Generalizability of Genetic Findings Related to Kidney Function and Albuminuria

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Nephrology has benefited from several recent molecular genetics breakthroughs involving susceptibility to FSGS and focal global glomerulosclerosis, encompassing both rare and common gene variants (1–6). To date, the search for diabetic nephropathy genes has been somewhat less rewarding, although genes with modest effects have been elucidated for diabetic and non-diabetic CKD (7–11). As a result, nephrologists are now being inundated with a veritable “alphabet soup” of exotic-sounding gene symbols, denoting genes whose markers reportedly associate with kidney function or albuminuria in population-based samples, some replicated and others not. This editorial addresses practical genetics issues for clinicians in the context of the report by Franceschini et al. evaluating American Indians from the Strong Heart Family Study in this issue of CJASN (12).

The rapid evolution of genotyping technologies and biostatistical software over the past 20 years has been astounding; affordable whole-genome sequencing is now on the horizon. With these tools, nephrology research progressed from often underpowered candidate gene studies that inadequately assessed genetic variation, to the current era of well powered family-based linkage, admixture mapping, and genome-wide association studies (GWAS) (13–16). GWAS have evaluated common (often noncoding or intronic) and, more recently, rare (coding or exonic) variants. Family-based analyses are particularly useful for assessing rare variants tracking through pedigrees, avoiding potential errant calls. These newer methods search entire genomes in an unbiased fashion to detect markers statistically linked or associated with diseases and phenotypes. Clinicians need to be aware that study results may be limited by the following: quality of phenotypes (mixed disease etiology, variable severity, imprecise measures, and disease misclassification), participant composition (population based versus case control) and heterogeneity, complex disease processes (multifactorial nature of disease and unaccounted interactions and effect modifiers), and sample size (limitations in power). Validation requires replication in different study samples and is strengthened through consistency in different ancestral groups. The latter can be complicated because some disease variants occur more frequently in (or are limited to) one ancestral group, as in IgA nephropathy and the spectrum of apolipoprotein L1 gene (APOL1)-associated nephropathy (5,17,18).

Franceschini et al. evaluated 25 genetic variants for relationships with renal traits in an American Indian population (12). The markers, termed single-nucleotide polymorphisms (SNPs), are located in or near 23 genes that were associated with estimated GFR (eGFR) in GWAS performed before 2011 in population-based samples of European ancestry (http://www.genome.gov/gwastudies/) (16). The powerful APOL1 kidney failure gene, whose G1 and G2 coding risk variants are common in populations with recent African ancestry, was also included. The relatively large American Indian sample included 3282 individuals from 92 multigenerational families. Of these, 3218 individuals also had eGFR and urine albumin/creatinine ratio (UACR) measurements.

Clinicians should be aware that these American Indian families were not enriched for members with CKD, although American Indians face higher rates of CKD and diabetes than Europeans. This was a population-based report and the majority of participants had normal kidney function and normoalbuminuria. Similar to many genetic studies for the trait of UACR, one limitation of the study by Franceschini et al. is that albuminuria often fluctuates widely (12). Many patients with diabetes and microalbuminuria revert to normoalbuminuria and others have decreasing eGFR despite the presence of normoalbuminuria. In addition, with the exceptions of nominal associations for the uromodulin (UMOD) (19,20), glucokinase regulator (GCKR) (8), and possibly cubilin genes (CUBN) (21), most gene variants identified in European-based GWAS associated with UACR and eGFR do not strongly associate with ESRD; modest associations have been reported for CKD (8). It should also be noted that markers in one of the most strongly eGFR-associated genes from prior GWAS, SHROOM 3, were not evaluated. Most importantly, although the original SNPs associated with eGFR in European GWAS were tested in American Indians, no additional markers in the 23 genes were assessed. Structural differences exist in the genomes of American Indians, Europeans, Asians, and Africans. SNPs are often in high linkage disequilibrium (LD), meaning they are coinherited with adjacent SNPs and comprise haplotype blocks. Haplotype block structures may differ between ancestral groups. Because a significant proportion of the 25 SNPs tested were not likely disease-causing in Europeans, but...
are inherited in LD with potentially causal variants, differing haplotype block structures could have contributed to a lack of association in American Indians. Not unexpectedly, the frequency of the SNPs was often markedly different between the American Indian and European populations. Thus, if a SNP failed to replicate in this study, it does not exclude a role for the gene region in which that SNP resides. For example, when Liu et al. (22) tested for association of many of these same European-derived renal function-related SNPs in African Americans, only 2 of 24 SNPs replicated. Testing additional “flanking” SNPs in these regions (to account for differential LD patterns in Europeans and African Americans) revealed that 12 of the gene regions replicated. Finally, this analysis was not a genome-wide effort but was a limited replication study of markers in 23 gene regions. Since early 2011, numerous additional SNPs associated with eGFR and UACR have been detected; these were not examined (22–26).

