GENETICS IN 2020

New genetic insights into kidney physiology and disease

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Genetic research in nephrology is rapidly advancing. Key studies published in 2020 demonstrate that genetic findings can provide new tools for patient diagnosis and risk stratification as well as important insights into kidney physiology and disease mechanisms that could potentially lead to novel therapies.

Novel sequencing technologies and computational approaches enable rapid examination of the genomes of patients with kidney disease, identification of genetic programmes that shape kidney function in large population studies, and integration of genetic data with additional molecular data and with data from electronic health records (EHRs) to elucidate the consequences of genetic variation. Together with technical advances that permit studies of single cells and molecules with important roles in kidney disease, these genetic studies not only empower nephrologists to provide patients with more accurate diagnoses and appropriate treatments, but also deliver a basis for novel approaches to treat and prevent kidney disease. Four research studies published in 2020 exemplify the value of genetic studies and their potential in nephrology (FIG. 1).

> “genetic studies … deliver a basis for novel approaches to treat and prevent kidney disease”

First, a state-of-the-art genome-wide association study (GWAS) of primary membranous nephropathy (MN) elucidates the genetic architecture of this rare disease and potentially provides immediate clinical applications. This collaborative study involved 3,782 patients with MN and 9,038 healthy individuals from Europe, North America and East Asia[1]. In addition to confirming known risk loci for MN, the study identified two novel genome-wide significant loci encoding the p105 subunit of NF-κB (NF-κB1) and interferon regulatory factor 4 (IRF4), which are master regulators of inflammation. These findings provide genetic support for the prioritization of NF-κB and interferon pathways as potential drug targets for MN. The researchers also fine-mapped the *PLA2R1* risk locus[2], which encodes the main podocyte autoantigen in MN, to a variant in the putative regulatory region that exhibited kidney-specific effects on *PLA2R1* expression. The risk allele was associated with higher mRNA expression of *PLA2R1* in the glomerulus but lower expression in non-kidney tissues. Moreover, the study confirmed strong effects of the HLA locus (for example, a 3.4-fold increase in risk for each *HLA-DRB1*0301* risk allele) and provided evidence for ancestry-specific effects of HLA risk alleles. A genetic risk score (GRS) based on the risk loci and their interactions explained an unusually large fraction of the disease risk for GWAS, estimated at 32% in East Asians and 25% in Europeans. Effects of this magnitude are comparable to those of Mendelian variants, suggesting that the GRS might aid diagnosis of MN. Indeed, when combined with serum anti-PLA2R ELISA, the GRS correctly re-classified 20–37% of antibody-negative patients in independent validation studies. Thus, the GRS provided complementary diagnostic information to serum anti-PLA2R ELISA, improving its sensitivity while maintaining high specificity. These findings demonstrate that GWAS can lead to clinically meaningful diagnostic applications in nephrology.

The second study illustrates how unbiased molecular data and EHRs can be integrated with genetic data to gain insights into how the kidney handles metabolites. Using genomic and metabolomic data from >1,600 patients with chronic kidney disease (CKD), the researchers performed genome-wide scans to identify genetic variants that were associated with the urinary levels of 1,172 metabolites[3]. The detected and replicated genes were strongly enriched in tissues and cell types in the intestine, liver and kidney (particularly in the proximal tubule) that are known to have important roles in the absorption, distribution, metabolism and excretion of small molecules. Hence, this study shows that urine metabolite levels are an integrated read-out of systemic processes that generate metabolites and the subsequent active transport and detoxification of these metabolites along the nephron. Although the study of some metabolites was facilitated by their accumulation in patients with CKD, most of the genetic effects translated to a validation sample of people with normal kidney function, suggesting that the analysis identified physiological functions of the candidate genes. This study highlights many biologically plausible reactions and transport processes and provides a comprehensive resource of genetic targets for biotransformation, detoxification and transport along with their candidate substrates and target cell types for experimental follow-up.

The third study explores the interplay between monogenic and polygenic risk for familial hypercholesterolaemia (which increases the risk of coronary artery disease), hereditary breast and ovarian cancer, and Lynch syndrome (which increases the risk of colon cancer)[4]. The US Centers for Disease Control and Prevention classifies these conditions as having tier 1 genomic applications with a significant potential for a positive impact on public health. About 1% of asymptomatic adults carry a pathogenic or likely pathogenic monogenic risk variant that is associated with one of these three tier 1 genomic conditions[5]. As the disease variants have incomplete penetrance and variable expressivity, Fahed et al.[4] hypothesized that their penetrance was partly determined by polygenic risk — the cumulative impact of thousands of genetic variants across the genome[6]. To test this hypothesis, they computed polygenic

Key advances

- A genome-wide association study (GWAS) of membranous nephropathy identifies novel loci and validates a genetic risk score that could improve diagnosis of this rare disease[1].
- GWAS that integrate genomic and metabolomic data from patients with chronic kidney disease identify novel candidate mechanisms of metabolite detoxification and excretion in the kidney[3].
- Analysis of the contributions of monogenic variants and polygenic risk scores to probability of disease in carriers of risk variants for tier 1 genomic conditions demonstrates that polygenic background modifies the risk of monogenic diseases[4].
- High-resolution imaging of uromodulin, which is encoded by an important kidney disease gene, identifies a potential mechanism by which this protein might defend against urinary tract infections[8].

