mutant receptors. *J Clin Endocrinol Metab* 95: E229–E233, 2010. doi:10.1210/jc.2010-0651.

426. Li C, Grosdidier A, Crambert G, Horisberger J-D, Michielin O, Geering K. Structural and functional interaction sites between Na,K-ATPase and FXYD proteins. *J Biol Chem* 279: 38895–38902, 2004. doi:10.1074/jbc.M406697200.

427. Li C, Han L, Levin AM, Song H, Yan S, Wang Y, Wang Y, Meng D, Lv S, Ji Y, Xu X, Liu X, Wang Y, Zhou L, Miao Z, Mi Q-S. Multiple single nucleotide polymorphisms in the human urate transporter 1 (hURAT1) gene are associated with hyperuricaemia in Han Chinese. *J Med Genet* 47: 204–210, 2010. doi:10.1136/jmg.2009.068619.

428. Li M, Du J, Jiang J, Ratzan W, Su L-T, Runnels LW, Yue L. Molecular determinants of Mg^{2+} and Ca^{2+} permeability and pH sensitivity in TRPM6 and TRPM7. *J Biol Chem* 282: 25817–25830, 2007. doi:10.1074/jbc.M608972200.

429. Li M, Jiang J, Yue L. Functional characterization of homo- and heteromeric channel kinases TRPM6 and TRPM7. *J Gen Physiol* 127: 525–537, 2006. doi:10.1085/jgp.200609502.

430. Li S, Sanna S, Maschio A, Busonero F, Usala G, Mulas A, Lai S, Dei M, Orrù M, Albai G, Bandinelli S, Schlessinger D, Lakatta E, Scuteri A, Najjar SS, Guralnik J, Naitza S, Crisponi L, Cao A, Abecasis G, Ferrucci L, Uda M, Chen W-M, Nagaraja R. The GLUT9 gene is associated with serum uric acid levels in Sardinia and Chianti cohorts. *PLoS Genet* 3: e194, 2007. doi:10.1371/journal.pgen.0030194.

431. Liddle GW, Bledsoe T, Coppage WS. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. *Trans Assoc Am Physicians* 76: 199–213, 1963.

432. Lienhardt A, Garabédian M, Bai M, Sinding C, Zhang Z, Lagarde J-P, Boulesteix J, Rigaud M, Brown EM, Kottler M-L. A large homozygous or heterozygous in-frame deletion within the calcium-sensing receptor's carboxylterminal cytoplasmic tail that causes autosomal dominant hypocalcemia. *J Clin Endocrinol Metab* 85: 1695–1702, 2000. doi:10.1210/jcem.85.4.6570.

433. Lima WR, Parreira KS, Devuyst O, Caplanusi A, N'kuli F, Marien B, Van Der Smissen P, Alves PMS, Verroust P, Christensen EI, Terzi F, Matter K, Balda MS, Pierreux CE, Courtoy PJ. ZONAB promotes proliferation and represses differentiation of proximal

tubule epithelial cells. *J Am Soc Nephrol* 21: 478–488, 2010. doi:10.1681/ASN.2009070698.

434. Lin S-H, Shiang J-C, Huang C-C, Yang S-S, Hsu Y-J, Cheng C-J. Phenotype and genotype analysis in Chinese patients with Gitelman's syndrome. *J Clin Endocrinol Metab* 90: 2500–2507, 2005. doi:10.1210/jc.2004-1905.

435. Liu B, Du H, Rutkowski R, Gartner A, Wang X. LAAT-1 is the lysosomal lysine/arginine transporter that maintains amino acid homeostasis. *Science* 337: 351–354, 2012. doi:10.1126/science.1220281.

436. Liu B-C, Tang T-T, Lv L-L, Lan H-Y. Renal tubule injury: a driving force toward chronic kidney disease. *Kidney Int* 93: 568–579, 2018. doi:10.1016/j.kint.2017.09.033.

437. Liu Z, Wang H-R, Huang C-L. Regulation of ROMK channel and K^+ homeostasis by kidney-specific WNK1 kinase. *J Biol Chem* 284: 12198–12206, 2009. doi:10.1074/jbc.M806551200.

438. Liu Z, Xie J, Wu T, Truong T, Auchus RJ, Huang C-L. Downregulation of NCC and NKCC2 cotransporters by kidney-specific WNK1 revealed by gene disruption and transgenic mouse models. *Hum Mol Genet* 20: 855–866, 2011. doi:10.1093/hmg/ddq525.

439. Lloyd SE, Pearce SH, Fisher SE, Steinmeyer K, Schwappach B, Scheinman SJ, Harding B, Bolino A, Devoto M, Goodyer P, Rigden SP, Wrong O, Jentsch TJ, Craig IW, Thakker RV. A common molecular basis for three inherited kidney stone diseases. *Nature* 379: 445–449, 1996. doi:10.1038/379445a0.

440. Lo Y-F, Nozu K, Iijima K, Morishita T, Huang C-C, Yang S-S, Sytwu H-K, Fang Y-W, Tseng M-H, Lin S-H. Recurrent deep intronic mutations in the SLC12A3 gene responsible for Gitelman's syndrome. *Clin J Am Soc Nephrol* 6: 630–639, 2011. doi:10.2215/CJN.06730810.

441. Lochmüller H, Badowska DM, Thompson R, Knoers NV, Aartsma-Rus A, Gut I, Wood L, Harmuth T, Durudas A, Graessner H, Schaefer F, Riess O; RD-Connect Consortium; NeurOmics Consortium; EURenOmics Consortium. RD-Connect, NeurOmics and EURenOmics: collaborative European initiative for rare diseases. *Eur J Hum Genet* 26: 778–785, 2018. doi:10.1038/s41431-018-0115-5.

442. Loffing J, Vallon V, Loffing-Cueni D, Aregger F, Richter K, Pietri L, Bloch-Faure M, Hoenderop JGJ, Shull GE, Meneton P, Kaissling B. Altered renal distal tubule structure and renal Na(+) and Ca(2+) handling in a mouse model for Gitelman's syndrome. *J Am Soc Nephrol* 15: 2276–2288, 2004. doi:10.1097/01.ASN.0000138234.18569.63.

443. Lorenz JN, Baird NR, Judd LM, Noonan WT, Andringa A, Doetschman T, Manning PA, Liu LH, Miller ML, Shull GE. Impaired renal NaCl absorption in mice lacking the ROMK potassium channel, a model for type II Bartter's syndrome. *J Biol Chem* 277: 37871–37880, 2002. doi:10.1074/jbc.M205627200.

444. Louis-Dit-Picard H, Barc J, Trujillano D, Miserey-Lenkei S, Bouatia-Naji N, Pylypenko O, Beaurain G, Bonnefond A, Sand O, Simian C, Vidal-Petiot E, Soukaseum C, Mandet C, Broux F, Chabre O, Delahousse M, Esnault V, Fiquet B, Houillier P, Bagnis CI, Koenig J, Konrad M, Landais P, Mourani C, Niaudet P, Probst V, Thauvin C, Unwin RJ, Soroka SD, Ehret G, Ossowski S, Caulfield M, Bruneval P, Estivill X, Froguel P, Hadchouel J, Schott J-J, Jeunemaitre X; International Consortium for Blood Pressure (ICBP). KLHL3 mutations cause familial hyperkalemic hypertension by impairing ion transport in the distal nephron. [Corrigendum in *Nat Genet* 44: 609, 2012.] *Nat Genet* 44: 456–460, 2012. doi:10.1038/ng.2218.

445. Loupy A, Ramakrishnan SK, Wootla B, Chambrey R, de la Faille R, Bourgeois S, Bruneval P, Mandet C, Christensen EI, Faure H, Cheval L, Laghmani K, Collet C, Eladari D, Dodd RH, Ruat M, Houillier P. PTH-independent regulation of blood calcium concentration by the calcium-sensing receptor. *J Clin Invest* 122: 3355–3367, 2012. doi:10.1172/JCI57407.

446. Lourdel S, Grand T, Burgos J, González W, Sepúlveda FV, Teulon J. ClC-5 mutations associated with Dent's disease: a major role of the dimer interface. *Pflugers Arch* 463: 247–256, 2012. doi:10.1007/s00424-011-1052-0.

447. Lourdel S, Paulais M, Cluzeaud F, Bens M, Tanemoto M, Kurachi Y, Vandewalle A, Teulon J. An inward rectifier K(+) channel at the basolateral membrane of the mouse distal convoluted tubule: similarities with Kir4-Kir5.1 heteromeric channels. *J Physiol* 538: 391–404, 2002. doi:10.1113/jphysiol.2001.012961.

448. Lu M, Wang T, Yan Q, Yang X, Dong K, Knepper MA, Wang W, Giebisch G, Shull GE, Hebert SC. Absence of small conductance K^+ channel (SK) activity in apical membranes of thick ascending limb and cortical collecting duct in ROMK (Bartter's) knockout mice. *J Biol Chem* 277: 37881–37887, 2002. doi:10.1074/jbc.M206644200.

449. Luciani A, Sirac C, Terryn S, Javaugue V, Prange JA, Bender S, Bonaud A, Cogné M, Aucouturier P, Ronco P, Bridoux F, Devuyst O. Impaired Lysosomal Function Underlies Monoclonal Light Chain-Associated Renal Fanconi Syndrome. *J Am Soc Nephrol* 27: 2049–2061, 2016. doi:10.1681/ASN.2015050581.

450. Ma J, Guan M, Bowden DW, Ng MCY, Hicks PJ, Lea JP, Ma L, Gao C, Palmer ND, Freedman BI. Association Analysis of the Cubilin (CUBN) and Megalin (LRP2) Genes with ESRD in African Americans. *Clin J Am Soc Nephrol* 11: 1034–1043, 2016. doi:10.2215/CJN.12971215.

451. Madrigal G, Saborio P, Mora F, Rincon G, Guay-Woodford LM. Bartter syndrome in Costa Rica: a description of 20 cases. *Pediatr Nephrol* 11: 296–301, 1997. doi:10.1007/s004670050280.

452. Magen D, Sprecher E, Zelikovic I, Skorecki K. A novel missense mutation in SLC5A2 encoding SGLT2 underlies autosomal-recessive renal glucosuria and aminoaciduria. *Kidney Int* 67: 34–41, 2005. doi:10.1111/j.1523-1755.2005.00053.x.

453. Mandal AK, Mount DB. The molecular physiology of uric acid homeostasis. *Annu Rev Physiol* 77: 323–345, 2015. doi:10.1146/annurev-physiol-021113-170343.

454. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, Evans RM. The nuclear receptor superfamily: the second decade. *Cell* 83: 835–839, 1995. doi:10.1016/0092-8674(95)90199-X.

455. Manolio TA, Brooks LD, Collins FS. A HapMap harvest of insights into the genetics of common disease. *J Clin Invest* 118: 1590–1605, 2008. doi:10.1172/JCI34772.

456. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TFC, McCarroll SA, Visscher PM. Finding the missing heritability of complex diseases. *Nature* 461: 747–753, 2009. doi:10.1038/nature08494.

457. Mansfield TA, Simon DB, Farfel Z, Bia M, Tucci JR, Lebe M, Gutkin M, Vialettes B, Christofilis MA, Kauppinen-Makelin R, Mayan H, Risch N, Lifton RP. Multilocus linkage of familial hyperkalaemia and hypertension, pseudohypoaldosteronism type II, to chromosomes 1q31-42 and 17p11-q21. *Nat Genet* 16: 202–205, 1997. doi:10.1038/ng0697-202.

458. Mansour-Hendili L, Blanchard A, Le Pottier N, Roncelin I, Lourdel S, Treard C, González W, Vergara-Jaque A, Morin G, Colin E, Holder-Espinasse M, Bacchetta J, Baudouin V, Benoit S, Bérard E, Bourdat-Michel G, Bouchireb K, Burtey S, Cailliez M, Cardon G, Cartery C, Champion G, Chauveau D, Cochat P, Dahan K, De la Faille R, Debray F-G, Dehoux L, Deschenes G, Desport E, Devuyst O, Dieguez S, Emma F, Fischbach M, Fouque D, Fourcade J, François H, Gilbert-Dussardier B, Hannedouche T, Houillier P, Izzedine H, Janner M, Karras A, Knebelmann B, Lavocat M-P, Lemoine S, Leroy V, Loirat C, Macher M-A, Martin-Coignard D, Morin D, Niaudet P, Nivet H, Nobili F, Novo R, Faivre L, Rigothier C, Roussey-Kesler G, Salomon R, Schleich A, Sellier-Leclerc A-L, Soulami K, Tiple A, Ulinski T, Vanhille P, Van Regemorter N, Jeunemaître X, Vargas-Poussou R. Mutation Update of the CLCN5 Gene Responsible for Dent Disease 1. *Hum Mutat* 36: 743–752, 2015. doi:10.1002/humu.22804.

459. Marsenic O. Glucose control by the kidney: an emerging target in diabetes. *Am J Kidney Dis* 53: 875–883, 2009. doi:10.1053/j.ajkd.2008.12.031.

460. Martin A, David V, Quarles LD. Regulation and function of the FGF23/klotho endocrine pathways. *Physiol Rev* 92: 131–155, 2012. doi:10.1152/physrev.00002.2011.

461. Marx SJ, Attie MF, Levine MA, Spiegel AM, Downs RW Jr, Lasker RD. The hypocalciuric or benign variant of familial hypercalcemia: clinical and biochemical features in fifteen kindreds. *Medicine (Baltimore)* 60: 397–412, 1981. doi:10.1097/00005792-198111000-00002.

462. Marx SJ, Attie MF, Spiegel AM, Levine MA, Lasker RD, Fox M. An association between neonatal severe primary hyperparathyroidism and familial hypocalciuric hypercalcemia in three kindreds. *N Engl J Med* 306: 257–264, 1982. doi:10.1056/NEJM198202043060502.

463. Marx SJ, Stock JL, Attie MF, Downs RW Jr, Gardner DG, Brown EM, Spiegel AM, Doppman JL, Brennan MF. Familial hypocalciuric hypercalcemia: recognition among patients referred after unsuccessful parathyroid exploration. *Ann Intern Med* 92: 351–356, 1980. doi:10.7326/0003-4819-92-3-351.

464. Masilamani S, Kim GH, Mitchell C, Wade JB, Knepper MA. Aldosterone-mediated regulation of ENaC alpha, beta, and gamma subunit proteins in rat kidney. *J Clin Invest* 104: R19–R23, 1999. doi:10.1172/JCI7840.

465. Mather A, Pollock C. Renal glucose transporters: novel targets for hyperglycemia management. *Nat Rev Nephrol* 6: 307–311, 2010. doi:10.1038/nrneph.2010.38.

466. Matsumura Y, Uchida S, Kondo Y, Miyazaki H, Ko SB, Hayama A, Morimoto T, Liu W, Arisawa M, Sasaki S, Marumo F. Overt nephrogenic diabetes insipidus in mice lacking the CLC-K1 chloride channel. *Nat Genet* 21: 95–98, 1999. doi:10.1038/5036.

467. Matsuo H, Chiba T, Nagamori S, Nakayama A, Domoto H, Phetdee K, Wiriyasermkul P, Kikuchi Y, Oda T, Nishiyama J, Nakamura T, Morimoto Y, Kamakura K, Sakurai Y, Nonoyama S, Kanai Y, Shinomiya N. Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. *Am J Hum Genet* 83: 744–751, 2008. doi:10.1016/j.ajhg.2008.11.001.

468. Matsuo H, Nakayama A, Sakiyama M, Chiba T, Shimizu S, Kawamura Y, Nakashima H, Nakamura T, Takada Y, Oikawa Y, Takada T, Nakaoka H, Abe J, Inoue H, Wakai K, Kawai S, Guang Y, Nakagawa H, Ito T, Niwa K, Yamamoto K, Sakurai Y, Suzuki H, Hosoya T, Ichida K, Shimizu T, Shinomiya N. ABCG2 dysfunction causes hyperuricemia due to both renal urate underexcretion and renal urate overload. *Sci Rep* 4: 3755, 2015. doi:10.1038/srep03755.

469. Matsuo H, Takada T, Ichida K, Nakamura T, Nakayama A, Ikebuchi Y, Ito K, Kusanagi Y, Chiba T, Tadokoro S, Takada Y, Oikawa Y, Inoue H, Suzuki K, Okada R, Nishiyama J, Domoto H, Watanabe S, Fujita M, Morimoto Y, Naito M, Nishio K, Hishida A, Wakai K, Asai Y, Niwa K, Kamakura K, Nonoyama S, Sakurai Y, Hosoya T, Kanai Y, Suzuki H, Hamajima N, Shinomiya N. Common defects of ABCG2, a high-capacity urate exporter, cause gout: a function-based genetic analysis in a Japanese population. *Sci Transl Med* 1: 5ra11, 2009. doi:10.1126/scitranslmed.3000237.

470. Matzkin H, Lotan D, Boichis H. Primary hypomagnesemia with a probable double magnesium transport defect. *Nephron* 52: 83–86, 1989. doi:10.1159/000185588.

471. Mayan H, Munter G, Shaharabany M, Mouallem M, Pauzner R, Holtzman EJ, Farfel Z. Hypercalciuria in familial hyperkalemia and hypertension accompanies hyperkalemia and precedes hypertension: description of a large family with the Q565E WNK4 mutation. *J Clin Endocrinol Metab* 89: 4025–4030, 2004. doi:10.1210/jc.2004-0037.

472. Mayr B, Schnabel D, Dörr H-G, Schöfl C. Genetics in endocrinology: Gain and loss of function mutations of the calcium-sensing receptor and associated proteins: current treatment concepts. *Eur J Endocrinol* 174: R189–R208, 2016. doi:10.1530/EJE-15-1028.

473. McCredie DA, Rotenberg E, Williams AL. Hypercalciuria in potassium-losing nephropathy: a variant of Bartter's syndrome. *Aust Paediatr J* 10: 286–295, 1974. doi:10.1111/j.1440-1754.1974.tb02786.x.

474. McDonald FJ, Yang B, Hrstka RF, Drummond HA, Tarr DE, McCray PB Jr, Stokes JB, Welsh MJ, Williamson RA. Disruption of the beta subunit of the epithelial Na^+ channel in mice: hyperkalemia and neonatal death associated with a pseudohypoaldosteronism phenotype. *Proc Natl Acad Sci USA* 96: 1727–1731, 1999. doi:10.1073/pnas.96.4.1727.

