Kidney Medicine

APOL1 High-Risk Genotypes and Kidney Disease Risk in Middle-Aged Black Adults: More Questions Than Answers

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The pace of knowledge generation around *APOL1* risk variants and their impact on kidney function is heartening. Studies have begun to uncover molecular mechanisms by which *APOL1* high-risk variants induce kidney damage, leading to the development of targeted therapeutics that have shown early signs of safety and efficacy in small, randomized trials.[1-3] Because of this, it is no longer beyond the pale to envision the availability of drugs that can effectively treat individuals carrying high-risk variants who have evidence of kidney damage, such as proteinuria. This is critically important given evidence that these individuals have much faster progression to kidney failure requiring kidney replacement therapy than their counterparts who do not carry high-risk genotypes.[4]

Related article, 100828

The potential effect of emerging new therapeutics on individuals carrying APOL1 high-risk variants who do not show any evidence of kidney damage is less clear. Epidemiologic studies have shown that the majority of individuals in this latter category will never experience kidney disease progression, lending support to the hypothesis that APOL1-induced kidney disease follows a two-hit model—that is, carriage of APOL1 high-risk variants is necessary but not sufficient to cause kidney disease.[5,6] Instead, it requires a second hit, such as activation of the immune system in response to infection or other stimuli, to manifest kidney damage. This has cast doubt on the utility of determining the APOL1 genotype in high-risk populations (individuals of more recent African descent) given that knowledge of high- or low-risk status may not provide meaningful information about the risk for future kidney disease but, instead, may cause unintended consequences, such as anxiety about future health outcomes that are unlikely to occur. Nonetheless, there is at least one scenario in which such information could be potentially helpful for shared decision making: individuals who are considering becoming kidney donors. In this scenario, the second hit (nephrectomy) would be predictable, and the implications of having high-risk variants much more relevant.

Few studies have attempted to address the potential utility of obtaining *APOL1* genotype in assessing living kidney donor risk in African Americans. In a study of mostly healthy young adults participating in the Coronary Artery Disease Risk in Young Adults (CARDIA) study, carriage of a high-risk genotype was associated with a higher 25-year risk of developing an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 in African American adults compared with individuals who were not carriers of the high-risk genotype.[7] Other case reports suggest that living kidney donors with the high-risk genotype had greater risk of developing end-stage kidney disease (ESKD) than their counterparts who had low-risk genotypes.[8,9] These data suggest that knowledge of *APOL1* genotype may help inform long-term risk prediction for kidney failure. A long-term study rigorously examining this question is in progress, and the results are not yet available.[10] One key question that has not been examined in detail is the implication of carriage of the high-risk genotype among older individuals who appear otherwise healthy and, thus, could conceivably be considered as a living kidney donor. This is the population that is the focus of the study by Doshi et al[11] appearing in this edition of *Kidney Medicine*.

Doshi et al[11] examined the association of *APOL1* risk variants with kidney disease outcomes in a subgroup of adults participating in the Atherosclerosis Risk in Communities (ARIC) study ($n = 5{,}075$, average age ~ 52 years). The inclusion criteria for the subgroup were chosen to simulate a population of middle-aged adults who could be potential living kidney donors: free from cancer, blood pressure at the baseline visit $<140/90$ mm Hg, fasting blood glucose <126 mg/dL, not using antihypertensive or antiglycemic medications, and having an eGFR ≥ 80 mL/min/1.73 m^2 and a body mass index <35 kg/m^2. The primary analyses examined the association of *APOL1* genotype status (categorized as White, Black participants with low-risk genotypes, and Black participants with high-risk genotypes) with the following: (1) mean eGFR at 10, 25, and 30 years following the baseline visit; (2) proportion of individuals with chronic kidney disease (CKD) stage 3a or worse at these same timepoints; and (3) proportion of individuals with urine albumin-creatinine ratio ≥ 30 mg/g at 10 and 25 years following baseline. Secondary analyses examined the association of *APOL1* genotype status with the proportion of individuals developing ESKD, death or both, and mean annual decline in eGFR from enrollment to last follow-up.

