genetics of kidney disease

A multiomic resource to interpret genetic associations with kidney function

Pascal Schlosser[1,2,3] and Anna Köttgen[1,2,3]

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Chronic kidney disease (CKD) represents a global health challenge that affects ≈850 million people globally, resulting in significant morbidity and mortality.[1] Diagnosis and staging of CKD is typically based on the estimated glomerular filtration rate from serum creatinine (eGFRcrea). Investigating the genetic determinants of eGFR therefore has the potential to implicate genes and pathways involved in the regulation of kidney function, which could represent entry points for new therapies to slow CKD development and progression. However, interpreting results from large-scale genetic screens of millions of genetic variants spread across the entire human genome in the context of kidney biology is anything but trivial. In the article "Kidney Multiome-Based Genetic Scorecard Reveals Convergent Coding and Regulatory Variants" by Liu *et al.*,[2] the authors combine large-scale genetic association studies of eGFR with multiomic data sets generated from kidney tissue to create a comprehensive resource that enables the interpretation of such associations and can deliver new mechanistic insights (Figure 1).

What did the study show?

Liu *et al.* undertook a meta-analysis of genome-wide association studies (GWAS) of eGFRcrea based on data from >2.2 million individuals of diverse ancestries. In their screen of >13 million common genetic variants, they identified 1026 independent genomic segments that contained variants significantly associated with eGFR, 97 of which had not been reported previously. Many of the most strongly associated variants are located outside of the coding genome. This suggests that they may act on kidney function by affecting gene regulation. However, gene regulation is tissue specific, and without tissue context, it is difficult to identify the underlying causal genes for the associated variants. Therefore, the authors generated a comprehensive resource to enable their interpretation.

The authors integrated 32 different types of genetic and epigenetic evidence sources, that ranged from the effects of variant alleles on gene expression (termed ASE) and chromatin accessibility in bulk kidney tissue (termed bASA) as well as individual nuclei (termed snASA), to establish variant effects on gene expression (termed eQTL)[3] and DNA methylation (termed meQTL).[4] Some of these omics data sets were specifically generated for this study, and importantly, most of them were based on kidney tissue. Throughout the article, the authors show examples where only the integration of eGFR-associated variants with kidney gene expression or chromatin accessibility data can establish how these variants are linked to differential gene regulation. For instance, the shared genetic architecture between genetic variants in the *GATM* gene locus with eGFR and with differential expression of *GATM* was only detected when the authors examined ASE data from tubular and glomerular compartments of the kidney.

Using the complementary multiomics data sets as well as genetic information from common coding variants, the team developed the "Kidney Disease Genetic Scorecard," a tool that can help to prioritize potentially causal regulatory variants and genes for reduced kidney function. The authors used their approach to prioritize 601 genes

[1]*Institute of Genetic Epidemiology, Department of Data Driven Medicine, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany;* [2]*Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; and* [3]*Centre for Integrative Biological Signaling Studies (CIBSS), University of Freiburg, Freiburg, Germany*

Correspondence: *Anna Köttgen, Hugstetter Strasse 49, 79106 Freiburg, Germany. E-mail: anna.koettgen@uniklinik-freiburg.de*