475. Mehta ZB, Pietka G, Lowe M. The cellular and physiological functions of the Lowe syndrome protein OCRL1. *Traffic* 15: 471–487, 2014. doi:10.1111/tra.12160.

476. Meij IC, Koenderink JB, De Jong JC, De Pont JJHHM, Monnens LAH, Van Den Heuvel LPWJ, Knoers NVAM. Dominant isolated renal magnesium loss is caused by misrouting of the Na^+,K^+-ATPase gamma-subunit. *Ann N Y Acad Sci* 986: 437–443, 2003. doi:10.1111/j.1749-6632.2003.tb07226.x.

477. Meij IC, Koenderink JB, van Bokhoven H, Assink KF, Groenestege WT, de Pont JJ, Bindels RJ, Monnens LA, van den Heuvel LP, Knoers NV. Dominant isolated renal magnesium loss is caused by misrouting of the Na(+),K(+)-ATPase gamma-subunit. *Nat Genet* 26: 265–266, 2000. doi:10.1038/81543.

478. Meij IC, Saar K, van den Heuvel LP, Nuernberg G, Vollmer M, Hildebrandt F, Reis A, Monnens LA, Knoers NV. Hereditary isolated renal magnesium loss maps to chromosome 11q23. *Am J Hum Genet* 64: 180–188, 1999. doi:10.1086/302199.

479. Meij IC, van den Heuvel LPWJ, Hemmes S, van der Vliet WA, Willems JL, Monnens LAH, Knoers NVAM. Exclusion of mutations in FXYD2, CLDN16 and SLC12A3 in two families with primary renal Mg^{2+} loss. *Nephrol Dial Transplant* 18: 512–516, 2003. doi:10.1093/ndt/18.3.512.

480. Mendel DB, Khavari PA, Conley PB, Graves MK, Hansen LP, Admon A, Crabtree GR. Characterization of a cofactor that regulates dimerization of a mammalian homeodomain protein. *Science* 254: 1762–1767, 1991. doi:10.1126/science.1763325.

481. Mercer RW, Biemesderfer D, Bliss DP Jr, Collins JH, Forbush B III. Molecular cloning and immunological characterization of the gamma polypeptide, a small protein associated with the Na,K-ATPase. *J Cell Biol* 121: 579–586, 1993. doi:10.1083/jcb.121.3.579.

482. Meyer TE, Verwoert GC, Hwang S-J, Glazer NL, Smith AV, van Rooij FJA, Ehret GB, Boerwinkle E, Felix JF, Leak TS, Harris TB, Yang Q, Dehghan A, Aspelund T, Katz R, Homuth G, Kocher T, Rettig R, Ried JS, Gieger C, Prucha H, Pfeufer A, Meitinger T, Coresh J, Hofman A, Sarnak MJ, Chen Y-DI, Uitterlinden AG, Chakravarti A, Psaty BM, van Duijn CM, Kao WHL, Witteman JCM, Gudnason V, Siscovick DS, Fox CS, Köttgen A; Genetic Factors for Osteoporosis Consortium; Meta Analysis of Glucose and Insulin Related Traits Consortium. Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six Loci influencing serum magnesium levels. *PLoS Genet* 6: e1001045, 2010. doi:10.1371/journal.pgen.1001045.

483. Michelis MF, Bragdon RW, Fusco RD, Eichenbolz A, Davis BB. Parathyroid hormone responsiveness in hypoparathyroidism with hypomagnesemia. *Am J Med Sci* 270: 412–418, 1975. doi:10.1097/00000441-197511000-00001.

484. Mihout F, Devuyst O, Bensman A, Brocheriou I, Ridel C, Wagner CA, Mohebbi N, Boffa J-J, Plaisier E, Ronco P. Acute metabolic acidosis in a GLUT2-deficient patient with Fanconi-Bickel syndrome: new pathophysiology insights. *Nephrol Dial Transplant* 29, Suppl 4: iv113–iv116, 2014. doi:10.1093/ndt/gfu018.

485. Milatz S, Himmerkus N, Wulfmeyer VC, Drewell H, Mutig K, Hou J, Breiderhoff T, Müller D, Fromm M, Bleich M, Günzel D. Mosaic expression of claudins in thick ascending limbs of Henle results in spatial separation of paracellular Na^+ and Mg^{2+} transport. *Proc Natl Acad Sci USA* 114: E219–E227, 2017. doi:10.1073/pnas.1611684114.

486. Minor NT, Sha Q, Nichols CG, Mercer RW. The gamma subunit of the Na,K-ATPase induces cation channel activity. *Proc Natl Acad Sci USA* 95: 6521–6525, 1998. doi:10.1073/pnas.95.11.6521.

487. Mistry AC, Wynne BM, Yu L, Tomilin V, Yue Q, Zhou Y, Al-Khalili O, Mallick R, Cai H, Alli AA, Ko B, Mattheyses A, Bao H-F, Pochynyuk O, Theilig F, Eaton DC, Hoover RS. The sodium chloride cotransporter (NCC) and epithelial sodium channel (ENaC) associate. *Biochem J* 473: 3237–3252, 2016. doi:10.1042/BCJ20160312.

488. Mithal A, Kifor O, Kifor I, Vassilev P, Butters R, Krapcho K, Simin R, Fuller F, Hebert SC, Brown EM. The reduced responsiveness of cultured bovine parathyroid cells to extracellular Ca^{2+} is associated with marked reduction in the expression of extracellular Ca^{2+}-sensing receptor messenger ribonucleic acid and protein. *Endocrinology* 136: 3087–3092, 1995. doi:10.1210/endo.136.7.7789335.

489. Mittelman SD, Hendy GN, Fefferman RA, Canaff L, Mosesova I, Cole DEC, Burkett L, Geffner ME. A hypocalcemic child with a novel activating mutation of the calcium-sensing receptor gene: successful treatment with recombinant human parathyroid hormone. *J Clin Endocrinol Metab* 91: 2474–2479, 2006. doi:10.1210/jc.2005-2605.

490. Moe OW, Wright SH, Palacín M. Renal handling of organic solutes. In: *Brenner and Rector's The Kidney* (8th ed.). Philadelphia, PA: Elsevier, 2008.

491. Monette MY, Rinehart J, Lifton RP, Forbush B. Rare mutations in the human Na-K-Cl cotransporter (NKCC2) associated with lower blood pressure exhibit impaired processing and transport function. *Am J Physiol Renal Physiol* 300: F840–F847, 2011. doi:10.1152/ajprenal.00552.2010.

492. Montell C. Mg^{2+} homeostasis: the Mg^{2+}nificent TRPM chanzymes. *Curr Biol* 13: R799–R801, 2003. doi:10.1016/j.cub.2003.09.048.

493. Morales MM, Carroll TP, Morita T, Schwiebert EM, Devuyst O, Wilson PD, Lopes AG, Stanton BA, Dietz HC, Cutting GR, Guggino WB. Both the wild type and a functional isoform of CFTR are expressed in kidney. *Am J Physiol Renal Physiol* 270: F1038–F1048, 1996. doi:10.1152/ajprenal.1996.270.6.F1038.

494. Moreno E, Cristóbal PS, Rivera M, Vázquez N, Bobadilla NA, Gamba G. Affinity-defining domains in the Na-Cl cotransporter: a different location for Cl^- and thiazide binding. *J Biol Chem* 281: 17266–17275, 2006. doi:10.1074/jbc.M602614200.

495. Moriguchi T, Urushiyama S, Hisamoto N, Iemura S, Uchida S, Natsume T, Matsumoto K, Shibuya H. WNK1 regulates phosphorylation of cation-chloride-coupled cotransporters via the STE20-related kinases, SPAK and OSR1. *J Biol Chem* 280: 42685–42693, 2005. doi:10.1074/jbc.M510042200.

496. Moriwaki Y, Yamamoto T, Tsutsumi Z, Takahashi S, Hada T. Effects of angiotensin II infusion on renal excretion of purine bases and oxypurinol. *Metabolism* 51: 893–895, 2002. doi:10.1053/meta.2002.32801.

497. Moriyama Y, Nelson N. The purified ATPase from chromaffin granule membranes is an anion-dependent proton pump. *J Biol Chem* 262: 9175–9180, 1987.

498. Morizane R, Bonventre JV. Generation of nephron progenitor cells and kidney organoids from human pluripotent stem cells. *Nat Protoc* 12: 195–207, 2017. doi:10.1038/nprot.2016.170.

499. Morris RG, Hoorn EJ, Knepper MA. Hypokalemia in a mouse model of Gitelman's syndrome. *Am J Physiol Renal Physiol* 290: F1416–F1420, 2006. doi:10.1152/ajprenal.00421.2005.

500. Moulin F, Ponte B, Pruijm M, Ackermann D, Bouatou Y, Guessous I, Ehret G, Bonny O, Pechère-Bertschi A, Staessen JA, Paccaud F, Martin P-Y, Burnier M, Vogt B, Devuyst O, Bochud M. A population-based approach to assess the heritability and distribution of renal handling of electrolytes. *Kidney Int* 92: 1536–1543, 2017. doi:10.1016/j.kint.2017.06.020.

501. Moulin P, Igarashi T, Van der Smissen P, Cosyns J-P, Verroust P, Thakker RV, Scheinman SJ, Courtoy PJ, Devuyst O. Altered polarity and expression of H^+-ATPase without ultrastructural changes in kidneys of Dent's disease patients. *Kidney Int* 63: 1285–1295, 2003. doi:10.1046/j.1523-1755.2003.00851.x.

502. Mount DB. Molecular physiology and the four-component model of renal urate transport. *Curr Opin Nephrol Hypertens* 14: 460–463, 2005. doi:10.1097/01.mnh.0000170749.10785.04.

503. Mount DB. The kidney in hyperuricemia and gout. *Curr Opin Nephrol Hypertens* 22: 216–223, 2013. doi:10.1097/MNH.0b013e32835ddad2.

504. Muff R, Nemeth EF, Haller-Brem S, Fischer JA. Regulation of hormone secretion and cytosolic Ca^{2+} by extracellular Ca^{2+} in parathyroid cells and C-cells: role of voltage-sensitive Ca^{2+} channels. *Arch Biochem Biophys* 265: 128–135, 1988. doi:10.1016/0003-9861(88)90378-5.

505. Murayama A, Takeyama K, Kitanaka S, Kodera Y, Kawaguchi Y, Hosoya T, Kato S. Positive and negative regulations of the renal 25-hydroxyvitamin D_3 1alpha-hydroxylase gene by parathyroid hormone, calcitonin, and 1alpha,25$(OH)_2D_3$ in intact animals. *Endocrinology* 140: 2224–2231, 1999. doi:10.1210/endo.140.5.6691.

506. Murer H, Hopfer U, Kinne R. Sodium/proton antiport in brush-border-membrane vesicles isolated from rat small intestine and kidney. *Biochem J* 154: 597–604, 1976. doi:10.1042/bj1540597.

507. Mutig K, Kahl T, Saritas T, Godes M, Persson P, Bates J, Raffi H, Rampoldi L, Uchida S, Hille C, Dosche C, Kumar S, Castañeda-Bueno M, Gamba G, Bachmann S. Activation of the bumetanide-sensitive Na^+,K^+,$2Cl^-$ cotransporter (NKCC2) is facilitated by Tamm-Horsfall protein in a chloride-sensitive manner. *J Biol Chem* 286: 30200–30210, 2011. doi:10.1074/jbc.M111.222968.

508. Nair AV, Hocher B, Verkaart S, van Zeeland F, Pfab T, Slowinski T, Chen Y-P, Schlingmann KP, Schaller A, Gallati S, Bindels RJ, Konrad M, Hoenderop JG. Loss of insulin-induced activation of TRPM6 magnesium channels results in impaired glucose tolerance during pregnancy. *Proc Natl Acad Sci USA* 109: 11324–11329, 2012. doi:10.1073/pnas.1113811109.

509. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 377: 644–657, 2017. doi:10.1056/NEJMoa1611925.

510. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mellström D, Oefjord ES, Marcinowska-Suchowierska E, Salmi J, Mulder H, Halse J, Sawicki AZ, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 344: 1434–1441, 2001. doi:10.1056/NEJM200105103441904.

511. Nemeth EF, Scarpa A. Rapid mobilization of cellular Ca^{2+} in bovine parathyroid cells evoked by extracellular divalent cations. Evidence for a cell surface calcium receptor. *J Biol Chem* 262: 5188–5196, 1987.

512. Nesbit MA, Hannan FM, Howles SA, Babinsky VN, Head RA, Cranston T, Rust N, Hobbs MR, Heath H III, Thakker RV. Mutations affecting G-protein subunit α11 in hypercalcemia and hypocalcemia. *N Engl J Med* 368: 2476–2486, 2013. doi:10.1056/NEJMoa1300253.

513. Nesbit MA, Hannan FM, Howles SA, Reed AAC, Cranston T, Thakker CE, Gregory L, Rimmer AJ, Rust N, Graham U, Morrison PJ, Hunter SJ, Whyte MP, McVean G, Buck D, Thakker RV. Mutations in AP2S1 cause familial hypocalciuric hypercalcemia type 3. *Nat Genet* 45: 93–97, 2013. doi:10.1038/ng.2492.

514. Nesterov V, Krueger B, Bertog M, Dahlmann A, Palmisano R, Korbmacher C. In Liddle Syndrome, Epithelial Sodium Channel Is Hyperactive Mainly in the Early Part of the Aldosterone-Sensitive Distal Nephron. *Hypertension* 67: 1256–1262, 2016. doi:10.1161/HYPERTENSIONAHA.115.07061.

515. Nesterova G, Gahl W. Nephropathic cystinosis: late complications of a multisystemic disease. *Pediatr Nephrol* 23: 863–878, 2008. doi:10.1007/s00467-007-0650-8.

516. Neusch C, Rozengurt N, Jacobs RE, Lester HA, Kofuji P. Kir4.1 potassium channel subunit is crucial for oligodendrocyte development and in vivo myelination. *J Neurosci* 21: 5429–5438, 2001. doi:10.1523/JNEUROSCI.21-15-05429.2001.

516a. Nichols CG, Lopatin AN. Inward rectifier potassium channels. *Annu Rev Physiol* 59: 171–191, 1997. doi:10.1146/annurev.physiol.59.1.171.

517. Nicholson JC, Jones CL, Powell HR, Walker RG, McCredie DA. Familial hypomagnesaemia--hypercalciuria leading to end-stage renal failure. *Pediatr Nephrol* 9: 74–76, 1995. doi:10.1007/BF00858976.

518. Nicolet-Barousse L, Blanchard A, Roux C, Pietri L, Bloch-Faure M, Kolta S, Chappard C, Geoffroy V, Morieux C, Jeunemaitre X, Shull GE, Meneton P, Paillard M, Houillier P, De Vernejoul M-C. Inactivation of the Na-Cl co-transporter (NCC) gene is associated with high BMD through both renal and bone mechanisms: analysis of patients with Gitelman syndrome and Ncc null mice. *J Bone Miner Res* 20: 799–808, 2005. doi:10.1359/JBMR.041238.

519. Nielsen R, Christensen EI, Birn H. Megalin and cubilin in proximal tubule protein reabsorption: from experimental models to human disease. *Kidney Int* 89: 58–67, 2016. doi:10.1016/j.kint.2015.11.007.

520. Nielsen R, Christensen EI. Proteinuria and events beyond the slit. *Pediatr Nephrol* 25: 813–822, 2010. doi:10.1007/s00467-009-1381-9.

521. Nielsen R, Courtoy PJ, Jacobsen C, Dom G, Lima WR, Jadot M, Willnow TE, Devuyst O, Christensen EI. Endocytosis provides a major alternative pathway for lysosomal biogenesis in kidney proximal tubular cells. *Proc Natl Acad Sci USA* 104: 5407–5412, 2007. doi:10.1073/pnas.0700330104.

522. Nijenhuis T, Hoenderop JGJ, Loffing J, van der Kemp AWCM, van Os CH, Bindels RJM. Thiazide-induced hypocalciuria is accompanied by a decreased expression of Ca^{2+} transport proteins in kidney. *Kidney Int* 64: 555–564, 2003. doi:10.1046/j.1523-1755.2003.00128.x.

523. Nijenhuis T, Renkema KY, Hoenderop JGJ, Bindels RJM. Acid-base status determines the renal expression of Ca^{2+} and Mg^{2+} transport proteins. *J Am Soc Nephrol* 17: 617–626, 2006. doi:10.1681/ASN.2005070732.

524. Nijenhuis T, Vallon V, van der Kemp AWCM, Loffing J, Hoenderop JGJ, Bindels RJM. Enhanced passive Ca^{2+} reabsorption and reduced Mg^{2+} channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. *J Clin Invest* 115: 1651–1658, 2005. doi:10.1172/JCI24134.

525. Nishigori H, Yamada S, Kohama T, Utsugi T, Shimizu H, Takeuchi T, Takeda J. Mutations in the hepatocyte nuclear factor-1 alpha gene (MODY3) are not a major cause of early-onset non-insulin-dependent (type 2) diabetes mellitus in Japanese. *J Hum Genet* 43: 107–110, 1998. doi:10.1007/s100380050049.

526. Nissen PH, Christensen SE, Heickendorff L, Brixen K, Mosekilde L. Molecular genetic analysis of the calcium sensing receptor gene in patients clinically suspected to have familial hypocalciuric hypercalcemia: phenotypic variation and mutation spectrum in a Danish population. *J Clin Endocrinol Metab* 92: 4373–4379, 2007. doi:10.1210/jc.2007-0322.

527. Nomura N, Kamiya K, Ikeda K, Yui N, Chiga M, Sohara E, Rai T, Sakaki S, Uchida S. Treatment with 17-allylamino-17-demethoxygeldanamycin ameliorated symptoms of Bartter syndrome type IV caused by mutated Bsnd in mice. *Biochem Biophys Res Commun* 441: 544–549, 2013. doi:10.1016/j.bbrc.2013.10.129.

528. Nomura N, Tajima M, Sugawara N, Morimoto T, Kondo Y, Ohno M, Uchida K, Mutig K, Bachmann S, Soleimani M, Ohta E, Ohta A, Sohara E, Okado T, Rai T, Jentsch TJ, Sasaki S, Uchida S. Generation and analyses of R8L barttin knockin mouse. *Am J Physiol Renal Physiol* 301: F297–F307, 2011. doi:10.1152/ajprenal.00604.2010.

