Genetic Contribution to Risk for Diabetic Kidney Disease

Stephen S. Rich

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Center for Public Health Genomics, Department of Public Health Sciences, University of Virginia, Charlottesville, Virginia

Correspondence: Dr. Stephen S. Rich, Center for Public Health Genomics, University of Virginia, 3232 West Complex, PO Box 800717, Charlottesville, VA 22908-0717. Email: ssr4n@virginia.edu

Diabetic kidney disease is a significant complication of diabetes (of all forms) and a major cause of morbidity and mortality that has increased in frequency, despite advances in glycemic control and pharmaceutical interventions (1). There are several aspects of diabetes that represent nonmodifiable risk factors associated with risk of diabetic kidney disease, including age at diabetes onset, sex, ethnic origin (2), and the form of diabetes (*e.g.*, diabetic kidney disease is more common in type 1 diabetes and type 2 diabetes than in some forms of maturity-onset diabetes in youth [MODY], latent autoimmune diabetes in adulthood, and syndromic types of diabetes). One major risk factor, also not modifiable yet futuristically useful in early prediction of risk, intervention, management, and therapeutics, is genetics.

The effect of genetics on risk of diabetic kidney disease was first noted (3) in a small study of families having two or more siblings with type 1 diabetes; however, in one set, the index patient had no evidence of diabetic kidney disease, and in the other set, the index patient had undergone kidney transplantation due to diabetic kidney disease. In the affected siblings of index patients with a kidney transplant, 83% had evidence of kidney disease, whereas in the other set, only 17% had evidence of kidney disease. This difference in rates (83% versus 17%) could not be explained by known risk factors (*e.g.*, duration of type 1 diabetes, glycemic control, or BP), thus showing that familial (genetic) factors represented a major contributor to risk of diabetic kidney disease. This observation was soon replicated in a large-scale epidemiologic study of type 1 diabetes (4) as well as in studies of other other ethnic groups with both type 1 diabetes and type 2 diabetes.

After the risk of diabetic kidney disease was shown to be due, in part, to genetic factors, the next phase of research was to identify those genetic factors. There are many complex pathways and morphologic changes that occur in an individual with diabetes that lead to diabetic kidney disease, explaining, in part, why the risk of kidney disease in those with diabetes is significantly <100%; however, risk varies by ethnicity but increases with increasing duration of diabetes (5). Difficulty in gene discovery is due to the unknown genetic architecture in terms of genetic variant effect sizes, the number of causal variants within a gene, the type of variant, whether the variants affect protein-coding (exons) regions or DNA regulatory regions, and potential ethnic differences in frequencies of the variants.

Initial research on the genetic basis of diabetic kidney disease focused on families with multiple members with diabetes and kidney disease (pedigrees, often in type 1 diabetes, or affected sibling pair families in type 1 diabetes and type 2 diabetes). These studies were often small in number of families and typically focused on candidate genes with very few polymorphic sites. Unfortunately, the statistical power of these studies was low, and many "discoveries" that were published were followed by many reports that provided strong evidence against replication.

A number of genome-wide family studies were conducted later to detect gene variants in linkage to diabetic kidney disease, with outcomes defined by presence of nephropathy or end-stage kidney disease. Several regions of susceptibility were identified by these studies, but still, there was insufficient power to robustly detect putative genes linked to risk of diabetic kidney disease. Although several large-scale, family-based studies were conducted (including FIND, the Family Investigation of Nephropathy and Diabetes consortium), the human genetics field moved, almost exclusively, from family studies to large patient-control studies with dense single nucleotide polymorphism (SNP) genotyping pioneered by the Wellcome Trust Case Control Consortium of 2000 patients in each of seven cohorts (no cohort with diabetic kidney disease) contrasted with 3000 shared controls (6).

The analysis of SNPs associated with a trait on a genome-wide level (genome wide association study [GWAS]) was computationally efficient and removed the burden of ascertainment and collection of families. Multiple SNP testing required a stringent significance threshold (*e.g.*, $P<5\times10-8$;) and care in sampling. Critical issues in GWAS data, however, include the composition of the patient group (diagnostic criteria), the composition of the control group (misclassification and presence of risk factors in controls), geographical variation, and population stratification that could increase false discovery. An early major GWAS in diabetic kidney disease was the Genetics of Kidneys in Diabetes (GoKinD) Study formed by recruitment of 820 well phenotyped patients with type 1 diabetes (duration of at least 10 years with end-stage kidney disease

or persistent proteinuria) and 885 "controls" (duration of type 1 diabetes of at least 15 years with normal albuminuria without treatment). Although a major research effort was made to accumulate this number of patients (approximately 800) and controls (approximately 900), the statistical power of the study was robust only for common SNPs (minor allele frequency >0.05 in the population), with effects (odds ratios) >1.20; however, most SNPs associated with common disease have much smaller effects (odds ratio, <1.10). Thus, this effort was underpowered, and like many others, it had difficulty with replication of findings.