> GWAS can lead to clinically meaningful diagnostic applications in nephrology

risk scores for coronary artery disease, breast cancer and colorectal cancer, and assessed the combined contributions of these scores and of monogenic risk variants for the tier 1 conditions on disease risk in large cohorts from population-based biobanks. Among carriers of the monogenic risk variants, they found substantial gradients in disease risk based on polygenic background, ranging from 17% to 78% for coronary artery disease, 13% to 76% for breast cancer and 11% to 80% for colon cancer. These results support the notion that polygenic background is an important determinant of penetrance in Mendelian disease and suggest that polygenic scores could substantially improve risk stratification for individuals who carry monogenic disease variants. Moreover, the striking consistency of the risk patterns across the tier 1 conditions suggests that these findings might be broadly applicable to other inherited conditions, including Mendelian forms of kidney disease.

The final study provides novel insights into the function of uromodulin, which is encoded by *UMOD*, one of the most important kidney disease risk genes. Rare *UMOD* mutations are a cause of autosomal-dominant tubulointerstitial kidney disease, whereas common regulatory variants are associated with increased risk of CKD, gout and hypertension, as well as with reduced risk of kidney stones and urinary tract infections (UTIs). Although uromodulin is the most abundant protein in human urine, its physiological functions are still incompletely understood[7]. Using cryo-electron tomography, Weiss et al.[8] identify the high-resolution structure of uromodulin and show that this structure enables it to bind uropathogens and mediate bacterial aggregation, thereby likely preventing their adhesion and promoting their clearance in urine. They report that the unique zigzag-shaped backbone and glycosylated arms of uromodulin allow it to function as a multivalent ligand for the bacterial type 1 pilus adhesin. The resulting protective effect against UTIs provides a plausible explanation for the high abundance of uromodulin in urine and may explain the high frequency of CKD-associated *UMOD* variants[9].

In summary, the highlighted studies demonstrate important returns on the GWAS investment in nephrology, including a novel clinical diagnostic tool and new insights into kidney physiology and disease that could accelerate drug development. Demonstration of the interplay of monogenic and polygenic risk underscores another potential clinical utility of GWAS in risk stratification that could be relevant to the future management of inherited kidney diseases. Lastly, the anti-bacterial properties of uromodulin uncovered by elegant imaging studies support the role of UTIs as a potential selective pressure that might have shaped the frequency of *UMOD* risk variants for CKD, gout and hypertension that have been discovered using GWAS.

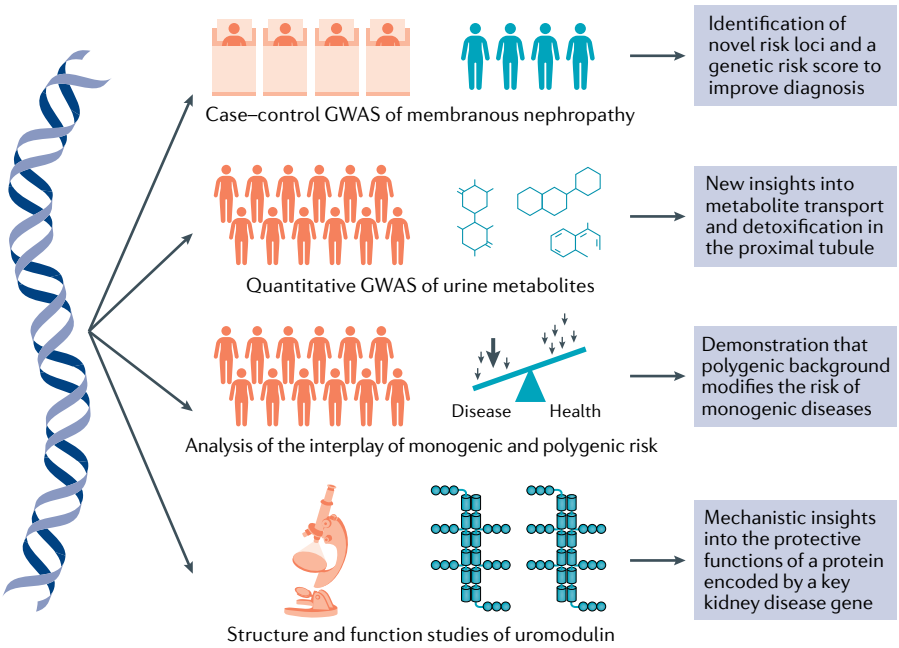

Fig. 1 | **Genetics as a tool to understand kidney function in health and disease.** Key studies published in 2020 demonstrate the ability of genome-wide association studies (GWAS) and their experimental follow-up to provide insights into kidney physiology and disease with potential clinical implications.

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Competing interests
The authors declare no competing interests.