529. Novarino G, Weinert S, Rickheit G, Jentsch TJ. Endosomal chloride-proton exchange rather than chloride conductance is crucial for renal endocytosis. *Science* 328: 1398–1401, 2010. doi:10.1126/science.1188070.

530. Nozu K, Fu XJ, Nakanishi K, Yoshikawa N, Kaito H, Kanda K, Krol RP, Miyashita R, Kamitsuji H, Kanda S, Hayashi Y, Satomura K, Shimizu N, Iijima K, Matsuo M. Molec-

ular analysis of patients with type III Bartter syndrome: picking up large heterozygous deletions with semiquantitative PCR. *Pediatr Res* 62: 364–369, 2007. doi:10.1203/PDR.0b013e318123fb90.

531. Nozu K, Iijima K, Nozu Y, Ikegami E, Imai T, Fu XJ, Kaito H, Nakanishi K, Yoshikawa N, Matsuo M. A deep intronic mutation in the SLC12A3 gene leads to Gitelman syndrome. *Pediatr Res* 66: 590–593, 2009. doi:10.1203/PDR.0b013e3181b9b4d3.

532. Nozu K, Inagaki T, Fu XJ, Nozu Y, Kaito H, Kanda K, Sekine T, Igarashi T, Nakanishi K, Yoshikawa N, Iijima K, Matsuo M. Molecular analysis of digenic inheritance in Bartter syndrome with sensorineural deafness. *J Med Genet* 45: 182–186, 2007. doi:10.1136/jmg.2007.052944.

533. O'Seaghdha CM, Wu H, Yang Q, Kapur K, Guessous I, Zuber AM, Köttgen A, Stoudmann C, Teumer A, Kutalik Z, Mangino M, Dehghan A, Zhang W, Eiriksdottir G, Li G, Tanaka T, Portas L, Lopez LM, Hayward C, Lohman K, Matsuda K, Padmanabhan S, Firsov D, Sorice R, Ulivi S, Brockhaus AC, Kleber ME, Mahajan A, Ernst FD, Gudnason V, Launer LJ, Macé A, Boerwinckle E, Arking DE, Tanikawa C, Nakamura Y, Brown MJ, Gaspoz J-M, Theler J-M, Siscovick DS, Psaty BM, Bergmann S, Vollenweider P, Vitart V, Wright AF, Zemunik T, Boban M, Kolcic I, Navarro P, Brown EM, Estrada K, Ding J, Harris TB, Bandinelli S, Hernandez D, Singleton AB, Girotto G, Ruggiero D, d'Adamo AP, Robino A, Meitinger T, Meisinger C, Davies G, Starr JM, Chambers JC, Boehm BO, Winkelmann BR, Huang J, Murgia F, Wild SH, Campbell H, Morris AP, Franco OH, Hofman A, Uitterlinden AG, Rivadeneira F, Völker U, Hannemann A, Biffar R, Hoffmann W, Shin S-Y, Lescuyer P, Henry H, Schurmann C, Munroe PB, Gasparini P, Pirastu N, Ciullo M, Gieger C, März W, Lind L, Spector TD, Smith AV, Rudan I, Wilson JF, Polašek O, Deary IJ, Pirastu M, Ferrucci L, Liu Y, Kestenbaum B, Kooner JS, Witteman JCM, Nauck M, Kao WHL, Wallaschofski H, Bonny O, Fox CS, Bochud M; SUNLIGHT Consortium; GEFOS Consortium. Meta-analysis of genome-wide association studies identifies six new Loci for serum calcium concentrations. *PLoS Genet* 9: e1003796, 2013. doi:10.1371/journal.pgen.1003796.

534. O'Shaughnessy KM, Fu B, Johnson A, Gordon RD. Linkage of Gordon's syndrome to the long arm of chromosome 17 in a region recently linked to familial essential hypertension. *J Hum Hypertens* 12: 675–678, 1998. doi:10.1038/sj.jhh.1000705.

535. Oberfield SE, Levine LS, Carey RM, Bejar R, New MI. Pseudohypoaldosteronism: multiple target organ unresponsiveness to mineralocorticoid hormones. *J Clin Endocrinol Metab* 48: 228–234, 1979. doi:10.1210/jcem-48-2-228.

536. Oda Y, Tu CL, Chang W, Crumrine D, Kömüves L, Mauro T, Elias PM, Bikle DD. The calcium sensing receptor and its alternatively spliced form in murine epidermal differentiation. *J Biol Chem* 275: 1183–1190, 2000. doi:10.1074/jbc.275.2.1183.

537. Oemar BS, Byrd DJ, Brodehl J. Complete absence of tubular glucose reabsorption: a new type of renal glucosuria (type 0). *Clin Nephrol* 27: 156–160, 1987.

538. Ohlsson A, Sieck U, Cumming W, Akhtar M, Serenius F. A variant of Bartter's syndrome. Bartter's syndrome associated with hydramnios, prematurity, hypercalciuria and nephrocalcinosis. *Acta Paediatr Scand* 73: 868–874, 1984. doi:10.1111/j.1651-2227.1984.tb17793.x.

539. Ohta A, Schumacher F-R, Mehellou Y, Johnson C, Knebel A, Macartney TJ, Wood NT, Alessi DR, Kurz T. The CUL3-KLHL3 E3 ligase complex mutated in Gordon's hypertension syndrome interacts with and ubiquitylates WNK isoforms: disease-causing mutations in KLHL3 and WNK4 disrupt interaction. *Biochem J* 451: 111–122, 2013. doi:10.1042/BJ20121903.

540. Ohta A, Yang S-S, Rai T, Chiga M, Sasaki S, Uchida S. Overexpression of human WNK1 increases paracellular chloride permeability and phosphorylation of claudin-4 in MDCKII cells. *Biochem Biophys Res Commun* 349: 804–808, 2006. doi:10.1016/j.bbrc.2006.08.101.

541. Ohta T, Sakano T, Ogawa T, Kato J, Awaya Y, Kihara H, Kinoshita Y. Exercise-induced acute renal failure with renal hypouricemia: a case report and a review of the literature. *Clin Nephrol* 58: 313–316, 2002. doi:10.5414/CNP58313.

542. Okada Y, Sim X, Go MJ, Wu J-Y, Gu D, Takeuchi F, Takahashi A, Maeda S, Tsunoda T, Chen P, Lim S-C, Wong T-Y, Liu J, Young TL, Aung T, Seielstad M, Teo Y-Y, Kim YJ, Lee J-Y, Han B-G, Kang D, Chen C-H, Tsai F-J, Chang L-C, Fann S-JC, Mei H, Rao DC, Hixson JE, Chen S, Katsuya T, Isono M, Ogihara T, Chambers JC, Zhang W, Kooner JS, Albrecht E, Yamamoto K, Kubo M, Nakamura Y, Kamatani N, Kato N, He J, Chen Y-T, Cho YS, Tai E-S, Tanaka T; KidneyGen Consortium; CKDGen Consortium; GUGC consortium. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. *Nat Genet* 44: 904–909, 2012. doi:10.1038/ng.2352.

543. Olesen ETB, Fenton RA. Aquaporin-2 membrane targeting: still a conundrum. *Am J Physiol Renal Physiol* 312: F744–F747, 2017. doi:10.1152/ajprenal.00010.2017.

544. Olinger E, Houillier P, Devuyst O. Claudins: a tale of interactions in the thick ascending limb. *Kidney Int* 93: 535–537, 2018. doi:10.1016/j.kint.2017.09.032.

545. Ottosson-Laakso E, Tuomi T, Forsén B, Gullström M, Groop P-H, Groop L, Vikman P. Influence of Familial Renal Glycosuria Due to Mutations in the SLC5A2 Gene on Changes in Glucose Tolerance over Time. *PLoS One* 11: e0146114, 2016. doi:10.1371/journal.pone.0146114.

546. Pacheco-Alvarez D, Cristóbal PS, Meade P, Moreno E, Vázquez N, Muñoz E, Díaz A, Juárez ME, Giménez I, Gamba G. The Na^+:Cl^- cotransporter is activated and phosphorylated at the amino-terminal domain upon intracellular chloride depletion. *J Biol Chem* 281: 28755–28763, 2006. doi:10.1074/jbc.M603773200.

547. Padmanabhan S, Melander O, Johnson T, Di Blasio AM, Lee WK, Gentilini D, Hastie CE, Menni C, Monti MC, Delles C, Laing S, Corso B, Navis G, Kwakernaak AJ, van der Harst P, Bochud M, Maillard M, Burnier M, Hedner T, Kjeldsen S, Wahlstrand B, Sjögren M, Fava C, Montagnana M, Danese E, Torffvit O, Hedblad B, Snieder H, Connell JMC, Brown M, Samani NJ, Farrall M, Cesana G, Mancia G, Signorini S, Grassi G, Eyheramendy S, Wichmann H-E, Laan M, Strachan DP, Sever P, Shields DC, Stanton A, Vollenweider P, Teumer A, Völzke H, Rettig R, Newton-Cheh C, Arora P, Zhang F, Soranzo N, Spector TD, Lucas G, Kathiresan S, Siscovick DS, Luan J, Loos RJF, Wareham NJ, Penninx BW, Nolte IM, McBride M, Miller WH, Nicklin SA, Baker AH, Graham D, McDonald RA, Pell JP, Sattar N, Welsh P, Munroe P, Caulfield MJ, Zanchetti A, Dominiczak AF; Global BPgen Consortium. Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. *PLoS Genet* 6: e1001177, 2010. doi:10.1371/journal.pgen.1001177.

548. Paganoni S, Schwarzschild MA. Urate as a Marker of Risk and Progression of Neurodegenerative Disease. *Neurotherapeutics* 14: 148–153, 2017. doi:10.1007/s13311-016-0497-4.

549. Parker MD, Boron WF. The divergence, actions, roles, and relatives of sodium-coupled bicarbonate transporters. *Physiol Rev* 93: 803–959, 2013. doi:10.1152/physrev.00023.2012.

550. Parrock S, Hussain S, Issler N, Differ A-M, Lench N, Guarino S, Oosterveld MJS, Keijzer-Veen M, Brilstra E, van Wieringen H, Konijnenberg AY, Amin-Rasip S, Dumitriu S, Klootwijk E, Knoers N, Bockenhauer D, Kleta R, Zdebik AA. KCNJ10 mutations display differential sensitivity to heteromerisation with KCNJ16. *Nephron Physiol* 123: 7–14, 2013. doi:10.1159/000356353.

551. Parving H-H, Lambers-Heerspink H, de Zeeuw D. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 375: 1800–1801, 2016. doi:10.1056/NEJMc1611290.

552. Paterson CR, Gunn A. Familial benign hypercalcaemia. *Lancet* 318: 61–63, 1981. doi:10.1016/S0140-6736(81)90410-4.

553. Pattaro C, Teumer A, Gorski M, Chu AY, Li M, Mijatovic V, Garnaas M, Tin A, Sorice R, Li Y, Taliun D, Olden M, Foster M, Yang Q, Chen M-H, Pers TH, Johnson AD, Ko Y-A, Fuchsberger C, Tayo B, Nalls M, Feitosa MF, Isaacs A, Dehghan A, d'Adamo P, Adeyemo A, Dieffenbach AK, Zonderman AB, Nolte IM, van der Most PJ, Wright AF, Shuldiner AR, Morrison AC, Hofman A, Smith AV, Dreisbach AW, Franke A, Uitterlinden AG, Metspalu A, Tönjes A, Lupo A, Robino A, Johansson Å, Demirkan A, Kollerits B, Freedman BI, Ponte B, Oostra BA, Paulweber B, Krämer BK, Mitchell BD, Buckley BM, Peralta CA, Hayward C, Helmer C, Rotimi CN, Shaffer CM, Müller C, Sala C, van Duijn CM, Saint-Pierre A, Ackermann D, Shriner D, Ruggiero D, Toniolo D, Lu Y, Cusi D, Czamara D, Ellinghaus D, Siscovick DS, Ruderfer D, Gieger C, Grallert H, Rochtchina E, Atkinson EJ, Holliday EG, Boerwinkle E, Salvi E, Bottinger EP, Murgia F, Rivadeneira F, Ernst F, Kronenberg F, Hu FB, Navis GJ, Curhan GC, Ehret GB, Homuth G, Coassin S, Thun GA, Pistis G, Gambaro G, Malerba G, Montgomery GW, Eiriksdottir G, Jacobs G, Li G, Wichmann H-E, Campbell H, Schmidt H, Wallaschofski H, Völzke H, Brenner H, Kroemer HK, Kramer H, Lin H, Leach IM, Ford I, Guessous I, Rudan I, Prokopenko I, Borecki I, Heid IM, Kolcic I, Persico I, Jukema JW, Wilson JF, Felix JF, Divers J, Lambert J-C, Stafford JM, Gaspoz J-M, Smith JA, Faul JD, Wang JJ, Ding J, Hirschhorn JN, Attia J, Whitfield JB, Chalmers J, Viikari J, Coresh J, Denny JC, Karjalainen J, Fernandes JK, Endlich K, Butterbach K, Keene KL, Lohman K, Portas L, Launer LJ, Lyytikäinen L-P, Yengo L, Franke L, Ferrucci L, Rose LM, Kedenko L, Rao M, Struchalin M, Kleber ME, Cavalieri M, Haun M, Cornelis MC, Ciullo M, Pirastu M, de Andrade M, McEvoy MA, Woodward M, Adam M, Cocca M, Nauck M, Imboden M, Waldenberger M, Pruijm M, Metzger M, Stumvoll M, Evans MK, Sale MM, Kähönen M, Boban M, Bochud M, Rheinberger M, Verweij N, Bouatia-Naji N, Martin NG, Hastie N, Probst-Hensch N, Soranzo N, Devuyst O, Raitakari O, Gottesman O, Franco OH, Polašek O, Gasparini P, Munroe PB, Ridker PM, Mitchell P, Muntner P, Meisinger C, Smit JH, Kovacs P, Wild PS, Froguel P, Rettig R, Mägi R,

Biffar R, Schmidt R, Middelberg RPS, Carroll RJ, Penninx BW, Scott RJ, Katz R, Sedaghat S, Wild SH, Kardia SLR, Ulivi S, Hwang S-J, Enroth S, Kloiber S, Trompet S, Stengel B, Hancock SJ, Turner ST, Rosas SE, Stracke S, Harris TB, Zeller T, Zemunik T, Lehtimäki T, Illig T, Aspelund T, Nikopensius T, Esko T, Tanaka T, Gyllensten U, Völker U, Emilsson V, Vitart V, Aalto V, Gudnason V, Chouraki V, Chen WM, Igl W, März W, Koenig W, Lieb W, Loos RJ, Liu Y, Snieder H, Pramstaller PP, Parsa A, O'Connell JR, Susztak K, Hamet P, Tremblay J, de Boer IH, Böger CA, Goessling W, Chasman DI, Köttgen A, Kao WH, Fox CS; ICBP Consortium; AGEN Consortium; CARDIOGRAM; CHARGe-Heart Failure Group; ECHOGen Consortium. Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. *Nat Commun* 7: 10023, 2016. doi:10.1038/ncomms10023.

554. Paulais M, Bloch-Faure M, Picard N, Jacques T, Ramakrishnan SK, Keck M, Sohet F, Eladari D, Houillier P, Lourdel S, Teulon J, Tucker SJ. Renal phenotype in mice lacking the Kir5.1 (Kcnj16) K^+ channel subunit contrasts with that observed in SeSAME/EAST syndrome. *Proc Natl Acad Sci USA* 108: 10361–10366, 2011. doi:10.1073/pnas.1101400108.

555. Paunier L, Radde IC, Kooh SW, Conen PE, Fraser D. Primary hypomagnesemia with secondary hypocalcemia in an infant. *Pediatrics* 41: 385–402, 1968.

556. Paver WK, Pauline GJ. Hypertension and hyperpotassaemia without renal disease in a young male. *Med J Aust* 2: 305–306, 1964.

557. Pearce S. Extracellular "calcistat" in health and disease. *Lancet* 353: 83–84, 1999. doi:10.1016/S0140-6736(05)76148-1.

558. Pearce SH, Bai M, Quinn SJ, Kifor O, Brown EM, Thakker RV. Functional characterization of calcium-sensing receptor mutations expressed in human embryonic kidney cells. *J Clin Invest* 98: 1860–1866, 1996. doi:10.1172/JCI118987.

559. Pearce SH, Williamson C, Kifor O, Bai M, Coulthard MG, Davies M, Lewis-Barned N, McCredie D, Powell H, Kendall-Taylor P, Brown EM, Thakker RV. A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calcium-sensing receptor. *N Engl J Med* 335: 1115–1122, 1996. doi:10.1056/NEJM199610103351505.

560. Pech V, Kim YH, Weinstein AM, Everett LA, Pham TD, Wall SM. Angiotensin II increases chloride absorption in the cortical collecting duct in mice through a pendrin-dependent mechanism. *Am J Physiol Renal Physiol* 292: F914–F920, 2007. doi:10.1152/ajprenal.00361.2006.

561. Perrier R, Boscardin E, Malsure S, Sergi C, Maillard MP, Loffing J, Loffing-Cueni D, Sørensen MV, Koesters R, Rossier BC, Frateschi S, Hummler E. Severe Salt-Losing Syndrome and Hyperkalemia Induced by Adult Nephron-Specific Knockout of the Epithelial Sodium Channel α-Subunit. *J Am Soc Nephrol* 27: 2309–2318, 2016. doi:10.1681/ASN.2015020154.

562. Perry YM, Finegold DN, Armitage MM, Ferell R. A missense mutation in the Ca-sensing receptor gene causes familial autosomal dominant hypoparathyroidism. *Am J Hum Genet* 55 Suppl: A17, 1994.

563. Peters M, Ermert S, Jeck N, Derst C, Pechmann U, Weber S, Schlingmann KP, Seyberth HW, Waldegger S, Konrad M. Classification and rescue of ROMK mutations underlying hyperprostaglandin E syndrome/antenatal Bartter syndrome. *Kidney Int* 64: 923–932, 2003. doi:10.1046/j.1523-1755.2003.00153.x.

564. Peters M, Jeck N, Reinalter S, Leonhardt A, Tönshoff B, Klaus G, Konrad M, Seyberth HW. Clinical presentation of genetically defined patients with hypokalemic salt-losing tubulopathies. *Am J Med* 112: 183–190, 2002. doi:10.1016/S0002-9343(01)01086-5.

