

APOLI and Cardiovascular Disease A Story in Evolution

Archna Bajaj, Katalin Susztak, Scott M. Damrauer

Observational studies have long established that African Americans have a higher risk for developing chronic kidney disease (CKD) with faster progression to end-stage renal disease compared with Americans not of African descent, independent of socioeconomic and traditional clinical risk factors.¹⁻³ But it was not until 2010 that the genetic basis behind this association became more apparent when 2 separate genome-wide association studies identified DNA variants in the *APOLI* gene that were strongly associated with kidney disease in blacks.^{4,5} The story of the *APOLI* gene that emerged is a fascinating example of natural selection against infectious disease, and discovery of its link to renal, and possibly cardiovascular, diseases has opened a new field of questions.

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APOLI encodes for apolipoprotein L-I, a component of dense high-density lipoprotein 3 particles.⁶ Circulating apolipoprotein L-I has the ability to lyse the parasite *Trypanosoma brucei*, which is found only in sub-Saharan Africa.⁷ Over time, 2 subspecies of *T. brucei*, *T. brucei gambiense* and *T. brucei rhodesiense*, evolved resistance by producing a protein that binds and neutralizes apolipoprotein L-I. Subsequently, 2 *APOLI* variants (G1 and G2) emerged, producing apolipoprotein L-I with decreased affinity for the trypanosome protein, conferring resistance to African sleeping sickness in carriers of these alleles.⁸ Although being protected from 1 disease, however, blacks with the *APOLI* variant alleles have been shown to be at increased risk for renal disease, as well as a faster progression to end-stage renal disease.⁹ Individuals that are homozygous for either variant, or compound heterozygotes, have been found to have a 10× to 17× higher odds for focal segmental glomerulosclerosis,^{5,10} a 7× higher odds for hypertension-associated end-stage renal disease,⁵ and 29× to 89× higher odds for HIV-associated nephropathy.^{10,11} Because of the initial natural selection, the prevalence of these variants in the population is significant: ≈40% of blacks carry 1 risk allele whereas 10% to 15% carry 2 risk alleles.^{5,12,13}

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(*Arterioscler Thromb Vasc Biol.* 2017;37:1587-1589.)

DOI: 10.1161/ATVBAHA.117.309756.)

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Arterioscler Thromb Vasc Biol is available at <http://atvb.ahajournals.org>
DOI: 10.1161/ATVBAHA.117.309756

APOLI is broadly expressed, including in the kidney and vasculature.¹⁴ Although the mechanistic role of *APOLI* variants in disease development has yet to be fully elucidated, recent work in mouse models has demonstrated that the expression of *APOLI* risk alleles alters podocyte function and results in kidney disease.¹⁵

Beyond the risk for kidney disease, African Americans are also disproportionately at greater risk for cardiovascular disease (CVD),¹⁶ prompting the question of whether or not *APOLI* variants underlie this association as well. In this issue of *ATVB*, Chen et al¹⁷ report on the association between the *APOLI* risk alleles and CVD outcomes in the AASK (African American Study of Kidney Disease and Hypertension), a well-characterized cohort of individuals with CKD attributed to hypertension. The study's authors compared the 160 AASK participants with 2 *APOLI* risk alleles (high-risk) with the 533 who had either 1 or no risk allele (low-risk). Using a broad composite definition of CVD, including cardiovascular death, myocardial infarction, cardiac revascularization, heart failure, and stroke, the authors failed to detect a significant difference in risk for CVD between the high- and low-risk groups in both unadjusted and adjusted models. Arguably, the study by Chen et al¹⁷ may have been underpowered to detect an association, and thus, a negative result is difficult to interpret. Based on 693 participants and 144 composite events during 12 years of follow-up, they had 80% power to detect a minimum hazard ratio of 1.85. Although this is within the range of some of the previously reported studies, the divergent nature of the published literature suggests that the true hazard ratio may in fact be below their level of detection. Nonetheless, these results contribute important additional data to our still evolving knowledge of the relationship between *APOLI* and CVD.

Prior studies on the association of *APOLI* variants and CVD outcomes have generated a field of conflicting data. In 2014, Ito et al¹⁸ demonstrated that among 1959 black participants in the Jackson Heart Study, individuals with 2 *APOLI* high-risk alleles were at twice the risk of incident CVD when compared with those without any risk alleles. The authors then replicated this association in 749 participants of African ancestry and without baseline CKD in the Women's Health Initiative. This was further bolstered by findings from Mukamal et al¹⁹ who showed that in >6000 blacks in the Cardiovascular Health Study, participants with high-risk *APOLI* genotypes had an 80% greater risk of incident myocardial infarction as compared with those with zero or only 1 risk allele; similar results were also found for peripheral vascular disease, suggesting a broader association between *APOLI* and atherosclerosis.

