AKR1A1 and Kidney Disease: Promise and Perils of the Multiverse

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COMMENTARY

Past years have seen a proliferation of omics-related databases, such as genomics, epigenomics, transcriptomics, proteomics, and metabolomics databases, that provide huge data sets with millions, if not billions, of potential associations with disease phenotypes. Genomics alone are seldom sufficient to identify the role of gene polymorphisms in the pathogenesis of diseases, as exemplified by two of the strongest genetic associations in metabolic diseases: TCF7L2 in type 2 diabetes and UMOD in chronic kidney disease (CKD). Diverse functions have been attributed to each of these proteins (1,2), but which of these functions might be relevant to therapeutically target for disease mitigation is unclear. Furthermore, gene polymorphisms often do not alter protein-coding sequence or are in noncoding regions of the genome, where their effects on protein expression level is unclear.

In this issue of *Diabetes*, a study by Li et al. (3) suggests that a polymorphism in AKR1A1 is associated with diabetic kidney disease (DKD). The authors' approach prioritized genes that changed in a similar direction with DKD versus normal kidney gene expression using proximal tubule single-cell transcriptomics and 1,305 proteins from kidney cortex. Twenty-four such concordant gene-protein pairs were identified. This transcriptomic approach inherently limits its discovery to proximal tubule genes and excludes genes selectively expressed in other kidney cells that might be detected by whole-kidney bulk RNA sequencing and is also constrained by the circumscribed proteomic exploration. While this directional concordance supports an effect of disease on protein expression, whether altered protein expression is a cause or effect of DKD is uncertain.

To address causation, the authors explored whether any single nucleotide polymorphisms (SNPs) associated with genetic risk of CKD were within 1 Mb of genes for any of these 24 gene-protein pairs. At present, over 800 genomic variants have been associated with increased serum creatinine and inferred kidney disease (4). Of these 24 gene-protein pairs, only an AKR1A1 CKD risk polymorphism was near its gene. Alterations in proximal tubule creatinine secretion may affect blood creatinine levels, resulting in misinterpretation of increased creatinine associated with gene polymorphism (e.g., Slc22A2) as representing decreased glomerular filtration rate (5). Thus, it is reassuring that this AKR1A1 CKD risk polymorphism is also associated with increased serum cystatin C, an orthogonal marker of glomerular filtration rate. Whether cross-sectional population measurements of increased serum creatinine can help identify progressive kidney disease is less certain. Recent studies have explored the association of genetic variants with the slope of increased serum creatinine over time and reassuringly found that some of these cross-sectional variants (e.g., UMOD) do result in more rapid increase in serum creatinine (6). Genome-wide association studies of CKD progression rate are important, but the numbers of cases need to be substantially increased to capture more genes. As of today, AKR1A1 SNPs have not been associated with CKD progression.

AKR1A1 mRNA is expressed in epithelial tissues, including kidney and liver, and at lower levels in brain and skeletal muscle. Based on human tissue mRNA expression in the Genotype-Tissue Expression (GTEx) resource, the SNP at rs499600 may be a *cis*-expression quantitative trait locus (*cis*-eQTL) that regulates AKR1A1 expression in nerve and skeletal muscle but, curiously, not in kidney. Unfortunately, the GTEx human tissue mRNA expression resource is relatively underpowered for kidney samples, with 5× to 10× fewer samples than those available for brain, nerve, and skeletal muscle, so whether the polymorphism at rs499600 affects kidney AKR1A1 expression in normal, nondiseased kidneys is uncertain. As resources with increased numbers of concordant transcriptomic and genomic sequences of normal and diseased human kidney tissues become widely available (like GTEx and the Kidney Precision Medicine Project [KPMP] [https://www.kpmp.org]), confidence in kidney eQTL calling should increase.

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See accompanying article, p. 1188.

With the preceding caveats, AKR1A1 remains a candidate gene that plays a role in DKD, but if this role is authentic, how this gene's deficiency in proximal tubules might contribute to DKD is a mystery. Altered intermediary metabolites might contribute to kidney injury, but which metabolite(s) and how it may be involved in kidney injury are speculative. Since AKR1A1 is predominantly expressed in proximal tubules, it would be important to explore the clinical and histopathologic features of AKR1A1 polymorphism-associated CKD. Is the disease a proteinuric disease or is it a nonproteinuric disease? Is it associated with tubulointerstitial disease or primarily glomerular disease? If it is associated with glomerular disease, how does injury to the downstream nephron affect the glomerulus?

For now, the AKR1A1 SNP joins the increasing list of DKD-associated gene polymorphisms in search of a mechanism. Whether this gene polymorphism affects protein expression is suggested but needs further study. Increased deep phenotyping (including for albuminuria, blood urea nitrogen, and creatinine) and genotyping of individual patients will be critical for identification of disease causation in people with DKD. Identifying mechanisms underlying individual instances of DKD pathogenesis will be critical for identifying potential therapeutic targets, thereby enabling translation of population genomics to precision medicine for individuals with kidney disease.

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