565. Phipson B, Er PX, Combes AN, Forbes TA, Howden SE, Zappia L, Yen H-J, Lawlor KT, Hale LJ, Sun J, Wolvetang E, Takasato M, Oshlack A, Little MH. Evaluation of variability in human kidney organoids. *Nat Methods* 16: 79–87, 2019. doi:10.1038/s41592-018-0253-2.

566. Piala AT, Moon TM, Akella R, He H, Cobb MH, Goldsmith EJ. Chloride sensing by WNK1 involves inhibition of autophosphorylation. *Sci Signal* 7: ra41, 2014. doi:10.1126/scisignal.2005050.

567. Picollo A, Pusch M. Chloride/proton antiporter activity of mammalian CLC proteins ClC-4 and ClC-5. *Nature* 436: 420–423, 2005. doi:10.1038/nature03720.

568. Pidasheva S, D'Souza-Li L, Canaff L, Cole DEC, Hendy GN. CASRdb: calcium-sensing receptor locus-specific database for mutations causing familial (benign) hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia. *Hum Mutat* 24: 107–111, 2004. doi:10.1002/humu.20067.

569. Pidasheva S, Grant M, Canaff L, Ercan O, Kumar U, Hendy GN. Calcium-sensing receptor dimerizes in the endoplasmic reticulum: biochemical and biophysical characterization of CASR mutants retained intracellularly. *Hum Mol Genet* 15: 2200–2209, 2006. doi:10.1093/hmg/ddl145.

570. Piwon N, Günther W, Schwake M, Bösl MR, Jentsch TJ. ClC-5 Cl^--channel disruption impairs endocytosis in a mouse model for Dent's disease. *Nature* 408: 369–373, 2000. doi:10.1038/35042597.

571. Plans V, Rickheit G, Jentsch TJ. Physiological roles of CLC Cl^-/H^+ exchangers in renal proximal tubules. *Pflugers Arch* 458: 23–37, 2009. doi:10.1007/s00424-008-0597-z.

572. Pollak MR, Brown EM, Chou Y-HW, Hebert SC, Marx SJ, Steinmann B, Levi T, Seidman CE, Seidman JG. Mutations in the human Ca(2+)-sensing receptor gene cause familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. *Cell* 75: 1297–1303, 1993. doi:10.1016/0092-8674(93)90617-Y.

573. Pollak MR, Brown EM, Estep HL, McLaine PN, Kifor O, Park J, Hebert SC, Seidman CE, Seidman JG. Autosomal dominant hypocalcaemia caused by a Ca(2+)-sensing receptor gene mutation. *Nat Genet* 8: 303–307, 1994. doi:10.1038/ng1194-303.

574. Pontoglio M, Barra J, Hadchouel M, Doyen A, Kress C, Bach JP, Babinet C, Yaniv M. Hepatocyte nuclear factor 1 inactivation results in hepatic dysfunction, phenylketonuria, and renal Fanconi syndrome. *Cell* 84: 575–585, 1996. doi:10.1016/S0092-8674(00)81033-8.

575. Porrmann J, Betcheva-Krajcir E, Di Donato N, Kahlert A-K, Schallner J, Rump A, Schröck E, Dobritzsch D, Roelofsen J, van Kuilenburg ABP, Tzschach A. Novel PRPS1 gain-of-function mutation in a patient with congenital hyperuricemia and facial anomalies. *Am J Med Genet A* 173: 2736–2742, 2017. doi:10.1002/ajmg.a.38359.

576. Pradervand S, Barker PM, Wang Q, Ernst SA, Beermann F, Grubb BR, Burnier M, Schmidt A, Bindels RJ, Gatzy JT, Rossier BC, Hummler E. Salt restriction induces pseudohypoaldosteronism type 1 in mice expressing low levels of the beta-subunit of the amiloride-sensitive epithelial sodium channel. *Proc Natl Acad Sci USA* 96: 1732–1737, 1999. doi:10.1073/pnas.96.4.1732.

577. Praga M, Vara J, González-Parra E, Andrés A, Alamo C, Araque A, Ortiz A, Rodicio JL. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. *Kidney Int* 47: 1419–1425, 1995. doi:10.1038/ki.1995.199.

578. Prange JA, Bieri M, Segerer S, Burger C, Kaech A, Moritz W, Devuyst O. Human proximal tubule cells form functional microtissues. *Pflugers Arch* 468: 739–750, 2016. doi:10.1007/s00424-015-1771-8.

579. Preitner F, Bonny O, Laverrière A, Rotman S, Firsov D, Da Costa A, Metref S, Thorens B. Glut9 is a major regulator of urate homeostasis and its genetic inactivation induces hyperuricosuria and urate nephropathy. *Proc Natl Acad Sci USA* 106: 15501–15506, 2009. doi:10.1073/pnas.0904411106.

580. Pressler CA, Heinzinger J, Jeck N, Waldegger P, Pechmann U, Reinalter S, Konrad M, Beetz R, Seyberth HW, Waldegger S. Late-onset manifestation of antenatal Bartter syndrome as a result of residual function of the mutated renal Na^+-K^+-$2Cl^-$ co-transporter. *J Am Soc Nephrol* 17: 2136–2142, 2006. doi:10.1681/ASN.2005101071.

581. Procino G, Mastrofrancesco L, Tamma G, Lasorsa DR, Ranieri M, Stringini G, Emma F, Svelto M, Valenti G. Calcium-sensing receptor and aquaporin 2 interplay in hypercalciuria-associated renal concentrating defect in humans. An in vivo and in vitro study. *PLoS One* 7: e33145, 2012. doi:10.1371/journal.pone.0033145.

582. Proesmans W, Devlieger H, Van Assche A, Eggermont E, Vandenberghe K, Lemmens F, Sieprath P, Lijnen P. Bartter syndrome in two siblings--antenatal and neonatal observations. *Int J Pediatr Nephrol* 6: 63–70, 1985.

583. Proesmans W. Bartter syndrome and its neonatal variant. *Eur J Pediatr* 156: 669–679, 1997. doi:10.1007/s004310050688.

584. Pu HX, Cluzeaud F, Goldshleger R, Karlish SJ, Farman N, Blostein R. Functional role and immunocytochemical localization of the gamma a and gamma b forms of the Na,K-ATPase gamma subunit. *J Biol Chem* 276: 20370–20378, 2001. doi:10.1074/jbc.M010836200.

585. Pujo L, Fagart J, Gary F, Papadimitriou DT, Claës A, Jeunemaître X, Zennaro M-C. Mineralocorticoid receptor mutations are the principal cause of renal type 1 pseudohypoaldosteronism. *Hum Mutat* 28: 33–40, 2007. doi:10.1002/humu.20371.

586. Punzi L, Calò L, Schiavon F, Pianon M, Rosada M, Todesco S. Chondrocalcinosis is a feature of Gitelman's variant of Bartter's syndrome. A new look at the hypomagnesemia associated with calcium pyrophosphate dihydrate crystal deposition disease. *Rev Rhum Engl Ed* 65: 571–574, 1998.

587. Quamme GA, de Rouffignac C. Epithelial magnesium transport and regulation by the kidney. *Front Biosci* 5: D694–D711, 2000. doi:10.2741/A544.

588. Quamme GA. Control of magnesium transport in the thick ascending limb. *Am J Physiol Renal Fluid Electrolyte Physiol* 256: F197–F210, 1989. doi:10.1152/ajprenal.1989.256.2.F197.

589. Rafey MA, Lipkowitz MS, Leal-Pinto E, Abramson RG. Uric acid transport. *Curr Opin Nephrol Hypertens* 12: 511–516, 2003. doi:10.1097/00041552-200309000-00005.

590. Rafiqi FH, Zuber AM, Glover M, Richardson C, Fleming S, Jovanović S, Jovanović A, O'Shaughnessy KM, Alessi DR. Role of the WNK-activated SPAK kinase in regulating blood pressure. *EMBO Mol Med* 2: 63–75, 2010. doi:10.1002/emmm.200900058.

591. Raggi C, Luciani A, Nevo N, Antignac C, Terryn S, Devuyst O. Dedifferentiation and aberrations of the endolysosomal compartment characterize the early stage of nephropathic cystinosis. *Hum Mol Genet* 23: 2266–2278, 2014. doi:10.1093/hmg/ddt617.

592. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. *Diabetes* 54: 3427–3434, 2005. doi:10.2337/diabetes.54.12.3427.

593. Ramsey IS, Delling M, Clapham DE. An introduction to TRP channels. *Annu Rev Physiol* 68: 619–647, 2006. doi:10.1146/annurev.physiol.68.040204.100431.

594. Reed AAC, Loh NY, Terryn S, Lippiat JD, Partridge C, Galvanovskis J, Williams SE, Jouret F, Wu FTF, Courtoy PJ, Nesbit MA, Rorsman P, Devuyst O, Ashcroft FM, Thakker RV. CLC-5 and KIF3B interact to facilitate CLC-5 plasma membrane expression, endocytosis, and microtubular transport: relevance to pathophysiology of Dent's disease. *Am J Physiol Renal Physiol* 298: F365–F380, 2010. doi:10.1152/ajprenal.00038.2009.

595. Reeders ST, Breuning MH, Davies KE, Nicholls RD, Jarman AP, Higgs DR, Pearson PL, Weatherall DJ. A highly polymorphic DNA marker linked to adult polycystic kidney disease on chromosome 16. *Nature* 317: 542–544, 1985. doi:10.1038/317542a0.

596. Reichold M, Klootwijk ED, Reinders J, Otto EA, Milani M, Broeker C, Laing C, Wiesner J, Devi S, Zhou W, Schmitt R, Tegtmeier I, Sterner C, Doellerer H, Renner K, Oefner PJ, Dettmer K, Simbuerger JM, Witzgall R, Stanescu HC, Dumitriu S, Iancu D, Patel V, Mozere M, Tekman M, Jaureguiberry G, Issler N, Kesselheim A, Walsh SB, Gale DP, Howie AJ, Martins JR, Hall AM, Kasgharian M, O'Brien K, Ferreira CR, Atwal PS, Jain M, Hammers A, Charles-Edwards G, Choe C-U, Isbrandt D, Cebrian-Serrano A, Davies B, Sandford RN, Pugh C, Konecki DS, Povey S, Bockenhauer D, Lichter-Konecki U, Gahl WA, Unwin RJ, Warth R, Kleta R. Glycine Amidinotransferase (GATM), Renal Fanconi Syndrome, and Kidney Failure. *J Am Soc Nephrol* 29: 1849–1858, 2018. doi:10.1681/ASN.2017111179.

597. Reichold M, Zdebik AA, Lieberer E, Rapedius M, Schmidt K, Bandulik S, Sterner C, Tegtmeier I, Penton D, Baukrowitz T, Hulton S-A, Witzgall R, Ben-Zeev B, Howie AJ, Kleta R, Bockenhauer D, Warth R. KCNJ10 gene mutations causing EAST syndrome (epilepsy, ataxia, sensorineural deafness, and tubulopathy) disrupt channel function. *Proc Natl Acad Sci USA* 107: 14490–14495, 2010. doi:10.1073/pnas.1003072107.

598. Reinalter S, Devlieger H, Proesmans W. Neonatal Bartter syndrome: spontaneous resolution of all signs and symptoms. *Pediatr Nephrol* 12: 186–188, 1998. doi:10.1007/s004670050433.

599. Reinalter SC, Gröne HJ, Konrad M, Seyberth HW, Klaus G. Evaluation of long-term treatment with indomethacin in hereditary hypokalemic salt-losing tubulopathies. *J Pediatr* 139: 398–406, 2001. doi:10.1067/mpd.2001.117007.

600. Reissinger A, Ludwig M, Utsch B, Prömse A, Baulmann J, Weisser B, Vetter H, Kramer HJ, Bokemeyer D. Novel NCCT gene mutations as a cause of Gitelman's syndrome and a systematic review of mutant and polymorphic NCCT alleles. *Kidney Blood Press Res* 25: 354–362, 2002. doi:10.1159/000068695.

601. Renkema KY, Bindels RJM, Hoenderop JGJ. Role of the calcium-sensing receptor in reducing the risk for calcium stones. *Clin J Am Soc Nephrol* 6: 2076–2082, 2011. doi:10.2215/CJN.00480111.

602. Reubi FC. Glucose titration in renal glucosuria. In: *Ciba Foundation Symposium: The Kidney*. New York: Wiley, 1954.

603. Riazuddin S, Anwar S, Fischer M, Ahmed ZM, Khan SY, Janssen AGH, Zafar AU, Scholl U, Husnain T, Belyantseva IA, Friedman PL, Riazuddin S, Friedman TB, Fahlke C. Molecular basis of DFNB73: mutations of BSND can cause nonsyndromic deafness or Bartter syndrome. *Am J Hum Genet* 85: 273–280, 2009. doi:10.1016/j.ajhg.2009.07.003.

604. Riccardi D, Hall AE, Chattopadhyay N, Xu JZ, Brown EM, Hebert SC. Localization of the extracellular Ca2+/polyvalent cation-sensing protein in rat kidney. *Am J Physiol Renal Physiol* 274: F611–F622, 1998. doi:10.1152/ajprenal.1998.274.3.F611.

605. Riccardi D, Lee WS, Lee K, Segre GV, Brown EM, Hebert SC. Localization of the extracellular Ca^{2+}-sensing receptor and PTH/PTHrP receptor in rat kidney. *Am J Physiol Renal Physiol* 271: F951–F956, 1996. doi:10.1152/ajprenal.1996.271.4.F951.

606. Riccardi D, Valenti G. Localization and function of the renal calcium-sensing receptor. *Nat Rev Nephrol* 12: 414–425, 2016. doi:10.1038/nrneph.2016.59.

607. Richardson C, Rafiqi FH, Karlsson HKR, Moleleki N, Vandewalle A, Campbell DG, Morrice NA, Alessi DR. Activation of the thiazide-sensitive Na^+-Cl^- cotransporter by the WNK-regulated kinases SPAK and OSR1. *J Cell Sci* 121: 675–684, 2008. doi:10.1242/jcs.025312.

608. Rickheit G, Maier H, Strenzke N, Andreescu CE, De Zeeuw CI, Muenscher A, Zdebik AA, Jentsch TJ. Endocochlear potential depends on Cl- channels: mechanism underlying deafness in Bartter syndrome IV. *EMBO J* 27: 2907–2917, 2008. doi:10.1038/emboj.2008.203.

609. Riepe FG, Finkeldei J, de Sanctis L, Einaudi S, Testa A, Karges B, Peter M, Viemann M, Grötzinger J, Sippell WG, Fejes-Toth G, Krone N. Elucidating the underlying molecular pathogenesis of NR3C2 mutants causing autosomal dominant pseudohypoaldosteronism type 1. *J Clin Endocrinol Metab* 91: 4552–4561, 2006. doi:10.1210/jc.2006-1161.

610. Riepe FG, van Bemmelen MXP, Cachat F, Plendl H, Gautschi I, Krone N, Holterhus P-M, Theintz G, Schild L. Revealing a subclinical salt-losing phenotype in heterozygous carriers of the novel S562P mutation in the alpha subunit of the epithelial sodium channel. *Clin Endocrinol (Oxf)* 70: 252–258, 2009. doi:10.1111/j.1365-2265.2008.03314.x.

611. Riepe FG. Clinical and molecular features of type I pseudohypoaldosteronism. *Horm Res* 72: 1–9, 2009. doi:10.1159/000224334.

612. Rieselbach RE, Steele TH. Influence of the kidney upon urate homeostasis in health and disease. *Am J Med* 56: 665–675, 1974. doi:10.1016/0002-9343(74)90633-0.

613. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL, et. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 245: 1066–1073, 1989. doi:10.1126/science.2475911.

614. Riveira-Munoz E, Chang Q, Godefroid N, Hoenderop JG, Bindels RJ, Dahan K, Devuyst O; Belgian Network for Study of Gitelman Syndrome. Transcriptional and functional analyses of SLC12A3 mutations: new clues for the pathogenesis of Gitelman syndrome. *J Am Soc Nephrol* 18: 1271–1283, 2007. doi:10.1681/ASN.2006101095.

615. Riveira-Munoz E, Devuyst O, Belge H, Jeck N, Strompf L, Vargas-Poussou R, Jeunemaître X, Blanchard A, Knoers NV, Konrad M, Dahan K. Evaluating PVALB as a candidate gene for SLC12A3-negative cases of Gitelman's syndrome. *Nephrol Dial Transplant* 23: 3120–3125, 2008. doi:10.1093/ndt/gfn229.

616. Rizzo F, Staub O. NEDD4-2 and salt-sensitive hypertension. *Curr Opin Nephrol Hypertens* 24: 111–116, 2015. doi:10.1097/MNH.0000000000000097.

617. Roch-Ramel F, Guisan B, Diezi J. Effects of uricosuric and antiuricosuric agents on urate transport in human brush-border membrane vesicles. *J Pharmacol Exp Ther* 280: 839–845, 1997.

618. Roch-Ramel F, Guisan B. Renal Transport of Urate in Humans. *News Physiol Sci* 14: 80–84, 1999.

619. Rodriguez L, Tu C, Cheng Z, Chen T-H, Bikle D, Shoback D, Chang W. Expression and functional assessment of an alternatively spliced extracellular Ca^{2+}-sensing receptor in growth plate chondrocytes. *Endocrinology* 146: 5294–5303, 2005. doi:10.1210/en.2005-0256.

620. Rodríguez-Soriano J, Vallo A, García-Fuentes M. Hypomagnesaemia of hereditary renal origin. *Pediatr Nephrol* 1: 465–472, 1987. doi:10.1007/BF00849255.

621. Rodríguez-Soriano J, Vallo A, Pérez de Nanclares G, Bilbao JR, Castaño L. A founder mutation in the CLCNKB gene causes Bartter syndrome type III in Spain. *Pediatr Nephrol* 20: 891–896, 2005. doi:10.1007/s00467-005-1867-z.

622. Ronzaud C, Loffing J, Bleich M, Gretz N, Gröne H-J, Schütz G, Berger S. Impairment of sodium balance in mice deficient in renal principal cell mineralocorticoid receptor. *J Am Soc Nephrol* 18: 1679–1687, 2007. doi:10.1681/ASN.2006090975.

623. Ronzaud C, Loffing-Cueni D, Hausel P, Debonneville A, Malsure SR, Fowler-Jaeger N, Boase NA, Perrier R, Maillard M, Yang B, Stokes JB, Koesters R, Kumar S, Hummler E, Loffing J, Staub O. Renal tubular NEDD4-2 deficiency causes NCC-mediated salt-dependent hypertension. *J Clin Invest* 123: 657–665, 2013. doi:10.1172/JCI61110.