The main results of the primary analyses were that, despite no meaningful differences in sociodemographic or clinical characteristics between the groups at baseline, mean eGFR at the year 10 follow-up visit was lower in White participants compared with Black participants, regardless of the presence of a high-risk genotype. These

differences were largely similar at the year 25 visit, but no longer observed at the year 30 visit. With respect to development of incident CKD stage 3a or worse, there were no differences between any group in follow-up, with similar findings for albuminuria and the development of ESKD or death. When examining annual rates of decline, the results were somewhat different—the annual rate of decline was the slower in White participants as compared with Black participants, with no statistically significant differences in Black participants by *APOL1* genotype status. The authors concluded from these results that *APOL1* high-risk genotypes may not increase the long-term risk of kidney disease in middle-aged healthy Black individuals with normal kidney function at baseline, with important potential implications for counseling this group of individuals about the long-term risks of kidney donation.

Doshi et al[11] provide useful information about the trajectory of kidney function in a unique subgroup of ARIC participants, enriching our understanding of kidney disease outcomes in Black individuals with high-risk genotypes who survive to middle age without evidence of kidney disease. Few prior studies specifically focused on this subgroup, making this a welcome addition to the literature. However, the results of the study should be interpreted cautiously given several aspects of the analytical approach. First, it is curious that, for the primary analyses, GFR at the baseline visit was estimated using the creatinine-based 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation without race whereas for the follow-up visits, the combined cystatin C and creatinine 2021 CKD-EPI equation without race was used. Although this was likely done because cystatin C was not available at the baseline visit, the authors never justified why they used different estimating equations for the baseline and follow-up visits. This decision was all the more curious given that the creatinine-based 2021 equation was used to estimate all GFRs in the secondary analysis (annual rate of decline), which is the more logical and straight-forward approach. More importantly, racial differences in attendance of follow-up visits may have had an important impact on the outcomes. To have a follow-up eGFR value, a participant would need to attend a follow-up visit to get blood drawn for creatinine and/or cystatin C measurement. There were significant differences in the number of participants who had follow-up visits across study groups, with Black individuals with high-risk genotypes experiencing the greatest drop-out rate over time, followed by Black individuals with low-risk genotypes and then White individuals. If these differences in drop-out rates were not random but instead related to differences in kidney function decline, this might have introduced bias into the analyses. For example, if Black individuals with high-risk genotypes had greater drop-out rates because they had proportionately higher number of individuals whose kidney function declined so rapidly that they could not attend a follow-up visit, this could have made follow-up eGFR measurements in high-risk genotype recipients appear higher than low-risk genotype or White participants by differentially removing individuals who had the most rapid kidney function decline from the high-risk genotype group. Unfortunately, we are not provided sufficient information about individuals who did not follow-up to understand whether this might have been the case. However, the data on ESKD provide some clues. Given that ESKD events were captured by linkage to USRDS, all individuals contributed risk time because all events would be captured irrespective of whether a participant attended a follow-up visit or not. As shown in Fig 3A of the article, rates of ESKD were generally higher in Black individuals versus White individuals overall (though these differences were not statistically significant because of low event numbers), consistent with known racial differences in ESKD risk. It is hard to reconcile these data with the observation that White individuals had lower eGFR than Black individuals at year 10 and 25 visits. Instead, the ESKD results were more in line with observed racial differences in annual rate of decline (Table 3 in the article by Doshi et al[11]), with Black individuals with high-risk genotypes having numerically faster rates of decline than Black individuals with low-risk genotypes and White individuals, consistent with known differences in kidney function decline by *APOL1* genotype.

Given these challenges in analytical approach, what can be concluded with reasonable certainty from these data? One conclusion is that Black individuals with high-risk genotypes who survive to middle age are generally a healthy subgroup with lower risk of kidney disease progression than individuals with high-risk genotypes who already manifest kidney injury. This information could reasonably help counsel individuals with high-risk genotypes about their long-term risk of progression to kidney failure after living kidney donation. Beyond this, these data provide a further reminder about how little is known about natural kidney disease progression in middle-aged adults with high-risk versus low-risk genotypes and the need for further studies to fill in these gaps. Until such high-quality data are available, appropriate caution about estimating long-term risk associated with nephrectomy in kidney donors carrying high-risk genotypes appears prudent.

ARTICLE INFORMATION

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