JAG1 of all trades, master of CKD? The role of *JAG1* in autosomal dominant tubulointerstitial kidney disease

Michael S. Wiesener[1] and Eric Olinger[2]

The current study by Menguy *et al.* describes *JAG1* as a novel candidate gene for the spectrum of autosomal dominant tubulointerstitial kidney disease. Patients have been shown to develop fibrosis and chronic kidney disease, when distinct pathogenic germline variants occur in *JAG1*. Interestingly, genetic alterations in the Jagged1/Notch2 pathway can cause the variable appearance of Alagille syndrome, which may also occur in the very same families. Haploinsufficiency is the likely pathomechanism, but future work will need to define the underlying mechanisms.

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With a global prevalence of approximately 12%, chronic kidney disease (CKD) is a major and growing health burden. A monogenic cause is found in 10%–30% of adults with CKD, most commonly autosomal dominant polycystic kidney disease, Alport syndrome, and autosomal dominant tubulointerstitial kidney disease (ADTKD), which together account for approximately 60% of adult genetic diagnoses. ADTKD is defined by nonspecific features such as interstitial fibrosis with tubular atrophy, absence of glomerulopathy, and progression to kidney failure in mid-adulthood, usually with a positive family history. It accounts for approximately 5% of monogenic CKD.[1,2] Pathogenic variants in *UMOD* and *MUC1* are by far the leading cause of ADTKD.[1] In analogy to autosomal dominant polycystic kidney disease, there are "major" ADTKD genes and "minor" genes that are either detected very rarely or for which ADTKD is a rare presentation (Table 1).

Kidney Disease: Improving Global Outcomes recommends subclassifying cases by gene (e.g., ADTKD-*UMOD*), or ADTKD-NOS (not otherwise specified) when no cause is found. Historically, approximately 40%–50% of cases were ADTKD-NOS, but this number is lower (approximately 15%–20%) when strict clinical criteria and broad testing are applied. Even in "typical" families, the diagnostic yield is not complete, suggesting undiscovered genes, undetected variants in known genes, or more complex oligogenic inheritance. Precise molecular diagnostics are increasingly important as targeted therapies emerge. Moreover, understanding the genetic basis of ADTKD may shed light on tubulointerstitial fibrosis, a common pathway in many CKD forms. However, given the nonspecific features of ADTKD and the absence of discriminatory positive diagnostic criteria, it should be noted that it is difficult to define "typical" cases of ADTKD. Possible causes of phenocopies, that is, "phenotype mimics," are broad and include a large number of nongenetic as well as genetic causes of progressive CKD[1] (Table 1).

In this issue, Menguy *et al.*[3] propose monoallelic *JAG1* pathogenic variants as a novel cause of ADTKD. They describe a large ADTKD-NOS family in which a heterozygous nonsense *JAG1* variant, initially identified in a girl with Alagille syndrome (ALGS) from this family, segregates with CKD in 5 relatives lacking typical ALGS features. Screening 203 ADTKD families from an internal cohort, including 35 ADTKD-NOS families, identified additional segregating *JAG1* variants in 2 unsolved pedigrees, again without consistent extrarenal manifestations of ALGS, though 1 case of biliary atresia was reported.

JAG1 and Alagille syndrome

JAG1 encodes Jagged1, a 1218-amino-acid single-pass transmembrane ligand involved in Notch signaling, mediating short-range cell communication. Canonical signaling requires binding of the ligand's (e.g., Jagged1) extracellular domain to its receptor (e.g., Notch2), triggering receptor proteolysis and release of the Notch intracellular domain, to act as a transcription factor in the nucleus. Dysregulated Notch signaling has been linked to developmental syndromes, adult diseases, and cancer.[4,5]

ALGS is a multisystem autosomal dominant disorder caused by pathogenic variants in *JAG1* (approximately 95%) and rarely *NOTCH2* (approximately 2.5%), with approximately 70% of cases arising *de novo*. ALGS shows wide phenotypic variability, with major features including bile duct paucity with cholestasis, congenital cardiopathy, butterfly vertebrae, ocular abnormalities, and characteristic facies. Prevalence is 1:30,000–1:50,000 live births. Kidney involvement occurs in

[1]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany; and [2]Center for Human Genetics, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Correspondence: Eric Olinger, Center for Human Genetics, Cliniques Universitaires Saint-Luc, Avenue Hippocrate, 10, 1200 Brussels, Belgium. E-mail: eric.olinger@saintluc.uclouvain.be