624. Rosenthal W, Seibold A, Antaramian A, Lonergan M, Arthus MF, Hendy GN, Birnbaumer M, Bichet DG. Molecular identification of the gene responsible for congenital nephrogenic diabetes insipidus. *Nature* 359: 233–235, 1992. doi:10.1038/359233a0.

625. Rossier BC, Bochud M, Devuyst O. The Hypertension Pandemic: An Evolutionary Perspective. *Physiology (Bethesda)* 32: 112–125, 2017. doi:10.1152/physiol.00026.2016.

626. Rotin D. Regulation of the epithelial sodium channel (ENaC) by accessory proteins. *Curr Opin Nephrol Hypertens* 9: 529–534, 2000. doi:10.1097/00041552-200009000-00012.

627. Rouse D, Ng RC, Suki WN. Calcium transport in the pars recta and thin descending limb of Henle of the rabbit, perfused in vitro. *J Clin Invest* 65: 37–42, 1980. doi:10.1172/JCI109657.

628. Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. *Clin Endocrinol (Oxf)* 5: 209–224, 1976. doi:10.1111/j.1365-2265.1976.tb01947.x.

629. Ruiz A, Gautschi I, Schild L, Bonny O. Human Mutations in SLC2A9 (Glut9) Affect Transport Capacity for Urate. *Front Physiol* 9: 476, 2018. doi:10.3389/fphys.2018.00476.

630. Runeberg L, Collan Y, Jokinen EJ, Lähdevirta J, Aro A. Hypomagnesemia due to renal disease of unknown etiology. *Am J Med* 59: 873–881, 1975. doi:10.1016/0002-9343(75)90481-7.

631. Russel FGM, Masereeuw R, van Aubel RAMH. Molecular aspects of renal anionic drug transport. *Annu Rev Physiol* 64: 563–594, 2002. doi:10.1146/annurev.physiol.64.081501.155913.

632. Sabath E, Meade P, Berkman J, de los Heros P, Moreno E, Bobadilla NA, Vázquez N, Ellison DH, Gamba G. Pathophysiology of functional mutations of the thiazide-sensitive Na-Cl cotransporter in Gitelman disease. *Am J Physiol Renal Physiol* 287: F195–F203, 2004. doi:10.1152/ajprenal.00044.2004.

633. Sakurai H. Urate transporters in the genomic era. *Curr Opin Nephrol Hypertens* 22: 545–550, 2013. doi:10.1097/MNH.0b013e328363ffc8.

634. Sala-Rabanal M, Kucheryavykh LY, Skatchkov SN, Eaton MJ, Nichols CG. Molecular mechanisms of EAST/SeSAME syndrome mutations in Kir4.1 (KCNJ10). *J Biol Chem* 285: 36040–36048, 2010. doi:10.1074/jbc.M110.163170.

635. Salido EC, Barajas L, Lechago J, Laborde NP, Fisher DA. Immunocytochemical localization of epidermal growth factor in mouse kidney. *J Histochem Cytochem* 34: 1155–1160, 1986. doi:10.1177/34.9.2426343.

636. Sands JM, Flores FX, Kato A, Baum MA, Brown EM, Ward DT, Hebert SC, Harris HW. Vasopressin-elicited water and urea permeabilities are altered in IMCD in hypercalcemic rats. *Am J Physiol Renal Physiol* 274: F978–F985, 1998. doi:10.1152/ajprenal.1998.274.5.F978.

637. Sands JM, Klein JD. Physiological insights into novel therapies for nephrogenic diabetes insipidus. *Am J Physiol Renal Physiol* 311: F1149–F1152, 2016. doi:10.1152/ajprenal.00418.2016.

638. Sanjad SA, Mansour FM, Hernandez RH, Hill LL. Severe hypertension, hyperkalemia, and renal tubular acidosis responding to dietary sodium restriction. *Pediatrics* 69: 317–324, 1982.

639. Sankarasubbaiyan S, Cooper C, Heilig CW. Identification of a novel form of renal glucosuria with overexcretion of arginine, carnosine, and taurine. *Am J Kidney Dis* 37: 1039–1043, 2001. doi:10.1016/S0272-6386(05)80021-6.

640. Sansanwal P, Sarwal MM. p62/SQSTM1 prominently accumulates in renal proximal tubules in nephropathic cystinosis. *Pediatr Nephrol* 27: 2137–2144, 2012. doi:10.1007/s00467-012-2227-4.

641. Santer R, Calado J. Familial renal glucosuria and SGLT2: from a mendelian trait to a therapeutic target. *Clin J Am Soc Nephrol* 5: 133–141, 2010. doi:10.2215/CJN.04010609.

642. Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M, Brodehl J, Daschner M, Ehrich JHH, Kemper M, Li Volti S, Neuhaus T, Skovby F, Swift PGF, Schaub J, Klaerke D. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. *J Am Soc Nephrol* 14: 2873–2882, 2003. doi:10.1097/01.ASN.0000092790.89332.D2.

643. Santer R, Kinner M, Schneppenheim R, Hillebrand G, Ehrich J. The molecular basis of renal glucosuria: mutations in the gene for a renal glucose transporter (SGLT2). *J Inherit Metab Dis* 23 Suppl 1: 178, 2000.

644. Santer R, Schneppenheim R, Dombrowski A, Götze H, Steinmann B, Schaub J. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. *Nat Genet* 17: 324–326, 1997. doi:10.1038/ng1197-324.

645. Sartorato P, Lapeyraque A-L, Armanini D, Kuhnle U, Khaldi Y, Salomon R, Abadie V, Di Battista E, Naselli A, Racine A, Bosio M, Caprio M, Poulet-Young V, Chabrolle J-P, Niaudet P, De Gennes C, Lecornec M-H, Poisson E, Fusco AM, Loli P, Lombès M, Zennaro M-C. Different inactivating mutations of the mineralocorticoid receptor in fourteen families affected by type I pseudohypoaldosteronism. *J Clin Endocrinol Metab* 88: 2508–2517, 2003. doi:10.1210/jc.2002-021932.

646. Sasaki E, Susa K, Mori T, Isobe K, Araki Y, Inoue Y, Yoshizaki Y, Ando F, Mori Y, Mandai S, Zeniya M, Takahashi D, Nomura N, Rai T, Uchida S, Sohara E. *KLHL3* Knockout Mice Reveal the Physiological Role of KLHL3 and the Pathophysiology of Pseudohypoaldosteronism Type II Caused by Mutant KLHL3. *Mol Cell Biol* 37: e00508–e00516, 2017. doi:10.1128/MCB.00508-16.

647. Sato K, Hasegawa Y, Nakae J, Nanao K, Takahashi I, Tajima T, Shinohara N, Fujieda K. Hydrochlorothiazide effectively reduces urinary calcium excretion in two Japanese patients with gain-of-function mutations of the calcium-sensing receptor gene. *J Clin Endocrinol Metab* 87: 3068–3073, 2002. doi:10.1210/jcem.87.7.8639.

648. Sällström J, Carlsson P-O, Fredholm BB, Larsson E, Persson AEG, Palm F. Diabetes-induced hyperfiltration in adenosine A(1)-receptor deficient mice lacking the tubuloglomerular feedback mechanism. *Acta Physiol (Oxf)* 190: 253–259, 2007. doi:10.1111/j.1748-1716.2007.01705.x.

649. Sällström J, Eriksson T, Fredholm BB, Persson AEG, Palm F. Inhibition of sodium-linked glucose reabsorption normalizes diabetes-induced glomerular hyperfiltration in conscious adenosine A_1-receptor deficient mice. *Acta Physiol (Oxf)* 210: 440–445, 2014. doi:10.1111/apha.12152.

650. Schaedel C, Marthinsen L, Kristoffersson AC, Kornfält R, Nilsson KO, Orlenius B, Holmberg L. Lung symptoms in pseudohypoaldosteronism type I are associated with deficiency of the alpha-subunit of the epithelial sodium channel. *J Pediatr* 135: 739–745, 1999. doi:10.1016/S0022-3476(99)70094-6.

651. Schaefer M. Homo- and heteromeric assembly of TRP channel subunits. *Pflugers Arch* 451: 35–42, 2005. doi:10.1007/s00424-005-1467-6.

652. Scheel O, Zdebik AA, Lourdel S, Jentsch TJ. Voltage-dependent electrogenic chloride/proton exchange by endosomal CLC proteins. *Nature* 436: 424–427, 2005. doi:10.1038/nature03860.

653. Scheinman SJ. X-linked hypercalciuric nephrolithiasis: clinical syndromes and chloride channel mutations. *Kidney Int* 53: 3–17, 1998. doi:10.1046/j.1523-1755.1998.00718.x.

654. Schieppati A, Henter J-I, Daina E, Aperia A. Why rare diseases are an important medical and social issue. *Lancet* 371: 2039–2041, 2008. doi:10.1016/S0140-6736(08)60872-7.

655. Schild L, Lu Y, Gautschi I, Schneeberger E, Lifton RP, Rossier BC. Identification of a PY motif in the epithelial Na channel subunits as a target sequence for mutations causing channel activation found in Liddle syndrome. *EMBO J* 15: 2381–2387, 1996. doi:10.1002/j.1460-2075.1996.tb00594.x.

656. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 43: 969–976, 2011. doi:10.1038/ng.940.

657. Schlingmann KP, Konrad M, Jeck N, Waldegger P, Reinalter SC, Holder M, Seyberth HW, Waldegger S. Salt wasting and deafness resulting from mutations in two chloride channels. *N Engl J Med* 350: 1314–1319, 2004. doi:10.1056/NEJMoa032843.

658. Schlingmann KP, Weber S, Peters M, Niemann Nejsum L, Vitzthum H, Klingel K, Kratz M, Haddad E, Ristoff E, Dinour D, Syrrou M, Nielsen S, Sassen M, Waldegger S, Seyberth HW, Konrad M. Hypomagnesemia with secondary hypocalcemia is caused by mutations in TRPM6, a new member of the TRPM gene family. *Nat Genet* 31: 166–170, 2002. doi:10.1038/ng889.

659. Schneider D, Gauthier B, Trachtman H. Hypercalciuria in children with renal glycosuria: evidence of dual renal tubular reabsorptive defects. *J Pediatr* 121: 715–719, 1992. doi:10.1016/S0022-3476(05)81898-0.

660. Scholl U, Hebeisen S, Janssen AGH, Müller-Newen G, Alekov A, Fahlke C. Barttin modulates trafficking and function of ClC-K channels. *Proc Natl Acad Sci USA* 103: 11411–11416, 2006. doi:10.1073/pnas.0601631103.

661. Scholl UI, Choi M, Liu T, Ramaekers VT, Häusler MG, Grimmer J, Tobe SW, Farhi A, Nelson-Williams C, Lifton RP. Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in KCNJ10. *Proc Natl Acad Sci USA* 106: 5842–5847, 2009. doi:10.1073/pnas.0901749106.

662. Scholl-Bürgi S, Santer R, Ehrich JHH. Long-term outcome of renal glucosuria type 0: the original patient and his natural history. *Nephrol Dial Transplant* 19: 2394–2396, 2004. doi:10.1093/ndt/gfh366.

663. Schrag D, Chung KY, Flombaum C, Saltz L. Cetuximab therapy and symptomatic hypomagnesemia. *J Natl Cancer Inst* 97: 1221–1224, 2005. doi:10.1093/jnci/dji242.

664. Schulte U, Hahn H, Konrad M, Jeck N, Derst C, Wild K, Weidemann S, Ruppersberg JP, Fakler B, Ludwig J. pH gating of ROMK (K(ir)1.1) channels: control by an Arg-Lys-Arg triad disrupted in antenatal Bartter syndrome. *Proc Natl Acad Sci USA* 96: 15298–15303, 1999. doi:10.1073/pnas.96.26.15298.

665. Schultheis PJ, Lorenz JN, Meneton P, Nieman ML, Riddle TM, Flagella M, Duffy JJ, Doetschman T, Miller ML, Shull GE. Phenotype resembling Gitelman's syndrome in mice lacking the apical Na^+-Cl^- cotransporter of the distal convoluted tubule. *J Biol Chem* 273: 29150–29155, 1998. doi:10.1074/jbc.273.44.29150.

666. Schumacher F-R, Siew K, Zhang J, Johnson C, Wood N, Cleary SE, Al Maskari RS, Ferryman JT, Hardege I, Yasmin, Figg NL, Enchev R, Knebel A, O'Shaughnessy KM, Kurz T. Characterisation of the Cullin-3 mutation that causes a severe form of familial hypertension and hyperkalaemia. *EMBO Mol Med* 7: 1285–1306, 2015. doi:10.15252/emmm.201505444.

667. Schurman SJ, Perlman SA, Sutphen R, Campos A, Garin EH, Cruz DN, Shoemaker LR. Genotype/phenotype observations in African Americans with Bartter syndrome. *J Pediatr* 139: 105–110, 2001. doi:10.1067/mpd.2001.115020.

668. Schwalbe RA, Bianchi L, Accili EA, Brown AM. Functional consequences of ROMK mutants linked to antenatal Bartter's syndrome and implications for treatment. *Hum Mol Genet* 7: 975–980, 1998. doi:10.1093/hmg/7.6.975.

669. Sebesta I. Genetic disorders resulting in hyper- or hypouricemia. *Adv Chronic Kidney Dis* 19: 398–403, 2012. doi:10.1053/j.ackd.2012.06.002.

670. Seeley HH, Loomba-Albrecht LA, Nagel M, Butani L, Bremer AA. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis in three siblings having the same genetic lesion but different clinical presentations. *World J Pediatr* 8: 177–180, 2012. doi:10.1007/s12519-011-0295-3.

671. Sekine T, Cha SH, Endou H. The multispecific organic anion transporter (OAT) family. *Pflugers Arch* 440: 337–350, 2000. doi:10.1007/s004240000297.

672. Sekine T, Komoda F, Miura K, Takita J, Shimadzu M, Matsuyama T, Ashida A, Igarashi T. Japanese Dent disease has a wider clinical spectrum than Dent disease in Europe/USA: genetic and clinical studies of 86 unrelated patients with low-molecular-weight proteinuria. *Nephrol Dial Transplant* 29: 376–384, 2014. doi:10.1093/ndt/gft394.

673. Semmekrot B, Monnens LA, Yoshida I, Tokunaga Y, Yamakawa R, Kato H. Furosemide versus thiazide in Gordon syndrome. *Eur J Pediatr* 155: 621, 1996. doi:10.1007/BF01957921.

674. Settembre C, Fraldi A, Medina DL, Ballabio A. Signals from the lysosome: a control centre for cellular clearance and energy metabolism. *Nat Rev Mol Cell Biol* 14: 283–296, 2013. doi:10.1038/nrm3565.

675. Seyberth HW, Königer SJ, Rascher W, Kühl PG, Schweer H. Role of prostaglandins in hyperprostaglandin E syndrome and in selected renal tubular disorders. *Pediatr Nephrol* 1: 491–497, 1987. doi:10.1007/BF00849259.

676. Seyberth HW, Rascher W, Schweer H, Kühl PG, Mehls O, Schärer K. Congenital hypokalemia with hypercalciuria in preterm infants: a hyperprostaglandinuric tubular syndrome different from Bartter syndrome. *J Pediatr* 107: 694–701, 1985. doi:10.1016/S0022-3476(85)80395-4.

677. Sha Q, Pearson W, Burcea LC, Wigfall DA, Schlesinger PH, Nichols CG, Mercer RW. Human FXYD2 G41R mutation responsible for renal hypomagnesemia behaves as an inward-rectifying cation channel. *Am J Physiol Renal Physiol* 295: F91–F99, 2008. doi:10.1152/ajprenal.00519.2007.

678. Shalev H, Ohali M, Kachko L, Landau D. The neonatal variant of Bartter syndrome and deafness: preservation of renal function. *Pediatrics* 112: 628–633, 2003. doi:10.1542/peds.112.3.628.

679. Shalev H, Phillip M, Galil A, Carmi R, Landau D. Clinical presentation and outcome in primary familial hypomagnesaemia. *Arch Dis Child* 78: 127–130, 1998. doi:10.1136/adc.78.2.127.

680. Shan Q, Himmerkus N, Hou J, Goodenough DA, Bleich M. Insights into driving forces and paracellular permeability from claudin-16 knockdown mouse. *Ann N Y Acad Sci* 1165: 148–151, 2009. doi:10.1111/j.1749-6632.2009.04041.x.

681. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. *Am J Physiol Renal Physiol* 284: F11–F21, 2003. doi:10.1152/ajprenal.00119.2002.

682. Shen H, Feng C, Jin X, Mao J, Fu H, Gu W, Liu A, Shu Q, Du L. Recurrent exercise-induced acute kidney injury by idiopathic renal hypouricemia with a novel mutation in the SLC2A9 gene and literature review. *BMC Pediatr* 14: 73, 2014. doi:10.1186/1471-2431-14-73.

683. Sheppard DN, Welsh MJ. Structure and function of the CFTR chloride channel. *Physiol Rev* 79, Suppl: S23–S45, 1999. doi:10.1152/physrev.1999.79.1.S23.

684. Shi PP, Cao XR, Sweezer EM, Kinney TS, Williams NR, Husted RF, Nair R, Weiss RM, Williamson RA, Sigmund CD, Snyder PM, Staub O, Stokes JB, Yang B. Salt-sensitive hypertension and cardiac hypertrophy in mice deficient in the ubiquitin ligase Nedd4-2. *Am J Physiol Renal Physiol* 295: F462–F470, 2008. doi:10.1152/ajprenal.90300.2008.

685. Shibata S, Zhang J, Puthumana J, Stone KL, Lifton RP. Kelch-like 3 and Cullin 3 regulate electrolyte homeostasis via ubiquitination and degradation of WNK4. *Proc Natl Acad Sci USA* 110: 7838–7843, 2013. doi:10.1073/pnas.1304592110.

686. Shimkets RA, Warnock DG, Bositis CM, Nelson-Williams C, Hansson JH, Schambelan M, Gill JR Jr, Ulick S, Milora RV, Findling JW, Canessa CM, Rossier BC, Lifton RP. Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. *Cell* 79: 407–414, 1994. doi:10.1016/0092-8674(94)90250-X.