A major effort to discover variants associated with diabetic kidney disease in type 1 diabetes was established by the Juvenile Diabetes Research Foundation (JDRF)—the Diabetic Nephropathy Collaborative Research Initiative (DNCRI). The DNCRI included the largest GWAS of nephropathy in type 1 diabetes, containing 15,590 participants of European ancestry with multiple definitions of disease. The SNP most significantly associated with disease was a missense (protein-coding, rs55703767, Asp326Tyr) variant in the *COL4A3* gene (7). The risk allele of this variant affected risk of macroalbuminuria or end-stage kidney disease and its frequency was common in Europeans (20%) and East Asians (13%) but infrequent in those of African ancestry (2%). The *COL4A3* SNP (rs55703767) has been implicated as being a splice site disruptor, consistent with a functional change in protein structure. Mutations in *COL4A3* have been implicated in diseases of basement membranes, including familial FSGS and Alport syndrome. In an independent sample, the *COL4A3* missense variant had an effect on width of the glomerular basement membrane, suggesting a mechanism of action (8). Furthermore, an independent evaluation of 47 candidate genes related to kidney structure in African ancestry type 2 diabetes nephropathy patients identified a different (independent) missense variant in *COL4A3* (rs34505188, Arg408His) associated with disease. Although the sample size was smaller (2041 patients and 1041 controls in discovery; 383 patients and 484 controls in replication), the comparable findings in type 1 diabetes and type 2 diabetes across two ethnic groups provide support for *COL4A3* variation having a role in etiology of diabetic kidney disease.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Wang *et al*. (9) report on whole-exome sequencing in a series of nine patients with MODY and biopsy-proven severe diabetic kidney disease. There was severe selection of patients for whole-exome sequencing. From 355 patients with diabetes, 120 had genetic information; 30 of these had a family history of diabetes, with a diagnosis of MODY in nine, with the index patient (proband) having severe diabetic kidney disease. The MODY in these Chinese subjects is strikingly different (four with *WFS1*-MODY, two with *CEL*-MODY, two with *PAX4*-MODY and one with *ABCC8*-MODY) from that expected in European populations (*HNF4A*-MODY, *GCK*-MODY, and *HNF1A*-MODY). Variants in *COL4A3* were identified as associated with diabetic kidney disease despite the few families, specifically an Met1209Iso in three patients and the Arg408His variant (seen in type 2 diabetes of African ancestry with low frequency) in four patients. The Asp326Tyr variant in the GWAS for type 1 diabetes of European ancestry was not observed.

How was this finding made? In general, the strategy was on the basis of the following. (*1*) The likely single-gene effect may be recessive, because the parents (including one with MODY) did not have significant kidney disease. (*2*) The severity of diabetic kidney disease suggests an extreme phenotype, possibly due to protein-coding variants. (*3*) Whole exome sequencing interrogates protein-coding variation. (*4*) There was a focus on 25 "known" nephropathy genes (containing 196 SNPs with predicted functional effect).

Although this report attempts to establish support for a series of protein-coding variants in the *COL4A3* gene influencing risk of diabetic kidney disease in Chinese MODY families, the major issue is an absence of statistical evaluation. Although a test (*e.g.*, the transmission disequilibrium test) could determine whether specific alleles are transmitted to affected offspring in a pseudo–patient-control analysis, the small number of families would not provide statistically robust results. In contrast to the analyses in type 2 diabetes of African ancestry subjects (10) and the GWAS in the JDRF DNCRI (7) with independent replication of potential function (8), this report is underpowered and observational in nature. There is no compelling evidence of how *COL4A3* variants were chosen compared with similar variants in other candidate genes.

Should *COL4A3* variation be broadly validated as a key component in diabetic kidney disease, how can this information be used in the context of "precision diabetic medicine"? First, the effect of *COL4A3* on risk may differ by type of diabetes and ethnicity, although it is a significant risk factor. Second, the identification of genetic variants across the landscape of diabetes will provide the opportunity to define a "genetic risk score" to assess genetic risk of kidney disease in individuals. Third, those at high genetic risk of diabetic kidney disease may be benefited by more frequent assessments to identify those with rapid decline in kidney function. Fourth, pharmacologic interventions could be more aggressively used in those at high genetic risk, including those compounds developed for treatment of Alport syndrome or FSGS. In essence, the knowledge of the genetic basis of diabetic kidney disease can provide insights on prediction, treatment, and intervention in the large portion of patients with all forms of diabetes.

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Disclosures

None.

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See related article, "*COL4A3* Gene Variants and Diabetic Kidney Disease in MODY," on pages 1162–1171.