Table 1 | ADTKD: major genes and gene candidates

Gene	First published	Demonstrated or suspected molecular pathomechanism	Optional (extrarenal) symptoms
Major ADTKD genes			
UMOD	Hart TC, Gorry MC, Hart PS, et al. Mutations of the *UMOD* gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. *J Med Genet*. 2002;39:882–92. https://doi.org/10.1136/jmg.39.12.882	Proteotoxicity (mostly missense variants and in-frame insertion/deletions), ER accumulation of mutant uromodulin aggregates, and ER stress	Early gout linked to reduced fractional uric acid excretion
MUC1	Kirby A, Gnirke A, Jaffe DB, et al. Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in *MUC1* missed by massively parallel sequencing. *Nat Genet*. 2013;45:299–303. https://doi.org/10.1038/ng.2543	Proteotoxicity (frameshift variants leading to neoprotein), accumulation in the secretory pathway, and possibly ER stress	NA
REN	Zivná M, Hůlková H, Matignon M, et al. Dominant renin gene mutations associated with early-onset hyperuricemia, anemia, and chronic kidney failure. *Am J Hum Genet*. 2009;85:204–213. https://doi.org/10.1016/j.ajhg.2009.07.010	Defective trafficking or proteotoxicity (missenses and in-frame deletion), defective prorenin/renin secretion	Childhood anemia and hypotension, hyperkalemia, and early gout
HNF1B[a]	Lindner TH, Njolstad PR, Horikawa Y, et al. A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1beta. *Hum Mol Genet*. 1999;8:2001–2008. https://doi.org/10.1093/hmg/8.11.2001	Haploinsufficiency (various variant types including whole-gene deletions), transcription factor with multiple roles in developing and adult kidney, a specific mechanism for ADTKD presentations not clear	CAKUT, MODY type 5, kidney cysts, hypomagnesemia, genital tract malformations, elevated liver enzymes
Minor ADTKD gene candidates			
SEC61A1	Bolar NA, Golzio C, Živná M, et al. Heterozygous loss-of-function *SEC61A1* mutations cause autosomal-dominant tubulo-interstitial and glomerulocystic kidney disease with anemia. *Am J Hum Genet*. 2016;7;99:174–187. https://doi.org/10.1016/j.ajhg.2016.05.028	Loss of function (missense variants), possibly protein translocation defects across ER membrane	Congenital anemia and neutropenia, cleft palate spectrum, polydactyly
DNAJB11	Cornec-Le Gall E, Olson RJ, Besse W, et al. Monoallelic mutations to *DNAJB11* cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet*. 2018;102:832–844. https://doi.org/10.1016/j.ajhg.2018.03.013	Haploinsufficiency (including frameshifting and nonsense variants), possibly a defect in folding and trafficking of ER proteins	Polycystic kidney disease, polycystic liver disease, vascular phenotype?
APOA4	Kmochová T, Kidd KO, Orr A, et al. Autosomal dominant ApoA4 mutations present as tubulointerstitial kidney disease with medullary amyloidosis. *Kidney Int*. 2024;105:799–811. https://doi.org/10.1016/j.kint.2023.11.021	Proteotoxicity (missense variants), medullary amyloid storage	NA
JAG1	Menguy *et al*., 2025[3]	Haploinsufficiency with disturbed Notch signaling?	Cholestasis, cardiac malformation, skeletal and ocular abnormalities, characteristic facial phenotype (and others)

AD, autosomal dominant; ADTKD, autosomal dominant tubulointerstitial kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract; ER, endoplasmic reticulum; MODY, maturity-onset diabetes of the young; NA, not applicable.

[a]The inclusion of *HNF1B* as a major ADTKD gene is debated based on the following: (i) the majority of cases are pediatric and present as CAKUT and should not be referred to as ADTKD-*HNF1B* and (ii) the mechanism linking *HNF1B* with a progressive fibrotic disease is not clear. In some instances, however, patients with pathogenic *HNF1B* variants can present as *bona fide* ADTKD-like presentations as part of their spectrum, and therefore, until the gene-disease relationship is further clarified, it is prudent to continue listing it as a major ADTKD gene, in accordance with the Kidney Disease: Improving Global Outcomes controversy conference 2015.[2]

Genes that have been reported in the context of ADTKD, either in the Kidney Disease: Improving Global Outcomes controversy conference 2015[2] or reported since then, causing an ADTKD phenotype when altered in the germline. The candidate genes were grouped into *major*, when pathomechanistic evidence is reasonably assured and/or the disease presentation is more frequent. *Minor* gene candidates were grouped because ADTKD-like presentations are probably part of a spectrum with potentially rare presentations, and pathomechanistic evidence is rather scarce. In numerous reports, alterations in other genes have been discussed to possibly phenocopy ADTKD, sometimes together with other kidney pathologies (such as focal segmental glomerulosclerosis, i.e., *PAX2*, *INF2*, *and COL4A3/4/5*), in the context of syndromic diseases (such as *SALL1*, *EYA1*, *and GATA3*) or non-autosomal dominant phenocopies such as autosomal recessive nephronophthisis (e.g., *NPHP1*-associated disease that can present as adult-onset kidney failure), *FAN1*-associated autosomal recessive interstitial nephritis, or certain maternally inherited point mutations in the mitochondrial genome.