687. Shirley DG, Walter SJ, Unwin RJ, Giebisch G. Contribution of Na^+-H^+ exchange to sodium reabsorption in the loop of henle: a microperfusion study in rats. *J Physiol* 513: 243–249, 1998. doi:10.1111/j.1469-7793.1998.243by.x.

688. Shrimpton AE, Hoopes RR Jr, Knohl SJ, Hueber P, Reed AAC, Christie PT, Igarashi T, Lee P, Lehman A, White C, Milford DV, Sanchez MR, Unwin R, Wrong OM, Thakker RV, Scheinman SJ. OCRL1 mutations in Dent 2 patients suggest a mechanism for phenotypic variability. *Nephron Physiol* 112: 27–36, 2009. doi:10.1159/000213506.

689. Sica DA, Schoolwerth AC. Renal handling of organic anions and cations: excretion of uric acid. In: *The Kidney*, edited by Brenner BM. Philadelphia, PA: Saunders, 2000, p. 680–700.

690. Simon DB, Bindra RS, Mansfield TA, Nelson-Williams C, Mendonca E, Stone R, Schurman S, Nayir A, Alpay H, Bakkaloglu A, Rodriguez-Soriano J, Morales JM, Sanjad SA, Taylor CM, Pilz D, Brem A, Trachtman H, Griswold W, Richard GA, John E, Lifton RP. Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. *Nat Genet* 17: 171–178, 1997. doi:10.1038/ng1097-171.

691. Simon DB, Karet FE, Hamdan JM, DiPietro A, Sanjad SA, Lifton RP. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat Genet* 13: 183–188, 1996. doi:10.1038/ng0696-183.

692. Simon DB, Karet FE, Rodriguez-Soriano J, Hamdan JH, DiPietro A, Trachtman H, Sanjad SA, Lifton RP. Genetic heterogeneity of Bartter's syndrome revealed by mutations in the K^+ channel, ROMK. *Nat Genet* 14: 152–156, 1996. doi:10.1038/ng1096-152.

693. Simon DB, Lu Y, Choate KA, Velazquez H, Al-Sabban E, Praga M, Casari G, Bettinelli A, Colussi G, Rodriguez-Soriano J, McCredie D, Milford D, Sanjad S, Lifton RP. Paracellin-1, a renal tight junction protein required for paracellular Mg^{2+} resorption. *Science* 285: 103–106, 1999. doi:10.1126/science.285.5424.103.

694. Simon DB, Nelson-Williams C, Bia MJ, Ellison D, Karet FE, Molina AM, Vaara I, Iwata F, Cushner HM, Koolen M, Gainza FJ, Gitleman HJ, Lifton RP. Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. *Nat Genet* 12: 24–30, 1996. doi:10.1038/ng0196-24.

695. Sirac C, Bridoux F, Essig M, Devuyst O, Touchard G, Cogné M. Toward understanding renal Fanconi syndrome: step by step advances through experimental models. *Contrib Nephrol* 169: 247–261, 2011. doi:10.1159/000313962.

696. Smart SL, Lopantsev V, Zhang CL, Robbins CA, Wang H, Chiu SY, Schwartzkroin PA, Messing A, Tempel BL. Deletion of the K(V)1.1 potassium channel causes epilepsy in mice. *Neuron* 20: 809–819, 1998. doi:10.1016/S0896-6273(00)81018-1.

697. Snyder PM, Olson DR, Thomas BC. Serum and glucocorticoid-regulated kinase modulates Nedd4-2-mediated inhibition of the epithelial Na^+ channel. *J Biol Chem* 277: 5–8, 2002. doi:10.1074/jbc.C100623200.

698. Snyder PM, Price MP, McDonald FJ, Adams CM, Volk KA, Zeiher BG, Stokes JB, Welsh MJ. Mechanism by which Liddle's syndrome mutations increase activity of a human epithelial Na^+ channel. *Cell* 83: 969–978, 1995. doi:10.1016/0092-8674(95)90212-0.

699. So A, Thorens B. Uric acid transport and disease. *J Clin Invest* 120: 1791–1799, 2010. doi:10.1172/JCI42344.

700. Sperling O. Hereditary renal hypouricemia. *Mol Genet Metab* 89: 14–18, 2006. doi:10.1016/j.ymgme.2006.03.015.

701. Starremans PGJF, Kersten FFJ, Knoers NVAM, van den Heuvel LPWJ, Bindels RJM. Mutations in the human Na-K-2Cl cotransporter (NKCC2) identified in Bartter syndrome type I consistently result in nonfunctional transporters. *J Am Soc Nephrol* 14: 1419–1426, 2003. doi:10.1097/01.ASN.0000064948.39199.A0.

702. Starremans PGJF, Kersten FFJ, Van Den Heuvel LPWJ, Knoers NVAM, Bindels RJM. Dimeric architecture of the human bumetanide-sensitive Na-K-Cl Co-transporter. *J Am Soc Nephrol* 14: 3039–3046, 2003. doi:10.1097/01.ASN.0000097370.29737.5B.

703. Starremans PGJF, van der Kemp AWCM, Knoers NVAM, van den Heuvel LPWJ, Bindels RJM. Functional implications of mutations in the human renal outer medullary potassium channel (ROMK2) identified in Bartter syndrome. *Pflugers Arch* 443: 466–472, 2002. doi:10.1007/s004240100708.

704. Staub O, Verrey F. Impact of Nedd4 proteins and serum and glucocorticoid-induced kinases on epithelial Na^+ transport in the distal nephron. *J Am Soc Nephrol* 16: 3167–3174, 2005. doi:10.1681/ASN.2005050454.

705. Stauber T, Jentsch TJ. Chloride in vesicular trafficking and function. *Annu Rev Physiol* 75: 453–477, 2013. doi:10.1146/annurev-physiol-030212-183702.

706. Steele TH. Urate secretion in man: the pyrazinamide suppression test. *Ann Intern Med* 79: 734–737, 1973. doi:10.7326/0003-4819-79-5-734.

707. Steinmann B, Gnehm HE, Rao VH, Kind HP, Prader A. Neonatal severe primary hyperparathyroidism and alkaptonuria in a boy born to related parents with familial hypocalciuric hypercalcemia. *Helv Paediatr Acta* 39: 171–186, 1984.

708. Stiburkova B, Gabrikova D, Čepek P, Šimek P, Kristian P, Cordoba-Lanus E, Claverie-Martin F. Prevalence of URAT1 allelic variants in the Roma population. *Nucleosides Nucleotides Nucleic Acids* 35: 529–535, 2016. doi:10.1080/15257770.2016.1168839.

709. Stiburkova B, Ichida K, Sebesta I. Novel homozygous insertion in SLC2A9 gene caused renal hypouricemia. *Mol Genet Metab* 102: 430–435, 2011. doi:10.1016/j.ymgme.2010.12.016.

710. Stiburkova B, Stekrova J, Nakamura M, Ichida K. Hereditary Renal Hypouricemia Type I and Autosomal Dominant Polycystic Kidney Disease. *Am J Med Sci* 350: 268–271, 2015. doi:10.1097/MAJ.0000000000000550.

711. Stiles PG, Lusk G. On the action of phlorhizin. *Am J Physiol* 10: 67–79, 1903. doi:10.1152/ajplegacy.1903.10.1.67.

712. Storm T, Tranebjærg L, Frykholm C, Birn H, Verroust PJ, Nevéus T, Sundelin B, Hertz JM, Holmström G, Ericson K, Christensen EI, Nielsen R. Renal phenotypic investigations of megalin-deficient patients: novel insights into tubular proteinuria and albumin filtration. *Nephrol Dial Transplant* 28: 585–591, 2013. doi:10.1093/ndt/gfs462.

713. Storm T, Zeitz C, Cases O, Amsellem S, Verroust PJ, Madsen M, Benoist J-F, Passemard S, Lebon S, Jønsson IM, Emma F, Koldsø H, Hertz JM, Nielsen R, Christensen EI, Kozyraki R. Detailed investigations of proximal tubular function in Imerslund-Gräsbeck syndrome. *BMC Med Genet* 14: 111, 2013. doi:10.1186/1471-2350-14-111.

714. Stransky L, Cotter K, Forgac M. The Function of V-ATPases in Cancer. *Physiol Rev* 96: 1071–1091, 2016. doi:10.1152/physrev.00035.2015.

715. Strautnieks SS, Thompson RJ, Gardiner RM, Chung E. A novel splice-site mutation in the gamma subunit of the epithelial sodium channel gene in three pseudohypoaldosteronism type 1 families. *Nat Genet* 13: 248–250, 1996. doi:10.1038/ng0696-248.

716. Stuiver M, Lainez S, Will C, Terryn S, Günzel D, Debaix H, Sommer K, Kopplin K, Thumfart J, Kampik NB, Querfeld U, Willnow TE, Němec V, Wagner CA, Hoenderop JG, Devuyst O, Knoers NVAM, Bindels RJ, Meij IC, Müller D. CNNM2, encoding a basolateral protein required for renal Mg^{2+} handling, is mutated in dominant hypomagnesemia. *Am J Hum Genet* 88: 333–343, 2011. doi:10.1016/j.ajhg.2011.02.005.

717. Subramanya AR, Ellison DH. Distal convoluted tubule. *Clin J Am Soc Nephrol* 9: 2147–2163, 2014. doi:10.2215/CJN.05920613.

718. Subramanya AR, Yang C-L, Zhu X, Ellison DH. Dominant-negative regulation of WNK1 by its kidney-specific kinase-defective isoform. *Am J Physiol Renal Physiol* 290: F619–F624, 2006. doi:10.1152/ajprenal.00280.2005.

719. Susa K, Sohara E, Rai T, Zeniya M, Mori Y, Mori T, Chiga M, Nomura N, Nishida H, Takahashi D, Isobe K, Inoue Y, Takeishi K, Takeda N, Sasaki S, Uchida S. Impaired degradation of WNK1 and WNK4 kinases causes PHAII in mutant KLHL3 knock-in mice. *Hum Mol Genet* 23: 5052–5060, 2014. doi:10.1093/hmg/ddu217.

720. Sutton RA, Mavichak V, Halabe A, Wilkins GE. Bartter's syndrome: evidence suggesting a distal tubular defect in a hypocalciuric variant of the syndrome. *Miner Electrolyte Metab* 18: 43–51, 1992.

721. Suzuki H, Nishizawa T, Tani K, Yamazaki Y, Tamura A, Ishitani R, Dohmae N, Tsukita S, Nureki O, Fujiyoshi Y. Crystal structure of a claudin provides insight into the architecture of tight junctions. *Science* 344: 304–307, 2014. doi:10.1126/science.1248571.

722. Suzuki H, Tani K, Tamura A, Tsukita S, Fujiyoshi Y. Model for the Architecture of Claudin-Based Paracellular Ion Channels through Tight Junctions. *J Mol Biol* 427: 291–297, 2015. doi:10.1016/j.jmb.2014.10.020.

723. Takahashi D, Mori T, Nomura N, Khan MZH, Araki Y, Zeniya M, Sohara E, Rai T, Sasaki S, Uchida S. WNK4 is the major WNK positively regulating NCC in the mouse kidney. *Biosci Rep* 34: e00107, 2014. doi:10.1042/BSR20140047.

724. Takahashi D, Mori T, Wakabayashi M, Mori Y, Susa K, Zeniya M, Sohara E, Rai T, Sasaki S, Uchida S. KLHL2 interacts with and ubiquitinates WNK kinases. *Biochem Biophys Res Commun* 437: 457–462, 2013. doi:10.1016/j.bbrc.2013.06.104.

725. Takahashi N, Chernavvsky DR, Gomez RA, Igarashi P, Gitelman HJ, Smithies O. Uncompensated polyuria in a mouse model of Bartter's syndrome. *Proc Natl Acad Sci USA* 97: 5434–5439, 2000. doi:10.1073/pnas.090091297.

726. Takahashi T, Tsuchida S, Oyamada T, Ohno T, Miyashita M, Saito S, Komatsu K, Takashina K, Takada G. Recurrent URAT1 gene mutations and prevalence of renal hypouricemia in Japanese. *Pediatr Nephrol* 20: 576–578, 2005. doi:10.1007/s00467-005-1830-z.

727. Takasato M, Er PX, Chiu HS, Little MH. Generation of kidney organoids from human pluripotent stem cells. *Nat Protoc* 11: 1681–1692, 2016. doi:10.1038/nprot.2016.098.

728. Takasato M, Er PX, Chiu HS, Maier B, Baillie GJ, Ferguson C, Parton RG, Wolvetang EJ, Roost MS, Chuva de Sousa Lopes SM, Little MH. Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis. *Nature* 526: 564–568, 2015. doi:10.1038/nature15695.

729. Takeuchi Y, Uchida S, Marumo F, Sasaki S. Cloning, tissue distribution, and intrarenal localization of ClC chloride channels in human kidney. *Kidney Int* 48: 1497–1503, 1995. doi:10.1038/ki.1995.439.

730. Takiue Y, Hosoyamada M, Kimura M, Saito H. The effect of female hormones upon urate transport systems in the mouse kidney. *Nucleosides Nucleotides Nucleic Acids* 30: 113–119, 2011. doi:10.1080/15257770.2010.551645.

731. Takumi T, Ishii T, Horio Y, Morishige K, Takahashi N, Yamada M, Yamashita T, Kiyama H, Sohmiya K, Nakanishi S, Kurachi Y. A novel ATP-dependent inward rectifier potassium channel expressed predominantly in glial cells. *J Biol Chem* 270: 16339–16346, 1995. doi:10.1074/jbc.270.27.16339.

732. Tanemoto M, Kittaka N, Inanobe A, Kurachi Y. In vivo formation of a proton-sensitive K^+ channel by heteromeric subunit assembly of Kir5.1 with Kir4.1. *J Physiol* 525: 587–592, 2000. doi:10.1111/j.1469-7793.2000.00587.x.

733. Tang X, Hang D, Sand A, Kofuji P. Variable loss of Kir4.1 channel function in SeSAME syndrome mutations. *Biochem Biophys Res Commun* 399: 537–541, 2010. doi:10.1016/j.bbrc.2010.07.105.

734. Taranta A, Petrini S, Palma A, Mannucci L, Wilmer MJ, De Luca V, Diomedi-Camassei F, Corallini S, Bellomo F, van den Heuvel LP, Levtchenko EN, Emma F. Identification and subcellular localization of a new cystinosin isoform. *Am J Physiol Renal Physiol* 294: F1101–F1108, 2008. doi:10.1152/ajprenal.00413.2007.

735. Tejpar S, Piessevaux H, Claes K, Piront P, Hoenderop JGJ, Verslype C, Van Cutsem E. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. *Lancet Oncol* 8: 387–394, 2007. doi:10.1016/S1470-2045(07)70108-0.

736. Terker AS, Yarbrough B, Ferdaus MZ, Lazelle RA, Erspamer KJ, Meermeier NP, Park HJ, McCormick JA, Yang C-L, Ellison DH. Direct and Indirect Mineralocorticoid Effects Determine Distal Salt Transport. *J Am Soc Nephrol* 27: 2436–2445, 2016. doi:10.1681/ASN.2015070815.

737. Terker AS, Zhang C, McCormick JA, Lazelle RA, Zhang C, Meermeier NP, Siler DA, Park HJ, Fu Y, Cohen DM, Weinstein AM, Wang W-H, Yang C-L, Ellison DH. Potassium modulates electrolyte balance and blood pressure through effects on distal cell voltage and chloride. *Cell Metab* 21: 39–50, 2015. doi:10.1016/j.cmet.2014.12.006.

738. Terryn S, Jouret F, Vandenabeele F, Smolders I, Moreels M, Devuyst O, Steels P, Van Kerkhove E. A primary culture of mouse proximal tubular cells, established on collagen-coated membranes. *Am J Physiol Renal Physiol* 293: F476–F485, 2007. doi:10.1152/ajprenal.00363.2006.

739. Terryn S, Tanaka K, Lengelé J-P, Olinger E, Dubois-Laforgue D, Garbay S, Kozyraki R, Van Der Smissen P, Christensen EI, Courtoy PJ, Bellanné-Chantelot C, Timsit J, Pontoglio M, Devuyst O. Tubular proteinuria in patients with HNF1α mutations: HNF1α drives endocytosis in the proximal tubule. *Kidney Int* 89: 1075–1089, 2016. doi:10.1016/j.kint.2016.01.027.

739a. The European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. *Cell* 78: 725, 1994.

740. Thebault S, Alexander RT, Tiel Groenestege WM, Hoenderop JG, Bindels RJ. EGF increases TRPM6 activity and surface expression. *J Am Soc Nephrol* 20: 78–85, 2009. doi:10.1681/ASN.2008030327.

741. Thébault S, Cao G, Venselaar H, Xi Q, Bindels RJM, Hoenderop JGJ. Role of the alpha-kinase domain in transient receptor potential melastatin 6 channel and regulation by intracellular ATP. *J Biol Chem* 283: 19999–20007, 2008. doi:10.1074/jbc.M800167200.

742. Therien AG, Karlish SJ, Blostein R. Expression and functional role of the gamma subunit of the Na, K-ATPase in mammalian cells. *J Biol Chem* 274: 12252–12256, 1999. doi:10.1074/jbc.274.18.12252.

743. Thöny B, Neuheiser F, Kierat L, Blaskovics M, Arn PH, Ferreira P, Rebrin I, Ayling J, Blau N. Hyperphenylalaninemia with high levels of 7-biopterin is associated with mutations in the PCBD gene encoding the bifunctional protein pterin-4a-carbinolamine dehydratase and transcriptional coactivator (DCoH). *Am J Hum Genet* 62: 1302–1311, 1998. doi:10.1086/301887.

744. Tin A, Woodward OM, Kao WHL, Liu C-T, Lu X, Nalls MA, Shriner D, Semmo M, Akylbekova EL, Wyatt SB, Hwang S-J, Yang Q, Zonderman AB, Adeyemo AA, Palmer C, Meng Y, Reilly M, Shlipak MG, Siscovick D, Evans MK, Rotimi CN, Flessner MF, Köttgen M, Cupples LA, Fox CS, Köttgen A; CARe and CHARGE Consortia. Genome-wide association study for serum urate concentrations and gout among African Americans identifies genomic risk loci and a novel URAT1 loss-of-function allele. *Hum Mol Genet* 20: 4056–4068, 2011. doi:10.1093/hmg/ddr307.