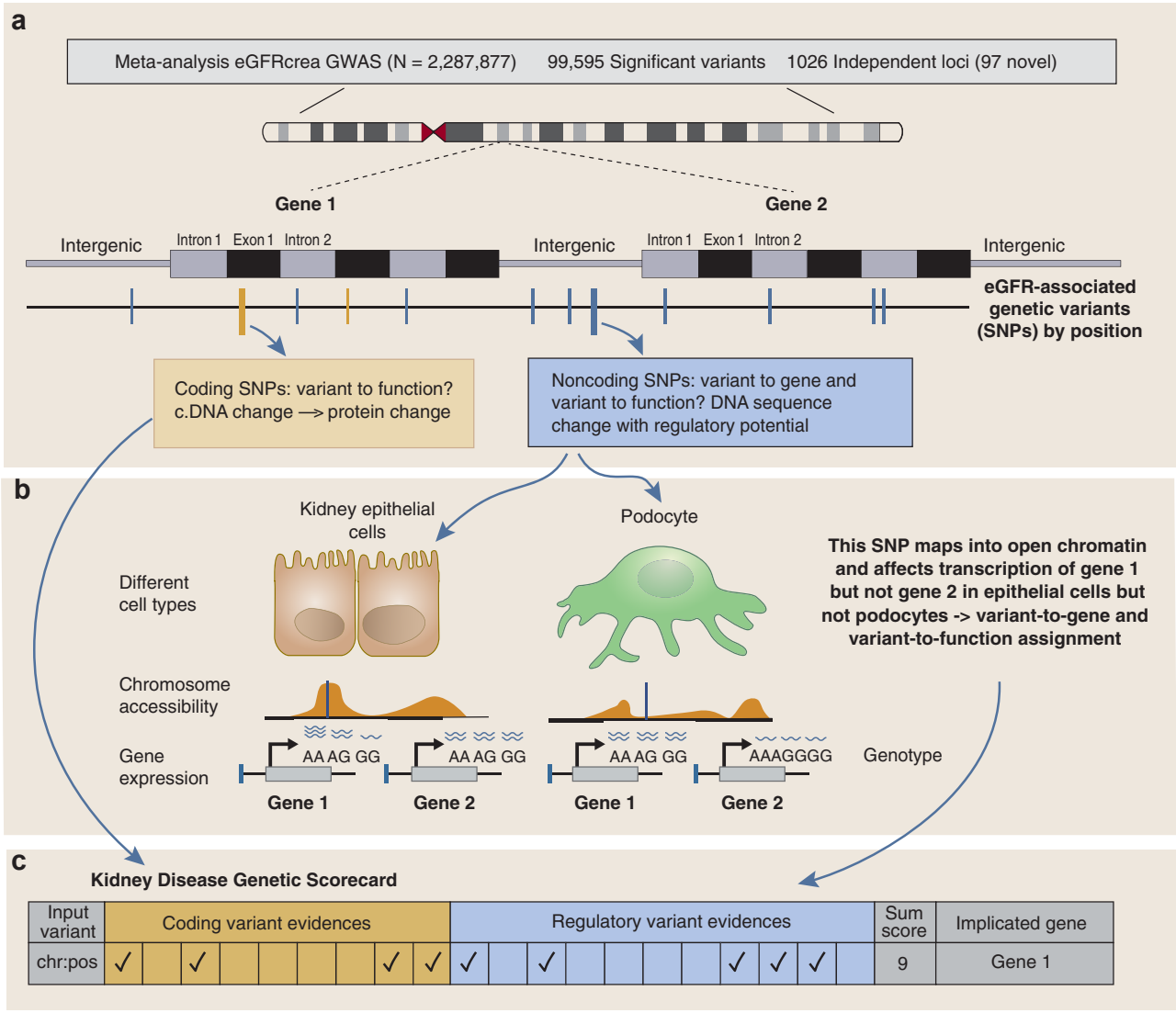

Figure 1 | The Kidney Disease Genetic Scorecard. Liu *et al.*[2] integrate large-scale genetic association studies of eGFR with multiomic data sets from kidney tissue, developing a comprehensive resource in which a score summarizing the connection of variants and genes to kidney function is provided. (**a**) The eGFR-associated genetic variants are illustrated by chromosomal location that needs to be interpreted. (**b**) A schematic of the various kidney cell type–specific evidence resources used to address the variant-to-gene and variant-to-function challenges for putative regulatory variants is displayed. (**c**) A schematic of the Kidney Disease Genetic Scorecard is shown; the schematic assembles the resources for coding variant information (yellow) and regulatory variant information (blue) and summarizes the combined evidence into a summary score (gray) for each variant.

as important for kidney function, among which 161 contained both regulatory as well as common coding variants independently associated with eGFRcrea (termed convergence). Moreover, 124 of the 601 genes are known targets of existing FDA-approved drugs, highlighting the resource's value to inform focused drug repurposing studies.

Why is the study important?

This study addresses longstanding challenges in complex trait genetics: the "variant-to-gene" and the "variant-to-function" problem. Although previous GWAS have mapped many loci associated with kidney function[4–7] and shown that they are preferentially located in kidney-specific regulatory regions,[3,4,8] effector genes often remained unclear. This is in part due to the more than a dozen different cell types found in the kidney, and the different methods available to assess gene regulation in genome-wide experiments. By applying a suite of complementary multiomic techniques, Liu *et al.* provide an integrated view into how eGFR-associated variants can affect different layers of gene regulation in the kidney. For instance, the integration of bulk and single-cell data enables not only the identification of

candidate genes, but also the mapping of these effects to specific kidney cell types. The study also contains important methodological advances: the authors generated so-called "multiome" data, where chromatin accessibility and transcription are profiled from the nucleus of the same kidney cell and are therefore suited for establishing cell type–specific links. They introduced a novel statistical tool, called Open4Gene, and used it to establish such kidney cell type–specific links between regulatory regions, where transcription factors may bind, and their putative target genes. Open4Gene compared favorably with existing methods and helped the authors to map >80% of variants in Open4Gene peaks to a single gene, thereby addressing the "variant-to-gene" problem.

The main deliverable of this study is the "Kidney Disease Genetic Scorecard" (Figure 1). The scorecard assembles the novel resources built in the current study as well as the complementary resources from published studies[3,4,9] in an additive score. It will be of great use to researchers interested in specific candidate genes or variants and will likely inform a wealth of experimental follow-up studies that investigate the mechanisms that connect these genes to kidney function and CKD. Especially, research focused on the 601 prioritized genes could accelerate translational studies.

Implications for future research

The comprehensive resource generated by Liu *et al.* not only identifies regulatory variants for further mechanistic study in specific kidney cell types and may prove useful in prioritizing opportunities for drug repurposing but could also serve as a blueprint for investigating other complex diseases. By integrating diverse data sets—from bulk tissue analyses to single-cell modalities—researchers can obtain a more nuanced view of disease biology that transcends the limitations of any single approach. This aspect is also highlighted in the genetic scorecard, where evidence sources varied even among highly scoring genes. Future research directions include the incorporation of additional evidence from rare coding variants into the genetic scorecard, because they are more likely to result in loss of function compared with common coding variants, evaluation of a weighted or nonadditive approach to scoring the different evidence sources included in the scorecard, as well as the generation of functional genomics data sets with improved coverage of rare kidney cell types and of transcripts of lower abundance.

Conclusion

Liu *et al.* have delivered an ambitious and highly integrative study that advances our understanding of the genetic underpinnings of kidney function and are sharing the generated data sets with researchers around the globe. Their innovative use of multiomic data has enabled the construction of the Kidney Disease Genetic Scorecard that provides researchers with an intuitive evidence score and the underlying data sources linking a given gene or variant to kidney function. This comprehensive resource, based on state-of-the-art single-cell techniques to profile kidney tissue and cell types with GWAS of kidney function in populations, represents a highly valuable resource for the nephrological but also the broader scientific community.

DISCLOSURE

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