Biologic Underpinnings of Type 1 Diabetic Kidney Disease

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doi: https://doi.org/10.1681/ASN.2019080803

Diabetic kidney disease (DKD) is the leading cause of progressive CKD and ESKD in developed countries, and its prevalence is rapidly increasing worldwide. The excess mortality associated with type 1 diabetes (T1D) and type 2 diabetes occur predominantly in patients with DKD.¹ Current management strategies, primarily glycemic and BP control, often slow but do not halt disease progression. Although DKD has a significant heritable component, underlying genetic variants have not been convincingly identified. This has been attributed to insufficient sample sizes, phenotypic heterogeneity, and a focus on albuminuria rather than marked declines in kidney function. Gene variants associated with all-cause CKD in large meta-analyses generally maintain significance when stratified by the presence of diabetes; however, patients with DKD had relatively preserved eGFR and low levels of albuminuria.² The applicability of these genetic associations to patients with progressive DKD who populate nephrology clinics remains uncertain.

Given these concerns, the article by Salem et al.³ in this issue of JASN significantly advances our understanding of the genetic basis of DKD. This study reports results of a genome-wide association study (GWAS) in 19,406 individuals with T1D from 17 well phenotyped cohorts. Gene-level and gene-set analyses were performed, as well as studies to determine whether significantly associated variants regulate transcript expression. In addition to assembling the largest case-control T1D-DKD sample to date, strengths included an unbiased approach to identifying associated genes, inclusion of low-frequency and exome array variants (more likely to be functional), use of novel analytic techniques, stringent correction for multiple testing, and inclusion of well defined and homogenous qualitative and continuous DKD phenotypes commonly used by nephrologists. The cohorts in discovery studies were of European ancestry; this complicates extrapolation of results to other ancestral populations.

The GWAS included approximately 250,000 genotyped single nucleotide polymorphisms (SNPs) across the genome that capture much of the individual’s genetic diversity (tagging SNPs), 200,000 genotyped exome-focused variants, and SNPs imputed from the genotyped data. Sixteen novel and independent genome-wide loci were significantly associated with one or more clinical definitions of T1D-DKD; four have previously been associated with non-DKDs, kidney structure, and/or biology. In contrast to prior candidate gene studies, loci regulating glycemic control and BP were not associated with DKD phenotypes.

The strongest association was SNP rs55703767, a common missense variant in the collagen type 4 α3 chain gene (COL4A3) with minor allele frequency 21% that was protective against several DKD phenotypes. This COL4A3 variant was protective for the main categorical DKD phenotype, any level of albuminuria, macroalbuminuria, and advanced DKD defined as eGFR<45 ml/min per 1.73 m² or ESKD. These are clinically important phenotypes representing severe disease, distinct from milder phenotypes employed in prior GWAS.² For unclear reasons, COL4A3 association with T1D-DKD was stronger in men than women. Two other variants with genome-wise significance are associated with collagen function. A SNP near the collectin subfamily member 11 gene, which contains a collagen-binding domain, was associated with reduced eGFR, and a variant in the discoidin domain receptor 1 gene, encoding a receptor tyrosine kinase that binds collagen, was associated with microalbuminuria. In addition, variants in several other genes were associated with microalbuminuria, including bone morphogenetic protein 7, a molecule that reportedly protects from DKD. Of note, microalbuminuria is a less informative phenotype that does not reliably predict future CKD. Approximately 2.5%–3% of the total variance in risk of T1D-DKD was accounted for by the top 12 associated SNPs that had effect allele frequencies >1%.

These GWAS results were supported by epidemiologic analyses that revealed stronger COL4A3 association with DKD in individuals with poorer glycemic control and kidney morphometry demonstrating protective reductions in glomerular basement membrane (GBM) width in individuals with associated COL4A3 variants. GBM thickening is a hallmark of DKD.³ Subsequent gene-level and gene-set analyses implicated additional loci and pathways on the basis of the DKD definitions applied. Expression and epigenetic analyses identified suggestive expression quantitative trait loci that could regulate genes in T1D-DKD-associated loci (cis-expression quantitative trait loci) and possible functional roles for non-coding variants. Studies in mice demonstrated expression of COL4A3, SNCAIP, and bone morphogenetic protein 7 almost exclusively in podocytes, supporting a critical role for these...
cells in DKD. Finally, previously reported GWAS associations for SCAF8/CNKSR3 and UMOD in DKD were replicated.6–8

The strongest and most consistent T1D-DKD–associated SNP was in COL4A3, encoding a component of type 4 collagen found in the GBM. Mutations in this gene cause autosomal recessive Alport syndrome, thin basement membrane nephropathy, and FSGS.9,10 This type 4 collagen chain is the target of the autoantibody that causes anti-GBM disease. The relationship between these presumably discordant kidney diseases is likely to be an abnormal GBM. Disruptions in the GBM produce hematuria in Alport syndrome and thin basement membrane nephropathy, and can hinder podocyte attachment with podocyte loss and resultant proteinuria in FSGS.

The goals of precision medicine are to develop new disease ontologies on the basis of molecular phenotypes. Genetic association often reclassifies diseases previously considered unrelated into a single spectrum. This was the case for apoL1 gene-associated kidney diseases. The intriguing connection, mediated by type 4 collagen, between kidney diseases viewed as clinically distinct suggests that “collagen gene-associated nephropathies” may be a more accurate taxonomy. Moreover, this unexpected association between seemingly disparate kidney diseases may yield novel therapies that benefit patients with DKD as well as other diseases associated with dysfunction of type 4 collagen.

Major strengths of these analyses included its large sample size and use of clinically important DKD phenotypes. An important lesson, applicable to the study of non-DKDs, is the need to focus on large numbers of individuals with clinical phenotypes characterizing patients routinely seen in hospital and nephrology clinic settings. Integrating other molecular phenotypes with clinical and genetic data generated using new “omics platforms” from kidney compartments and single cells is the focus of the Kidney Precision Medicine Project (https://www.niddk.nih.gov/research-funding/research-programs/kidney-precision-medicine-project-kpmp). Projects like these will help the nephrology community translate exciting discoveries from the bench into improved outcomes for patients and their families at risk for CKD.

**DISCLOSURES**

Dr. Freedman is a consultant for AstraZeneca Pharmaceuticals and Renalytix AI. Dr. Sedor is a consultant for Goldfinch Bio and Maze.

**FUNDING**

Dr. Sedor is supported by National Institutes of Health grants DK097836, DK108329, DK114908, AI135434, DK083912, and DK100846. Dr. Freedman is supported by National Institutes of Health grants MD009055, DK066358, DK116041, and DK116040.

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