genetics of kidney disease

On the way to translate GWAS into kidney disease mechanisms

Olivier Devuyst[1] and Krzysztof Kiryluk[2]

Refers to: Liu H, Doke T, Guo D, et al. Epigenomic and transcriptomic analyses define core cell types, genes and targetable mechanisms for kidney disease. *Nat Genet*. 2022;54:950–962.

Kidney International (2023) **103,** 16–18; https://doi.org/10.1016/j.kint.2022.10.004

KEYWORDS: cell signaling; chronic kidney disease; gene expression; proximal tubule; transcription regulation

Chronic kidney disease (CKD) is a global public health burden, affecting as many as 10% to 15% of the population worldwide and >20% of individuals older than 60 years.[1] Elucidating the mechanisms underlying genetic effects on kidney function and propensity to develop CKD will be critical to develop new therapeutic approaches to prevent and treat kidney diseases. Moreover, therapeutic targets that are supported by genetic evidence in humans have been considerably more successful in the drug development pipeline, motivating continued investment in genetic discovery.[2,3]

In less than 2 decades, population-based genome-wide association studies (GWAS) have identified common variants in hundreds of genomic regions associated with kidney function parameters such as estimated GFR based on serum creatinine (eGFRcr). Collectively, these variants explain ∼7% of eGFR variance and 20% of eGFR heritability. Despite rapid progress in genetic discovery, small effects of GWAS loci and mapping of most loci to non-coding regions of the genome have impeded mechanistic insights and clinical translation.[4] Some of these difficulties could be circumvented by the integration of multiple readouts into the GWAS signals (Figure 1), as illustrated in a seminal study conducted by Liu *et al.*[5]

What did the study show?

To maximize the power of new discovery, Liu *et al.* first conducted a multicohort meta-analysis of GWAS for eGFRcrea in >1.5 million individuals, identifying 878 independent loci (including 126 novel loci). They analyzed the genotype effect on gene expression in the kidney by integrating all presently available expression quantitative trait locus (eQTL) data sets. The GWAS loci were globally enriched in genes expressed in the kidney, including some with known roles in kidney function and metabolism.

Next, Liu *et al.* analyzed the genotype effect on DNA methylation, an epigenetic process that dynamically regulates tissue-specific gene transcription.[6] In mammals, DNA methylation is almost exclusively found in CpG dinucleotides (a cytosine and guanine separated by a phosphate group, where cytosine is methylated to form 5-methylcytosine; see Figure 1). When located in a gene promoter, DNA methylation typically acts to repress gene transcription. The analysis of methylation quantitative trait loci (meQTLs) in 443 kidney samples identified >100,000 meQTLs at CpG sites (mCpGs), including ∼20,000 kidney-specific mCpGs enriched in transcription factor–binding sites. The expected negative correlation between CpG methylation and target gene expression was mostly confirmed. Importantly, this variation in kidney-specific methylation (enriched at enhancers) explained a larger fraction of kidney function heritability than variation in gene expression.

The next step was to associate each genetic signal with a specific segment and cell type in the kidney.[7] Analysis of single-cell open chromatin information (snATAC-seq) in human kidney samples showed enrichment of methylation-mediated heritability of eGFRcrea in proximal tubule (PT)– and loop of Henle (LOH)–specific accessible chromatin regions. These approaches identified multiple target genes, including *LRP2* (encoding the multiligand megalin receptor in PT cells) and *UMOD* (encoding uromodulin expressed in the LOH). Interestingly, the lead variant at the *UMOD* locus mapped to an open chromatin

[1]*Department of Physiology, Mechanisms of Inherited Kidney Disorders, University of Zurich, Zurich, Switzerland; and* [2]*Division of Nephrology, Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York, USA*

Correspondence: *Olivier Devuyst, Department of Physiology, University of Zurich, Winterthurerstrasse 190, Zurich CH-8057, Switzerland. E-mail: olivier.devuyst@uzh.ch*