Not unexpectedly, the authors did not detect either one of the G1 or G2 coding APOL1 nephropathy variants in this American Indian sample. These renal risk variants are strongly associated with CKD in populations descended from selected geographic areas in Africa where these variants protect from endemic and otherwise lethal Trypanosoma brucei rhodesiense–related African sleeping sickness. Accordingly, the noncoding APOL1 variants that were tested in American Indians were not associated with renal traits. Moreover, APOL1 variants were tested in an additive model, whereas risk for CKD is strongest in recessive models with possession of two risk variants in populations of African ancestry.

Despite these potential limitations, it was striking that five of the SNPs (in PRKAG2, SLC6A13, UBE2Q2, PIP5K1B, and WDR72 genes) were associated with eGFR and one with UACR in this American Indian sample. It is possible, perhaps likely, that additional gene associations would have been detected had more SNPs in these 23 regions been tested. Although relatively strong generalizability of the effects of gene variation on the eGFR phenotype was identified in European and American Indian populations, this does not necessarily apply to other related renal phenotypes. For example, although albuminuria is a powerful predictor of risk for CKD, the underlying genetic pathways appear to be distinct from those governing eGFR (27). Similarly, the overlap between eGFR-associated SNPs and ESRD, while at times present, is much less pronounced. In the same vein, APOL1 risk variants that are strongly associated with a 5- to 30-fold increased risk for several nondiabetic etiologies of ESRD (5,28) are far more modestly associated with incident CKD and mild renal phenotypes in population-based samples (29–31). This finding suggests a more pronounced role in progression of kidney disease (18,32). Considering that CKD and ESRD are multifactorial and complex disease processes related to the convergence of multiple genetically mediated disease pathways and diverse environmental exposures, it is not surprising that variations in isolated genes often relate to a specific phenotype. In this context, an individual can manifest enhanced genetic susceptibility to ESRD based on the presence of a gene variant relating to factors such as kidney development, susceptibility to renal injury (e.g., diminished ability to cope with oxidative stress or hyperglycemia), or maladaptive injury response (e.g., heightened inflammatory or fibrotic reaction). These processes all have the potential to lead to increases in incident cases of nephropathy and/or more rapid progression of established CKD.

To put this study in perspective, there may not always be strong connections between common gene variants associated with eGFR in healthy populations and in those associated with CKD or ESRD. Relative to African and Native American populations, populations with European ancestry face generally low rates of nephropathy. The diseases commonly causing ESRD in European Americans (e.g., atherosclerotic renal artery disease, immune and non-immune complex glomerular diseases, and nonresolving AKI) suggest, in some cases, that discrete events and not steady decrements in eGFR lead to CKD. These factors, along with the multitude of accumulated processes related to CKD development, likely account for some of the partial disconnect between eGFR and renal physiology regulatory genes from those resulting in advanced CKD. What is apparent is that markers in the PRKAG2, SLC6A13, UBE2Q2, PIP5K1B, and WDR72 genes are associated with kidney function in population-based Europeans and American Indians. Evaluating these and other GWAS-identified genes and gene networks will identify previously unsuspected pathways related to kidney function and pathophysiology. Delineating the roles of these genes and pathways will, in turn, increase the probability of developing novel treatments that can modify the often relentless progressive loss of eGFR seen in CKD.

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Disclosures
None.

References
with end stage kidney disease risk previously attributed to the MYH9 gene.


See related article, “Generalization of Associations of Kidney-Related Genetic Loci to American Indians,” on pages 150–158.