approximately 40% of patients and includes congenital anomalies of the kidney and urinary tract, renal tubular acidosis, glomerulopathy, and renal artery stenosis. CKD develops in approximately 10% and kidney failure in approximately 2%, independent of liver disease. Histology may show lipid vacuoles in the mesangial matrix and mesangial foam cells.[5]

During human embryogenesis, *JAG1* expression correlates with organs affected in ALGS. In the kidney, *JAG1* and *NOTCH2* are expressed in developing glomeruli, proximal tubules, and collecting ducts, essential for glomeruli and tubule formation and stabilization of proximal tubule cell fate.[5] In the mouse kidney, Jagged1 signals primarily through Notch2.[5,6] Normally quiescent postdevelopment, Notch signaling can reactivate in various types of kidney injury and disease. Rat ischemia-reperfusion models implicate Notch2 in epithelial regeneration.[5] Mice with tubule-specific deletion of *Jag1* (or *Notch2*) showed no baseline phenotype but were protected from folic acid–induced fibrosis. Finally, *JAG1* and *NOTCH2* showed the strongest positive correlation with interstitial fibrosis in a large cohort of human kidney samples,[6] and as shown here,[3] *JAG1* is constitutively expressed in the adult human loop of Henle and distal tubules. These findings support a dual role for Jagged1/Notch2 signaling in the kidney: (i) developmental role implicated in ALGS and (ii) homeostatic role, maintaining adult nephron integrity, with disruption potentially driving degenerative phenotypes such as progressive CKD.[5]

Gene-disease association for ADTKD-*JAG1*

Definitive association of *JAG1* pathogenic variants with ADTKD will require replication over time in additional cohorts and mechanistic evidence. The segregation data reported here[3] in 3 large families are compelling but not enough by themselves to meet gene-disease association thresholds as proposed by ClinGen (https://clinicalgenome.org/), partly because genotypes were unavailable for some deceased affected relatives. Nonetheless, the authors carefully excluded alternative diagnoses, including haplotype analysis ruling out linkage to *MUC1* and *UMOD*, kidney panel, *MUC1* testing, and exome sequencing as well as whole genome sequencing to investigate rare noncoding or structural variants in known ADTKD genes. To extend evidence, they screened 937 patients with unsolved CKD from Necker Hospital with tubulointerstitial features, identifying 6 rare *JAG1* missenses, 2 previously reported in ALGS. Genomics England data suggest enrichment of rare *JAG1* variants in CKD G5 versus proteinuric disease. Strengthening the gene-disease relationship will require systematic assessment of additional ADTKD cohorts, with careful documentation of segregation and phenotypes as well as larger population datasets to test for reproducible enrichment of *JAG1* variants in CKD.

Pathomechanism of ADTKD-*JAG1*?

Three distinct *JAG1* pathogenic variants were identified in the 3 ADTKD families: a nonsense variant (p.Trp288*), a missense (p.Arg201Cys), and a splice-site variant (c.2372+3_2372+6del). Most functional evidence was provided from a patient with the latter splice-site variant, where the authors used urine-derived renal epithelial cells as well as one kidney biopsy to show that aberrant transcripts are detected in kidney cells (with no clear indication of nonsense-mediated decay), that Jagged1 protein levels were reduced (in cells and on biopsy) but without detection of abnormal protein isoforms or endoplasmic reticulum stress, and that the Notch pathway might be downregulated in the patient's urine-derived renal epithelial cells. No functional data are available for the nonsense variant, leaving nonsense-mediated decay unresolved there. Like ALGS, haploinsufficiency was suggested as the most likely explanation in the ADTKD pedigrees.

Future work will need to better define Notch pathway dysregulation in ADTKD-*JAG1*. While increased Notch signaling has been reported in CKD kidneys,[6] here reduced signaling was suggested in one patient's urine-derived renal epithelial cells. More sophisticated *in vitro* approaches, such as co-culture systems, may be required to identify signal-sending and signal-receiving cell types rather than measuring "bulk" Notch activity.[6] Direct patient tissue studies are essential, ideally using unbiased approaches such as single-cell RNA-seq coupled with confocal imaging to define the subcellular localization of Jagged1, exclude compensatory upregulation of other Notch ligands, define the expression profile of Notch2, analyze endoplasmic reticulum stress directly on human tissue, and identify other potential profibrotic pathways. As with other ADTKD entities, kidney tissue is unfortunately limited, as biopsies are uncommon in ADTKD. The reported link between aberrant Jagged1/Notch2 signaling, Tfam regulation (a key transcriptional regulator of mitochondria), metabolic reprogramming, and tubule epithelial dedifferentiation and proliferation[6] is particularly interesting given the evidence for abnormal mitochondrial biogenesis and repressed Tfam expression in ADTKD-*UMOD* models.[7] It will also be interesting to test for aberrant Notch signaling in established forms of ADTKD.