745. Tobin MD, Tomaszewski M, Braund PS, Hajat C, Raleigh SM, Palmer TM, Caulfield M, Burton PR, Samani NJ. Common variants in genes underlying monogenic hypertension and hypotension and blood pressure in the general population. *Hypertension* 51: 1658–1664, 2008. doi:10.1161/HYPERTENSIONAHA.108.112664.

746. Toka HR, Al-Romaih K, Koshy JM, DiBartolo S III, Kos CH, Quinn SJ, Curhan GC, Mount DB, Brown EM, Pollak MR. Deficiency of the calcium-sensing receptor in the kidney causes parathyroid hormone-independent hypocalciuria. *J Am Soc Nephrol* 23: 1879–1890, 2012. doi:10.1681/ASN.2012030323.

747. Topala CN, Schoeber JPH, Searchfield LE, Riccardi D, Hoenderop JGJ, Bindels RJM. Activation of the Ca^{2+}-sensing receptor stimulates the activity of the epithelial Ca^{2+} channel TRPV5. *Cell Calcium* 45: 331–339, 2009. doi:10.1016/j.ceca.2008.12.003.

748. Town M, Jean G, Cherqui S, Attard M, Forestier L, Whitmore SA, Callen DF, Gribouval O, Broyer M, Bates GP, van't Hoff W, Antignac C. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. *Nat Genet* 18: 319–324, 1998. doi:10.1038/ng0498-319.

749. Tronche F, Ringeisen F, Blumenfeld M, Yaniv M, Pontoglio M. Analysis of the distribution of binding sites for a tissue-specific transcription factor in the vertebrate genome. *J Mol Biol* 266: 231–245, 1997. doi:10.1006/jmbi.1996.0760.

750. Trudu M, Janas S, Lanzani C, Debaix H, Schaeffer C, Ikehata M, Citterio L, Demaretz S, Trevisani F, Ristagno G, Glaudemans B, Laghmani K, Dell'Antonio G, Loffing J, Rastaldi MP, Manunta P, Devuyst O, Rampoldi L; SKIPOGH team. Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med* 19: 1655–1660, 2013. doi:10.1038/nm.3384.

751. Tsukamoto T, Kobayashi T, Kawamoto K, Fukase M, Chihara K. Possible discrimination of Gitelman's syndrome from Bartter's syndrome by renal clearance study: report of two cases. *Am J Kidney Dis* 25: 637–641, 1995. doi:10.1016/0272-6386(95)90137-X.

752. Turk E, Zabel B, Mundlos S, Dyer J, Wright EM. Glucose/galactose malabsorption caused by a defect in the Na^+/glucose cotransporter. *Nature* 350: 354–356, 1991. doi:10.1038/350354a0.

753. Ulmann A, Hadj S, Lacour B, Bourdeau A, Bader C. Renal magnesium and phosphate wastage in a patient with hypercalciuria and nephrocalcinosis: effect of oral phosphorus and magnesium supplements. *Nephron* 40: 83–87, 1985. doi:10.1159/000183434.

754. Ungewickell A, Ward ME, Ungewickell E, Majerus PW. The inositol polyphosphate 5-phosphatase Ocrl associates with endosomes that are partially coated with clathrin. *Proc Natl Acad Sci USA* 101: 13501–13506, 2004. doi:10.1073/pnas.0405664101.

755. Vaisbich MH, Fujimura MD, Koch VH. Bartter syndrome: benefits and side effects of long-term treatment. *Pediatr Nephrol* 19: 858–863, 2004. doi:10.1007/s00467-004-1527-8.

756. Vallon V, Platt KA, Cunard R, Schroth J, Whaley J, Thomson SC, Koepsell H, Rieg T. SGLT2 mediates glucose reabsorption in the early proximal tubule. *J Am Soc Nephrol* 22: 104–112, 2011. doi:10.1681/ASN.2010030246.

757. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. *J Am Soc Nephrol* 10: 2569–2576, 1999.

758. Vallon V, Rose M, Gerasimova M, Satriano J, Platt KA, Koepsell H, Cunard R, Sharma K, Thomson SC, Rieg T. Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. *Am J Physiol Renal Physiol* 304: F156–F167, 2013. doi:10.1152/ajprenal.00409.2012.

759. Vallon V, Sharma K. Sodium-glucose transport: role in diabetes mellitus and potential clinical implications. *Curr Opin Nephrol Hypertens* 19: 425–431, 2010. doi:10.1097/MNH.0b013e32833bec06.

760. Vallon V, Thomson SC. Diabetes mellitus: cardiovascular and renal benefits of SGLT2 inhibition: insights from CANVAS. *Nat Rev Nephrol* 13: 517–518, 2017. doi:10.1038/nrneph.2017.113.

761. Van Aubel RAMH, Smeets PHE, van den Heuvel JJMW, Russel FGM. Human organic anion transporter MRP4 (ABCC4) is an efflux pump for the purine end metabolite urate with multiple allosteric substrate binding sites. *Am J Physiol Renal Physiol* 288: F327–F333, 2005. doi:10.1152/ajprenal.00133.2004.

762. Van den Heuvel LP, Assink K, Willemsen M, Monnens L. Autosomal recessive renal glucosuria attributable to a mutation in the sodium glucose cotransporter (SGLT2). *Hum Genet* 111: 544–547, 2002. doi:10.1007/s00439-002-0820-5.

763. Van der Wijst J, Bindels RJM, Hoenderop JGJ. Mg^{2+} homeostasis: the balancing act of TRPM6. *Curr Opin Nephrol Hypertens* 23: 361–369, 2014. doi:10.1097/01.mnh.0000447023.59346.ab.

764. Van der Wijst J, Blanchard MG, Woodroof HI, Macartney TJ, Gourlay R, Hoenderop JG, Bindels RJ, Alessi DR. Kinase and channel activity of TRPM6 are co-ordinated by a dimerization motif and pocket interaction. *Biochem J* 460: 165–175, 2014. doi:10.1042/BJ20131639.

765. Van der Wijst J, Konrad M, Verkaart SAJ, Tkaczyk M, Latta F, Altmüller J, Thiele H, Beck B, Schlingmann KP, de Baaij JHF. A de novo KCNA1 Mutation in a Patient with Tetany and Hypomagnesemia. *Nephron* 139: 359–366, 2018. doi:10.1159/000488954.

766. Van Goor MKC, Hoenderop JGJ, van der Wijst J. TRP channels in calcium homeostasis: from hormonal control to structure-function relationship of TRPV5 and TRPV6. *Biochim Biophys Acta* 1864: 883–893, 2017. doi:10.1016/j.bbamcr.2016.11.027.

767. Van Itallie CM, Rogan S, Yu A, Vidal LS, Holmes J, Anderson JM. Two splice variants of claudin-10 in the kidney create paracellular pores with different ion selectivities. *Am J Physiol Renal Physiol* 291: F1288–F1299, 2006. doi:10.1152/ajprenal.00138.2006.

768. Vargas-Poussou R, Dahan K, Kahila D, Venisse A, Riveira-Munoz E, Debaix H, Grisart B, Bridoux F, Unwin R, Moulin B, Haymann J-P, Vantyghem M-C, Rigothier C, Dussol B, Godin M, Nivet H, Dubourg L, Tack I, Gimenez-Roqueplo A-P, Houillier P, Blanchard A, Devuyst O, Jeunemaitre X. Spectrum of mutations in Gitelman syndrome. *J Am Soc Nephrol* 22: 693–703, 2011. doi:10.1681/ASN.2010090907.

769. Vargas-Poussou R, Feldmann D, Vollmer M, Konrad M, Kelly L, van den Heuvel LP, Tebourbi L, Brandis M, Karolyi L, Hebert SC, Lemmink HH, Deschênes G, Hildebrandt F, Seyberth HW, Guay-Woodford LM, Knoers NV, Antignac C. Novel molecular variants of the Na-K-2Cl cotransporter gene are responsible for antenatal Bartter syndrome. *Am J Hum Genet* 62: 1332–1340, 1998. doi:10.1086/301872.

770. Vargas-Poussou R, Huang C, Hulin P, Houillier P, Jeunemaître X, Paillard M, Planelles G, Déchaux M, Miller RT, Antignac C. Functional characterization of a calcium-sensing receptor mutation in severe autosomal dominant hypocalcemia with a Bartter-like syndrome. *J Am Soc Nephrol* 13: 2259–2266, 2002. doi:10.1097/01.ASN.0000025781.16723.68.

771. Velázquez H, Good DW, Wright FS. Mutual dependence of sodium and chloride absorption by renal distal tubule. *Am J Physiol Renal Physiol* 247: F904–F911, 1984. doi:10.1152/ajprenal.1984.247.6.F904.

772. Velázquez H, Silva T. Cloning and localization of KCC4 in rabbit kidney: expression in distal convoluted tubule. *Am J Physiol Renal Physiol* 285: F49–F58, 2003. doi:10.1152/ajprenal.00389.2002.

773. Verouti SN, Boscardin E, Hummler E, Frateschi S. Regulation of blood pressure and renal function by NCC and ENaC: lessons from genetically engineered mice. *Curr Opin Pharmacol* 21: 60–72, 2015. doi:10.1016/j.coph.2014.12.012.

774. Vicinanza M, Di Campli A, Polishchuk E, Santoro M, Di Tullio G, Godi A, Levtchenko E, De Leo MG, Polishchuk R, Sandoval L, Marzolo M-P, De Matteis MA. OCRL controls trafficking through early endosomes via PtdIns4,5P_2-dependent regulation of endosomal actin. *EMBO J* 30: 4970–4985, 2011. doi:10.1038/emboj.2011.354.

775. Vidal-Petiot E, Elvira-Matelot E, Mutig K, Soukaseum C, Baudrie V, Wu S, Cheval L, Huc E, Cambillau M, Bachmann S, Doucet A, Jeunemaitre X, Hadchouel J. WNK1-related Familial Hyperkalemic Hypertension results from an increased expression of L-WNK1 specifically in the distal nephron. *Proc Natl Acad Sci USA* 110: 14366–14371, 2013. doi:10.1073/pnas.1304230110.

776. Vinayagamoorthy N, Yim S-H, Jung S-H, Park S-W, Kim YJ, Kim B-J, Chung Y-J. Association of common variants in the calcium-sensing receptor gene with serum calcium levels in East Asians. *J Hum Genet* 60: 407–412, 2015. doi:10.1038/jhg.2015.46.

777. Vitari AC, Deak M, Morrice NA, Alessi DR. The WNK1 and WNK4 protein kinases that are mutated in Gordon's hypertension syndrome phosphorylate and activate SPAK and OSR1 protein kinases. *Biochem J* 391: 17–24, 2005. doi:10.1042/BJ20051180.

778. Vitart V, Rudan I, Hayward C, Gray NK, Floyd J, Palmer CNA, Knott SA, Kolcic I, Polašek O, Graessler J, Wilson JF, Marinaki A, Riches PL, Shu X, Janicijevic B, Smolej-Narancic N, Gorgoni B, Morgan J, Campbell S, Biloglav Z, Barac-Lauc L, Pericic M, Klaric IM, Zgaga L, Skaric-Juric T, Wild SH, Richardson WA, Hohenstein P, Kimber CH, Tenesa A, Donnelly LA, Fairbanks LD, Aringer M, McKeigue PM, Ralston SH, Morris AD, Rudan P, Hastie ND, Campbell H, Wright AF. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 40: 437–442, 2008. doi:10.1038/ng.106.

779. Vivante A, Hildebrandt F. Exploring the genetic basis of early-onset chronic kidney disease. *Nat Rev Nephrol* 12: 133–146, 2016. doi:10.1038/nrneph.2015.205.

780. Voets T, Nilius B, Hoefs S, van der Kemp AWCM, Droogmans G, Bindels RJM, Hoenderop JGJ. TRPM6 forms the Mg^{2+} influx channel involved in intestinal and renal Mg^{2+} absorption. *J Biol Chem* 279: 19–25, 2004. doi:10.1074/jbc.M311201200.

781. Wade JB, Liu J, Coleman R, Grimm PR, Delpire E, Welling PA. SPAK-mediated NCC regulation in response to low-K^+ diet. *Am J Physiol Renal Physiol* 308: F923–F931, 2015. doi:10.1152/ajprenal.00388.2014.

782. Wagner CA, Loffing-Cueni D, Yan Q, Schulz N, Fakitsas P, Carrel M, Wang T, Verrey F, Geibel JP, Giebisch G, Hebert SC, Loffing J. Mouse model of type II Bartter's syndrome. II. Altered expression of renal sodium- and water-transporting proteins. *Am J Physiol Renal Physiol* 294: F1373–F1380, 2008. doi:10.1152/ajprenal.00613.2007.

783. Wagner CA, Rubio-Aliaga I, Hernando N. Renal phosphate handling and inherited disorders of phosphate reabsorption: an update. *Pediatr Nephrol* 98: 6–11, 2017. doi:10.1007/s00467-017-3873-3.

784. Wakabayashi M, Mori T, Isobe K, Sohara E, Susa K, Araki Y, Chiga M, Kikuchi E, Nomura N, Mori Y, Matsuo H, Murata T, Nomura S, Asano T, Kawaguchi H, Nonoyama S, Rai T, Sasaki S, Uchida S. Impaired KLHL3-mediated ubiquitination of WNK4 causes human hypertension. *Cell Rep* 3: 858–868, 2013. doi:10.1016/j.celrep.2013.02.024.

785. Waldegger S, Jeck N, Barth P, Peters M, Vitzthum H, Wolf K, Kurtz A, Konrad M, Seyberth HW. Barttin increases surface expression and changes current properties of ClC-K channels. *Pflugers Arch* 444: 411–418, 2002. doi:10.1007/s00424-002-0819-8.

786. Walder RY, Landau D, Meyer P, Shalev H, Tsolia M, Borochowitz Z, Boettger MB, Beck GE, Englehardt RK, Carmi R, Sheffield VC. Mutation of TRPM6 causes familial hypomagnesemia with secondary hypocalcemia. *Nat Genet* 31: 171–174, 2002. doi:10.1038/ng901.

787. Walder RY, Yang B, Stokes JB, Kirby PA, Cao X, Shi P, Searby CC, Husted RF, Sheffield VC. Mice defective in Trpm6 show embryonic mortality and neural tube defects. *Hum Mol Genet* 18: 4367–4375, 2009. doi:10.1093/hmg/ddp392.

788. Wall SM, Lazo-Fernandez Y. The role of pendrin in renal physiology. *Annu Rev Physiol* 77: 363–378, 2015. doi:10.1146/annurev-physiol-021014-071854.

789. Wallach S. Effects of magnesium on skeletal metabolism. *Magnes Trace Elem* 9: 1–14, 1990.

790. Waller S, Kurzawinski T, Spitz L, Thakker R, Cranston T, Pearce S, Cheetham T, van't Hoff WG. Neonatal severe hyperparathyroidism: genotype/phenotype correlation and the use of pamidronate as rescue therapy. *Eur J Pediatr* 163: 589–594, 2004. doi:10.1007/s00431-004-1491-0.

791. Wang C-Y, Shi J-D, Yang P, Kumar PG, Li Q-Z, Run Q-G, Su Y-C, Scott HS, Kao K-J, She J-X. Molecular cloning and characterization of a novel gene family of four ancient conserved domain proteins (ACDP). *Gene* 306: 37–44, 2003. doi:10.1016/S0378-1119(02)01210-6.

792. Wang D, An SJ, Wang WH, McGiff JC, Ferreri NR. CaR-mediated COX-2 expression in primary cultured mTAL cells. *Am J Physiol Renal Physiol* 281: F658–F664, 2001. doi:10.1152/ajprenal.2001.281.4.F658.

793. Wang D, McGiff JC, Ferreri NR. Regulation of cyclooxygenase isoforms in the renal thick ascending limb: effects of extracellular calcium. *J Physiol Pharmacol* 51: 587–595, 2000.

794. Wang SS, Devuyst O, Courtoy PJ, Wang XT, Wang H, Wang Y, Thakker RV, Guggino S, Guggino WB. Mice lacking renal chloride channel, CLC-5, are a model for Dent's disease, a nephrolithiasis disorder associated with defective receptor-mediated endocytosis. *Hum Mol Genet* 9: 2937–2945, 2000. doi:10.1093/hmg/9.20.2937.

795. Wang W, Lu M, Balazy M, Hebert SC. Phospholipase A_2 is involved in mediating the effect of extracellular Ca^{2+} on apical K^+ channels in rat TAL. *Am J Physiol* 273: F421–F429, 1997. doi:10.1152/ajprenal.1997.273.3.F421.

796. Wang X, Yu M, Wang T, Zhang H, Ping F, Zhang Q, Xu J, Feng K, Xiao X. Genetic analysis and literature review of Chinese patients with familial renal glucosuria: Iden-

tification of a novel SLC5A2 mutation. *Clin Chim Acta* 469: 105–110, 2017. doi:10.1016/j.cca.2017.03.027.

797. Ward BK, Magno AL, Blitvich BJ, Rea AJ, Stuckey BGA, Walsh JP, Ratajczak T. Novel mutations in the calcium-sensing receptor gene associated with biochemical and functional differences in familial hypocalciuric hypercalcaemia. *Clin Endocrinol (Oxf)* 64: 580–587, 2006. doi:10.1111/j.1365-2265.2006.02512.x.

798. Ward DT. Calcium receptor-mediated intracellular signalling. *Cell Calcium* 35: 217–228, 2004. doi:10.1016/j.ceca.2003.10.017.

799. Warnock DG. Liddle syndrome: an autosomal dominant form of human hypertension. *Kidney Int* 53: 18–24, 1998. doi:10.1046/j.1523-1755.1998.00728.x.

800. Watanabe S, Fukumoto S, Chang H, Takeuchi Y, Hasegawa Y, Okazaki R, Chikatsu N, Fujita T. Association between activating mutations of calcium-sensing receptor and Bartter's syndrome. *Lancet* 360: 692–694, 2002. doi:10.1016/S0140-6736(02)09842-2.

801. Weber S, Schneider L, Peters M, Misselwitz J, Rönnefarth G, Böswald M, Bonzel KE, Seeman T, Suláková T, Kuwertz-Bröking E, Gregoric A, Palcoux JB, Tasic V, Manz F, Schärer K, Seyberth HW, Konrad M. Novel paracellin-1 mutations in 25 families with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. *J Am Soc Nephrol* 12: 1872–1881, 2001.