In contrast to these initial reports, and in keeping with the work by Chen et al¹⁷ presented in this issue, a 2015

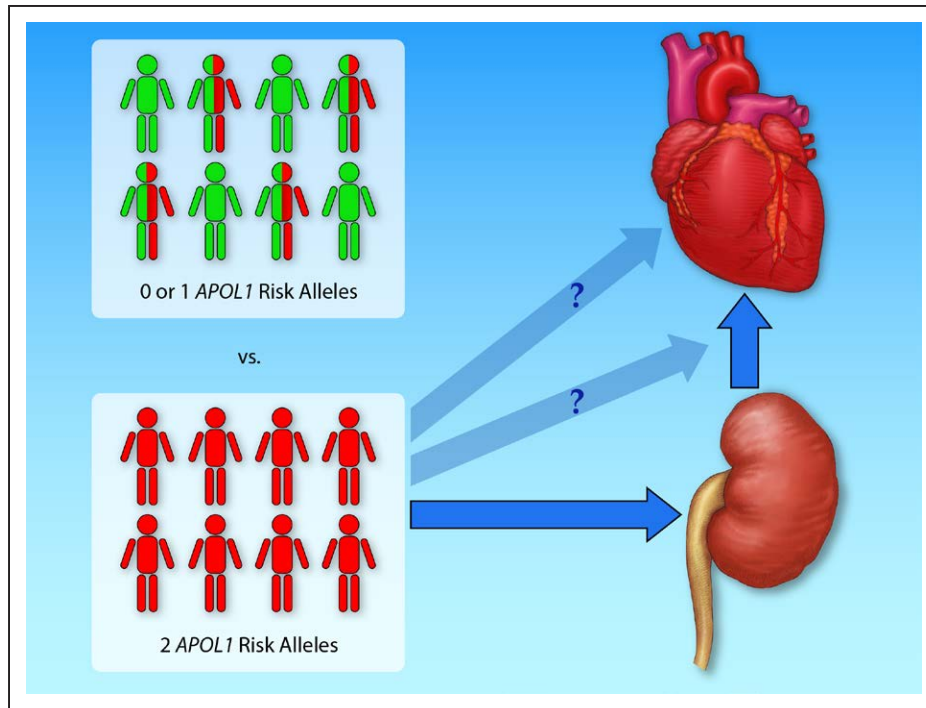


Figure. *APOL1* risk genotypes are known to associate with chronic kidney disease, dramatically increasing the risk of renal dysfunction. Although kidney disease in general leads to increased rates of cardiovascular disease (CVD) outcomes, the contribution of *APOL1* risk genotypes to the latter remains uncertain. Conflicting results have been reported with respect to the relationship between *APOL1* risk genotypes and CVD, leaving the question open as to the association of *APOL1* risk genotype and CVD.

study of 2571 black participants from the SPRINT (Systolic Blood Pressure Intervention Trial) failed to demonstrate an association between high-risk *APOL1* genotypes and CVD, despite showing a strong association with CKD.²⁰ Similarly, investigators with the ARIC study (Atherosclerosis Risk in Communities) found a strong association between the high-risk *APOL1* genotype and end-stage renal disease but failed to demonstrate any association with incident CVD in 3676 black participants.²¹

The discovery of the association of *APOL1* variants with CKD was an exciting start to a story that is still unfolding. The question remains as to whether there is a link between *APOL1* risk genotypes and CVD and if so, if it is distinct from a pathway to CVD driven by impairment in renal function (Figure). The results reported by Chen et al¹⁷ alone do not offer a definitive answer but rather provide one more piece to the puzzle. Given the wealth of data available, a meta-analysis of the existing literature offers a path forward to clarifying the true association between *APOL1* and CVD. One of the challenges of assessing the present collection of studies, and in contemplating a meta-analysis, however, is the heterogeneity of outcomes used to define CVD and the range of underlying pathophysiological processes these represent; almost every published study has used a different composite CVD definition. Accordingly, future studies that evaluate *APOL1* risk genotypes will need to carefully define outcomes. Electronic health records–based cohorts that allow for detailed phenotyping at a population scale represent a second pathway to elucidating the relationship between *APOL1* and CVD. Such cohorts will have the sample sizes large enough to provide the necessary statistical power to

detect, or not, associations between *APOL1* genotypes and CVD outcomes, which are likely smaller than those seen with renal pathologies; both the current Veterans Affairs Million Veteran Program²² and the developing National Institute of Health's All of Us Research Program²³ will be key resources in this area. Discovering the pathways in which *APOL1* connects to renal disease and CVD may guide the development of future therapies, preventive measures, and precision medicine in the high-risk black population.

Sources of Funding

K. Susztak is supported by N.I.H. R01 DK105821.

Disclosures

None.

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KEY WORDS: Editorials ■ apolipoproteins ■ cardiovascular diseases ■ kidney failure, chronic ■ prevalence ■ risk factors

Arteriosclerosis, Thrombosis, and Vascular Biology



JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 2017;37:1587-1589

doi: 10.1161/ATVBAHA.117.309756

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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