Kidney disease in ADTKD-*JAG1* and phenotype variability

The ADTKD-*JAG1* phenotype as described here[3] includes progressive CKD without overt proteinuria or hematuria, small- or normal-sized kidneys with sometimes a few cysts, interstitial fibrosis with tubular atrophy on 2 biopsies, and hyperuricemia/gout with advanced CKD. Kidney failure occurred in late adulthood with a range of 49–84 years in affected individuals. CKD progression was variable because 2 patients from the missense variant family had only moderate CKD in their seventies, and one 64-year-old woman from the same family retained normal estimated glomerular filtration rate. Interestingly, urine-derived renal

epithelial cells from the latter showed less reduction of Jagged1, though genotype-phenotype correlations remain speculative.

In ALGS, disease is mediated by *JAG1* haploinsufficiency. Indeed, most ALGS-associated *JAG1* variants are loss of function, including large deletions encompassing *JAG1* and many missense variants, particularly loss of cysteines, impair protein trafficking, glycosylation, and Notch signaling.[5,8] Because no alternative pathomechanism has been demonstrated in ADTKD-*JAG1*, the molecular basis for the phenotypic variability remains unclear. Although some reports describe adult patients with *JAG1* variants presenting with kidney disease, retrophenotyping often reveals subtle ALGS features. In the present cohort, 14 adult patients had CKD with pathogenic *JAG1* variants but no extrarenal involvement, including 4 individuals from 2 families who underwent detailed reassessment. However, in 2 families, a child had hepatic disease consistent with ALGS. Importantly, the 3 *JAG1* variants reported here have each been previously described in a patient with ALGS, although phenotype and/or segregation data were scarce. Overall, the presented evidence, especially phenotype variability within families and shared pathomechanism, suggests that the nonspecific presentation of ADTKD without extrarenal manifestations may be part of the ALGS/haploinsufficiency spectrum rather than a distinct mechanism and is not in favor of an allelic effect, that is, a specific phenotype associated with distinct *JAG1* variants.

The modifying factors underlying the *JAG1* disease spectrum are unknown. An intriguing parallel is *HNF1B*, which can cause autosomal dominant multisystem developmental disease but has also been described in a few patients with an ADTKD-like phenotype. Hepatocyte nuclear factor 1β (HNF1β) is a transcription factor expressed in several developing and adult organs. In the kidney, it has roles in nephrogenesis, segment fate acquisition, and maintenance of tubular function via roles in ureteric bud branching, Wingless/Int1 (WNT) signaling, regulation of epithelial-mesenchymal transition, and transforming growth factor–β signaling, among others. Its downstream targets include *Pkhd1*, *Pkd2*, and *Umod*, and it is linked to mitochondrial regulation via peroxisome proliferator–activated receptor-γ, suggesting a mitochondrial component possibly linked with ADTKD-like presentations.[1] Like *JAG1*, haploinsufficiency is the proposed mechanism, but the variable expressivity ranging from developmental phenotypes (congenital anomalies of the kidney and urinary tract) in most and ADTKD-like presentations in some patients remains unexplained. It is noteworthy that the reduced *UMOD* expression expected under *HNF1B* haploinsufficiency would oppose the gain-of-toxic-function mechanism documented to cause ADTKD-*UMOD*, suggesting possible mechanisms unrelated to uromodulin in the ADTKD-like cases. In mice, *Hnf1b* inactivation causes rudimentary nephrons with strong downregulation of Notch pathway components, including *Jag1*.[9] Notch signaling and HNF1β are also implicated in bile duct morphogenesis, where HNF1B is upregulated by Notch signaling, highlighting the interconnection between the pathways.

Conclusion

JAG1 has developmental roles and postdevelopment functions in nephron maintenance and fibrosis but was linked only to the developmental disorder ALGS. Menguy *et al.* now provide compelling evidence that monoallelic *JAG1* pathogenic variants can also cause ADTKD without extrarenal ALGS features, though with intrafamilial variability. As haploinsufficiency is the likely mechanism in both conditions, ADTKD may represent an adult degenerative spectrum of *JAG1*-associated disease, similar to what is described for *HNF1B*. Future work should confirm the gene-disease relationship, establish ADTKD-*JAG1* prevalence, and clarify underlying mechanisms and the role of Notch signaling in ADTKD more broadly. According to Kidney Disease: Improving Global Outcomes, the diagnosis ADTKD-*JAG1* should be reserved for patients with isolated CKD fulfilling ADTKD criteria.[2]

DISCLOSURE

All the authors declared no competing interests.

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