Commentary on Lessons from CKD–Related Genetic Association Studies—Moving Forward

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Clin J Am Soc Nephrol 13: 153–154, 2018. doi: https://doi.org/10.2215/CJN.12421117

Introduction

Rapid technologic advances have enabled the measurements of single-nucleotide polymorphisms across the human genome at relatively low cost. These advances have made possible research studies associating genetic polymorphisms with measures of kidney function, such as the GFR and albuminuria, and with specific kidney diseases, such as membranous nephropathy and some forms of FSGS. Findings from many of these studies are succinctly summarized in the review by Parsa and colleagues (1) in this issue of the *Clinical Journal of the American Society of Nephrology* Evidence-Based Nephrology series and include the following:

- Genetic polymorphisms associated with variation in eGFR among the general population are not generally associated with variation in proteinuria/albuminuria, suggesting distinct genetic influences on these measures of kidney function.
- The common genetic variants associated with GFR together account for only 4% of the variation in this measurement.
- Among persons of African ancestry, common variants in the *Apoliprotein 1* (*APOL1*) gene are powerful predictors for the development and progression of FSGS and human immunodeficiency virus–associated nephropathy and also, more moderately predict rapid progression of diabetic and nondiabetic CKD.
- Variants in three genes (*Uromodulin*, *sickle cell*, and *APOL1*), which appear to exert favorable effects on resistance to infection, are also associated with increased risks of kidney disease.
- For the development of membranous nephropathy, two genetic variants (in PLA2R1 and HLA-DQ1) have major epistatic effects, with an odds ratio of 78 for those with variants in both genes.
- Evidence from numerous studies shows that the effects of genetic variants on CKD risk are not fixed but often vary dramatically between study populations (*e.g.*, general versus high-risk populations and different genetic ancestry) and across different phenotypically defined kidney diseases.

Teaching Statement: Etiology Versus Prediction in Genetic Association Studies of CKD

Genetic association studies of kidney disease have facilitated discovery of previously unrecognized biologic pathways that might contribute to the disease process. For example, a genetic polymorphism located near the shroom family member 3 (*SHROOM3*) gene is among the most highly significant variants associated with reduced GFR in large population-based studies (2). This genetic association motivated follow-up studies showing an important role for the SHROOM3 protein in maintaining podocyte architecture *via* modulation of the actin cytoskeleton (3).

With few exceptions, common genetic polymorphisms associated with kidney functions or kidney diseases do not perform well as screening, diagnostic, or prognostic tools. For example, the presence of adenine, instead of guanine, at the SHROOM3 locus described above is associated with an odds ratio of 1.08 for CKD (P value $=1.1\times10^{-19}$). The exceedingly low P value excludes chance with a high degree of certainty; however, the modest size of the odds ratio precludes use of the SHROOM3 polymorphism to reliably discriminate people who will and will not develop CKD. As shown in Table 1, testing for this polymorphism would negligibly affect the probability of developing CKD beyond what is already known on the basis of the frequency of this condition in the population. For example, a person who is 60–69 years old has an estimated 13% pretest probability of having CKD on the basis of the prevalence of this condition in the United States population. If this person was found to have the SHROOM3 risk allele, then the post-test probability of CKD would increase to 13.5%. In contrast, if this person was found not have the risk allele, the post-test probability of CKD would decrease to 12.6%.

This example highlights the different requirements for associations used to investigate disease causality versus clinical decision making (4). The association between a risk factor and disease must be substantially large for that factor to reliably distinguish individuals who have or do not have the disease of interest. Most genetic associations found in studies of kidney disease, excepting APOL1 and PLA2, are of insufficient magnitude to promote clinical application. Some studies have combined the results of multiple genetic loci to create risk scores that more strongly associate with the disease than any single gene variant alone. Such scores may be useful for addressing causal relationships of specific biomarkers with disease (*e.g.*, Mendelian randomization studies) but still lack

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Table 1. Pre- and postprobabilities of CKD on the basis of genetic test

Age Group, yr	Prevalence of CKD,[a,b] %	Probability of CKD if Test Is Positive (Positive Predictive Value),[c] %	Probability of Disease if Test Is Negative (1− Negative Predictive Value),[c] %
40–59	4	4.2	3.9
60–69	13	13.5	12.6
≥70	36	37.0	35.3

[a]CKD is defined as an eGFR<60 ml/min per 1.73 m^2.
[b]Prevalence is estimated from the work by Coresh *et al*. (5) on the basis of the National Health and Nutrition Examination 1999–2004 data.
[c]Calculations are on the basis of a reported odds ratio of 1.08 and a minor allele frequency of 43% shroom family member 3.

sufficient strength of association to warrant clinical use for prediction or prognosis.

Disclosures

None.

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Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Lessons from CKD-Related Genetic Association Studies–Moving Forward" on pages 140–152.