802. Weiner ID, Verlander JW. Ammonia Transporters and Their Role in Acid-Base Balance. *Physiol Rev* 97: 465–494, 2017. doi:10.1152/physrev.00011.2016.

803. Welling PA, Ho K. A comprehensive guide to the ROMK potassium channel: form and function in health and disease. *Am J Physiol Renal Physiol* 297: F849–F863, 2009. doi:10.1152/ajprenal.00181.2009.

804. Welling PA. Roles and Regulation of Renal K Channels. *Annu Rev Physiol* 78: 415–435, 2016. doi:10.1146/annurev-physiol-021115-105423.

805. Wells RG, Mohandas TK, Hediger MA. Localization of the Na^+/glucose cotransporter gene SGLT2 to human chromosome 16 close to the centromere. *Genomics* 17: 787–789, 1993. doi:10.1006/geno.1993.1411.

806. Wells RG, Pajor AM, Kanai Y, Turk E, Wright EM, Hediger MA. Cloning of a human kidney cDNA with similarity to the sodium-glucose cotransporter. *Am J Physiol Renal Fluid Electrolyte Physiol* 263: F459–F465, 1992. doi:10.1152/ajprenal.1992.263.3.F459.

807. Wesche D, Deen PMT, Knoers NVAM. Congenital nephrogenic diabetes insipidus: the current state of affairs. *Pediatr Nephrol* 27: 2183–2204, 2012. doi:10.1007/s00467-012-2118-8.

808. Whang R, Whang DD, Ryan MP. Refractory potassium repletion. A consequence of magnesium deficiency. *Arch Intern Med* 152: 40–45, 1992. doi:10.1001/archinte.1992.00400130066006.

809. White E, McKenna J, Cavanaugh A, Breitwieser GE. Pharmacochaperone-mediated rescue of calcium-sensing receptor loss-of-function mutants. *Mol Endocrinol* 23: 1115–1123, 2009. doi:10.1210/me.2009-0041.

810. Will C, Breiderhoff T, Thumfart J, Stuiver M, Kopplin K, Sommer K, Günzel D, Querfeld U, Meij IC, Shan Q, Bleich M, Willnow TE, Müller D. Targeted deletion of murine Cldn16 identifies extra- and intrarenal compensatory mechanisms of Ca^{2+} and Mg^{2+} wasting. *Am J Physiol Renal Physiol* 298: F1152–F1161, 2010. doi:10.1152/ajprenal.00499.2009.

811. Williams DM, Lopes CMB, Rosenhouse-Dantsker A, Connelly HL, Matavel A, O-Uchi J, McBeath E, Gray DA. Molecular basis of decreased Kir4.1 function in SeSAME/EAST syndrome. *J Am Soc Nephrol* 21: 2117–2129, 2010. doi:10.1681/ASN.2009121227.

812. Willnow T, Antignac C, Brändli A, Christensen E, Cox R, Davidson D, Davies J, Devuyst O, Eichele G, Hastie N, Verroust P, Schedl A, Meij I. The European renal genome project: an integrated approach towards understanding the genetics of kidney development and disease. *Organogenesis* 2: 42–47, 2005. doi:10.4161/org.2.2.2118.

813. Willnow TE. Nanotubes, the fast track to treatment of Dent disease? *Kidney Int* 91: 776–778, 2017. doi:10.1016/j.kint.2016.12.030.

814. Wilson FH, Disse-Nicodème S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, Gunel M, Milford DV, Lipkin GW, Achard JM, Feely MP, Dussol B, Berland Y, Unwin RJ, Mayan H, Simon DB, Farfel Z, Jeunemaitre X, Lifton RP. Human hypertension caused by mutations in WNK kinases. *Science* 293: 1107–1112, 2001. doi:10.1126/science.1062844.

815. Wilson FH, Kahle KT, Sabath E, Lalioti MD, Rapson AK, Hoover RS, Hebert SC, Gamba G, Lifton RP. Molecular pathogenesis of inherited hypertension with hyperkalemia: the Na-Cl cotransporter is inhibited by wild-type but not mutant WNK4. *Proc Natl Acad Sci USA* 100: 680–684, 2003. doi:10.1073/pnas.242735399.

816. Woodward OM, Köttgen A, Coresh J, Boerwinkle E, Guggino WB, Köttgen M. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. *Proc Natl Acad Sci USA* 106: 10338–10342, 2009. doi:10.1073/pnas.0901249106.

817. Woodward OM. ABCG2: the molecular mechanisms of urate secretion and gout. *Am J Physiol Renal Physiol* 309: F485–F488, 2015. doi:10.1152/ajprenal.00242.2015.

818. Woudenberg-Vrenken TE, Sukinta A, van der Kemp AW, Bindels RJM, Hoenderop JGJ. Transient receptor potential melastatin 6 knockout mice are lethal whereas heterozygous deletion results in mild hypomagnesemia. *Nephron Physiol* 117: 11–19, 2011. doi:10.1159/000320580.

819. Wright EM, Hirayama BA, Loo DF. Active sugar transport in health and disease. *J Intern Med* 261: 32–43, 2007. doi:10.1111/j.1365-2796.2006.01746.x.

820. Wright EM, Turk E. The sodium/glucose cotransport family SLC5. *Pflugers Arch* 447: 813–815, 2004. doi:10.1007/s00424-003-1202-0.

821. Wright EM. Renal Na^+-glucose cotransporters. *Am J Physiol Renal Physiol* 280: F10–F18, 2001. doi:10.1152/ajprenal.2001.280.1.F10.

822. Wright EM. Glucose transport families SLC5 and SLC50. *Mol Aspects Med* 34: 183–196, 2013. doi:10.1016/j.mam.2012.11.002.

823. Wu F, Reed AAC, Williams SE, Loh NY, Lippiat JD, Christie PT, Large O, Bettinelli A, Dillon MJ, Goldraich NP, Hoppe B, Lhotta K, Loirat C, Malik R, Morel D, Kotanko P, Roussel B, Rubinger D, Schrander-Stumpel C, Serdaroglu E, Nesbit MA, Ashcroft F, Thakker RV. Mutational analysis of CLC-5, cofilin and CLC-4 in patients with Dent's disease. *Nephron Physiol* 112: 53–62, 2009. doi:10.1159/000225944.

824. Wu F, Roche P, Christie PT, Loh NY, Reed AAC, Esnouf RM, Thakker RV. Modeling study of human renal chloride channel (hCLC-5) mutations suggests a structural-functional relationship. *Kidney Int* 63: 1426–1432, 2003. doi:10.1046/j.1523-1755.2003.00859.x.

825. Wu X, Wakamiya M, Vaishnav S, Geske R, Montgomery C Jr, Jones P, Bradley A, Caskey CT. Hyperuricemia and urate nephropathy in urate oxidase-deficient mice. *Proc Natl Acad Sci USA* 91: 742–746, 1994. doi:10.1073/pnas.91.2.742.

826. Wu XW, Lee CC, Muzny DM, Caskey CT. Urate oxidase: primary structure and evolutionary implications. *Proc Natl Acad Sci USA* 86: 9412–9416, 1989. doi:10.1073/pnas.86.23.9412.

827. Wu X, Muzny DM, Lee CC, Caskey CT. Two independent mutational events in the loss of urate oxidase during hominoid evolution. *J Mol Evol* 34: 78–84, 1992. doi:10.1007/BF00163854.

828. Wuttke M, Köttgen A. Insights into kidney diseases from genome-wide association studies. *Nat Rev Nephrol* 12: 549–562, 2016. doi:10.1038/nrneph.2016.107.

829. Wynne BM, Mistry AC, Al-Khalili O, Mallick R, Theilig F, Eaton DC, Hoover RS. Aldosterone Modulates the Association between NCC and ENaC. *Sci Rep* 7: 4149, 2017. doi:10.1038/s41598-017-03510-5.

830. Xie J, Sun B, Du J, Yang W, Chen H-C, Overton JD, Runnels LW, Yue L. Phosphatidylinositol 4,5-bisphosphate (PIP(2)) controls magnesium gatekeeper TRPM6 activity. *Sci Rep* 1: 146, 2011. doi:10.1038/srep00146.

831. Xu B-E, Stippec S, Chu P-Y, Lazrak A, Li X-J, Lee B-H, English JM, Ortega B, Huang C-L, Cobb MH. WNK1 activates SGK1 to regulate the epithelial sodium channel. *Proc Natl Acad Sci USA* 102: 10315–10320, 2005. doi:10.1073/pnas.0504422102.

832. Xu H, Cui N, Yang Z, Qu Z, Jiang C. Modulation of kir4.1 and kir5.1 by hypercapnia and intracellular acidosis. *J Physiol* 524: 725–735, 2000. doi:10.1111/j.1469-7793.2000.00725.x.

833. Yamamoto T, Moriwaki Y, Takahashi S, Tsutsumi Z, Hada T. Effect of norepinephrine on the urinary excretion of purine bases and oxypurinol. *Metabolism* 50: 1230–1233, 2001. doi:10.1053/meta.2001.26709.

834. Yamauchi K, Rai T, Kobayashi K, Sohara E, Suzuki T, Itoh T, Suda S, Hayama A, Sasaki S, Uchida S. Disease-causing mutant WNK4 increases paracellular chloride permeability and phosphorylates claudins. *Proc Natl Acad Sci USA* 101: 4690–4694, 2004. doi:10.1073/pnas.0306924101.

835. Yamazaki D, Funato Y, Miura J, Sato S, Toyosawa S, Furutani K, Kurachi Y, Omori Y, Furukawa T, Tsuda T, Kuwabata S, Mizukami S, Kikuchi K, Miki H. Basolateral Mg^{2+} extrusion via CNNM4 mediates transcellular Mg^{2+} transport across epithelia: a mouse model. *PLoS Genet* 9: e1003983, 2013. doi:10.1371/journal.pgen.1003983.

836. Yang C-L, Angell J, Mitchell R, Ellison DH. WNK kinases regulate thiazide-sensitive Na-Cl cotransport. *J Clin Invest* 111: 1039–1045, 2003. doi:10.1172/JCI17443.

837. Yang Q, Köttgen A, Dehghan A, Smith AV, Glazer NL, Chen M-H, Chasman DI, Aspelund T, Eiriksdottir G, Harris TB, Launer L, Nalls M, Hernandez D, Arking DE, Boerwinkle E, Grove ML, Li M, Linda Kao WH, Chonchol M, Haritunians T, Li G, Lumley T, Psaty BM, Shlipak M, Hwang S-J, Larson MG, O'Donnell CJ, Upadhyay A, van Duijn CM, Hofman A, Rivadeneira F, Stricker B, Uitterlinden AG, Paré G, Parker AN, Ridker PM, Siscovick DS, Gudnason V, Witteman JC, Fox CS, Coresh J. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet* 3: 523–530, 2010. doi:10.1161/CIRCGENETICS.109.934455.

838. Yang S-S, Morimoto T, Rai T, Chiga M, Sohara E, Ohno M, Uchida K, Lin S-H, Moriguchi T, Shibuya H, Kondo Y, Sasaki S, Uchida S. Molecular pathogenesis of pseudohypoaldosteronism type II: generation and analysis of a Wnk4(D561A/+) knockin mouse model. *Cell Metab* 5: 331–344, 2007. doi:10.1016/j.cmet.2007.03.009.

839. You G, Lee WS, Barros EJ, Kanai Y, Huo TL, Khawaja S, Wells RG, Nigam SK, Hediger MA. Molecular characteristics of Na(+)-coupled glucose transporters in adult and embryonic rat kidney. *J Biol Chem* 270: 29365–29371, 1995. doi:10.1074/jbc.270.49.29365.

840. Yu L, Hou P, Liu G-P, Zhang H. Novel *SLC5A2* mutation contributes to familial renal glucosuria: abnormal expression in renal tissues. *Exp Ther Med* 12: 649–652, 2016. doi:10.3892/etm.2016.3388.

841. Yu L, Hou P, Lv J-C, Liu G-P, Zhang H. A novel sodium-glucose co-transporter 2 gene (SGLT2) mutation contributes to the abnormal expression of SGLT2 in renal tissues in familial renal glucosuria. *Int Urol Nephrol* 46: 2237–2238, 2014. doi:10.1007/s11255-014-0755-5.

842. Yu L, Hou P, Lv J-C, Liu G-P, Zhang H. Novel SLC5A2 variants contribute to renal glucosuria in Chinese families: abnormal expression and dysfunction of variant SLC5A2. *Hum Mutat* 36: 79–86, 2015. doi:10.1002/humu.22714.

843. Yu L, Lv J-C, Zhou X-J, Zhu L, Hou P, Zhang H. Abnormal expression and dysfunction of novel SGLT2 mutations identified in familial renal glucosuria patients. *Hum Genet* 129: 335–344, 2011. doi:10.1007/s00439-010-0927-z.

844. Yu L, Xu Q, Hou P, Zhang H. Decreased expression and function of sodium-glucose co-transporter 2 from a novel C-terminal mutation: a case report. *BMC Nephrol* 17: 31, 2016. doi:10.1186/s12882-016-0244-4.

845. Yu W, Beaudry S, Negoro H, Boucher I, Tran M, Kong T, Denker BM. H_2O_2 activates G protein, α 12 to disrupt the junctional complex and enhance ischemia reperfusion injury. *Proc Natl Acad Sci USA* 109: 6680–6685, 2012. doi:10.1073/pnas.1116800109.

846. Zaffanello M, Taranta A, Palma A, Bettinelli A, Marseglia GL, Emma F. Type IV Bartter syndrome: report of two new cases. *Pediatr Nephrol* 21: 766–770, 2006. doi:10.1007/s00467-006-0090-x.

847. Zambrowicz BP, Abuin A, Ramirez-Solis R, Richter LJ, Piggott J, BeltrandelRio H, Buxton EC, Edwards J, Finch RA, Friddle CJ, Gupta A, Hansen G, Hu Y, Huang W, Jaing C, Key BW Jr, Kipp P, Kohlhauff B, Ma Z-Q, Markesich D, Payne R, Potter DG, Qian N, Shaw J, Schrick J, Shi Z-Z, Sparks MJ, Van Sligtenhorst I, Vogel P, Walke W, Xu N, Zhu Q, Person C, Sands AT. Wnk1 kinase deficiency lowers blood pressure in mice: a gene-trap screen to identify potential targets for therapeutic intervention. [Correction in *Proc Natl Acad Sci USA* 101: 4332, 2004.] *Proc Natl Acad Sci USA* 100: 14109–14114, 2003. doi:10.1073/pnas.2336103100.

848. Zaniew M, Bökenkamp A, Kolbuc M, La Scola C, Baronio F, Niemirska A, Szczepanska M, Bürger J, La Manna A, Miklaszewska M, Rogowska-Kalisz A, Gellermann J, Zampetoglou A, Wasilewska A, Roszak M, Moczko J, Krzemien A, Runowski D, Siten G, Zaluska-Lesniewska I, Fonduli P, Zurrida F, Paglialonga F, Gucev Z, Paripovic D, Rus R, Said-Conti V, Sartz L, Chung WY, Park SJ, Lee JW, Park YH, Ahn YH, Sikora P, Stefanidis CJ, Tasic V, Konrad M, Anglani F, Addis M, Cheong HI, Ludwig M, Bockenhauer D. Long-term renal outcome in children with OCRL mutations: retrospective analysis of a large international cohort. *Nephrol Dial Transplant* 33: 85–94, 2018. doi:10.1093/ndt/gfw350.

849. Zelikovic I, Szargel R, Hawash A, Labay V, Hatib I, Cohen N, Nakhoul F. A novel mutation in the chloride channel gene, CLCNKB, as a cause of Gitelman and Bartter syndromes. *Kidney Int* 63: 24–32, 2003. doi:10.1046/j.1523-1755.2003.00730.x.

850. Zennaro M-C, Hubert E-L, Fernandes-Rosa FL. Aldosterone resistance: structural and functional considerations and new perspectives. *Mol Cell Endocrinol* 350: 206–215, 2012. doi:10.1016/j.mce.2011.04.023.

851. Zhang C, Wang L, Zhang J, Su X-T, Lin D-H, Scholl UI, Giebisch G, Lifton RP, Wang W-H. KCNJ10 determines the expression of the apical Na-Cl cotransporter (NCC) in the early distal convoluted tubule (DCT1). *Proc Natl Acad Sci USA* 111: 11864–11869, 2014. doi:10.1073/pnas.1411705111.

852. Zhang X, Hartz PA, Philip E, Racusen LC, Majerus PW. Cell lines from kidney proximal tubules of a patient with Lowe syndrome lack OCRL inositol polyphosphate 5-phosphatase and accumulate phosphatidylinositol 4,5-bisphosphate. *J Biol Chem* 273: 1574–1582, 1998. doi:10.1074/jbc.273.3.1574.

853. Zhang X-L, Zhu Q-Q, Chen Y-H, Li X-L, Chen F, Huang J-A, Xu B. Cardiovascular Safety, Long-Term Noncardiovascular Safety, and Efficacy of Sodium-Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes Mellitus: A Systemic Review and Meta-Analysis With Trial Sequential Analysis. *J Am Heart Assoc* 7: e007165, 2018. doi:10.1161/JAHA.117.007165.

854. Zhang Z, Yu H, Huang J, Faouzi M, Schmitz C, Penner R, Fleig A. The TRPM6 kinase domain determines the Mg·ATP sensitivity of TRPM7/M6 heteromeric ion channels. *J Biol Chem* 289: 5217–5227, 2014. doi:10.1074/jbc.M113.512285.

855. Zhao X, Cui L, Lang Y, Liu T, Lu J, Wang C, Tuffery-Giraud S, Bottillo I, Wang X, Shao L. A recurrent deletion in the SLC5A2 gene including the intron 7 branch site responsible for familial renal glucosuria. *Sci Rep* 6: 33920, 2016. doi:10.1038/srep33920.

856. Zhou Z, Ma L, Zhou J, Song Z, Zhang J, Wang K, Chen B, Pan D, Li Z, Li C, Shi Y. Renal hypouricemia caused by novel compound heterozygous mutations in the SLC22A12 gene: a case report with literature review. *BMC Med Genet* 19: 142, 2018. doi:10.1186/s12881-018-0595-8.

857. Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 374: 1094, 2016. doi:10.1056/NEJMc1600827.

858. Zisman AL, Evan AP, Coe FL, Worcester EM. Do kidney stone formers have a kidney disease? *Kidney Int* 88: 1240–1249, 2015. doi:10.1038/ki.2015.254.