Editorial

APOL1 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 *APOL1* gene that were strongly associated with kidney disease in blacks.[4,5] The story of the *APOL1* 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.

See accompanying article on page 1765

APOL1 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 *APOL1* 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 *APOL1* 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] *APOL1* is broadly expressed, including in the kidney and vasculature.[14] Although the mechanistic role of *APOL1* variants in disease development has yet to be fully elucidated, recent work in mouse models has demonstrated that the expression of *APOL1* 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 *APOL1* variants underlie this association as well. In this issue of *ATVB*, Chen et al[17] report on the association between the *APOL1* 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 *APOL1* 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 al[17] 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 *APOL1* and CVD.

Prior studies on the association of *APOL1* variants and CVD outcomes have generated a field of conflicting data. In 2014, Ito et al[18] demonstrated that among 1959 black participants in the Jackson Heart Study, individuals with 2 *APOL1* 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 al[19] who showed that in >6000 blacks in the Cardiovascular Health Study, participants with high-risk *APOL1* 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 *APOL1* and atherosclerosis.

In contrast to these initial reports, and in keeping with the work by Chen et al[17] presented in this issue, a 2015

From the Division of General Internal Medicine, Department of Medicine (A.B.), Renal Electrolyte and Hypertension Division, Department of Medicine (K.S.), Department of Genetics (K.S.), Division of Vascular Surgery, Department of Surgery (S.M.D.), University of Pennsylvania, Philadelphia; and Department of Surgery, Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA (S.M.D.)

Correspondence to Scott M. Damrauer, MD, Division of Vascular Surgery, Department of Surgery, University of Pennsylvania, 3400 Spruce St, 4 Silverstein Pavilion, Philadelphia, PA 19104. E-mail scott.damrauer@uphs.upenn.edu

(*Arterioscler Thromb Vasc Biol*. 2017;37:1587-1589. DOI: 10.1161/ATVBAHA.117.309756.)

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

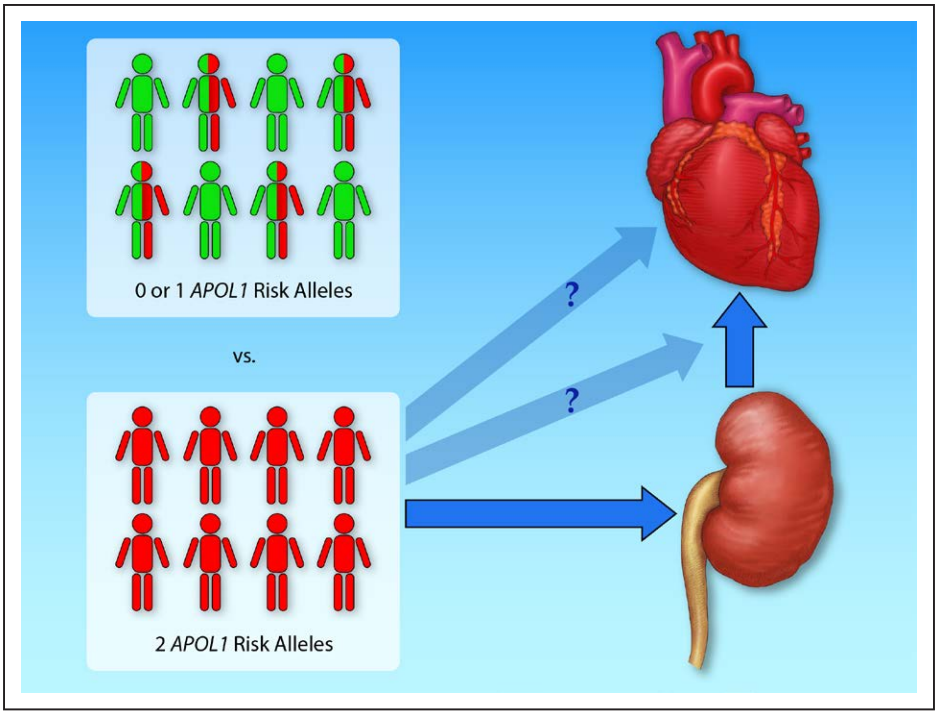

Figure. *APOL1* risk genotypes are known to associate with chronic kidney disease, dramatically increasing the risk of renal dysfunction. Although kidney disease in general leads to increased rates of cardiovascular disease (CVD) outcomes, the contribution of *APOL1* risk genotypes to the latter remains 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 al[17] 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 Program[22] and the developing National Institute of Health's All of Us Research Program[23] 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.

References

1. McClellan W, Tuttle E, Issa A. Racial differences in the incidence of hypertensive end-stage renal disease (ESRD) are not entirely explained by differences in the prevalence of hypertension. *Am J Kidney Dis*. 1988;12:285–290.
2. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med*. 1989;321:1074–1079. doi: 10.1056/NEJM198910193211603.
3. Lipworth L, Mumma MT, Cavanaugh KL, Edwards TL, Ikizler TA, Tarone RE, McLaughlin JK, Blot WJ. Incidence and predictors of end stage renal disease among low-income blacks and whites. *PLoS One*. 2012;7:e48407. doi: 10.1371/journal.pone.0048407.
4. Tzur S, Rosset S, Shemer R, Yudkovsky G, Selig S, Tarekegn A, Bekele E, Bradman N, Wasser WG, Behar DM, Skorecki K. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet*. 2010;128:345–350. doi: 10.1007/s00439-010-0861-0.

5. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329:841–845. doi: 10.1126/science.1193032.
6. Davidson WS, Silva RA, Chantepie S, Lagor WR, Chapman MJ, Kontush A. Proteomic analysis of defined HDL subpopulations reveals particle-specific protein clusters: relevance to antioxidative function. *Arterioscler Thromb Vasc Biol*. 2009;29:870–876. doi: 10.1161/ATVBAHA.109.186031.
7. Pérez-Morga D, Vanhollebeke B, Paturiaux-Hanocq F, Nolan DP, Lins L, Homblé F, Vanhamme L, Tebabi P, Pays A, Poelvoorde P, Jacquet A, Brasseur R, Pays E. Apolipoprotein L-I promotes trypanosome lysis by forming pores in lysosomal membranes. *Science*. 2005;309:469–472. doi: 10.1126/science.1114566.
8. Vanhamme L, Paturiaux-Hanocq F, Poelvoorde P, et al. Apolipoprotein L-I is the trypanosome lytic factor of human serum. *Nature*. 2003;422:83–87. doi: 10.1038/nature01461.
9. Parsa A, Kao WH, Xie D, et al; AASK Study Investigators; CRIC Study Investigators. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med*. 2013;369:2183–2196. doi: 10.1056/NEJMoa1310345.
10. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol*. 2011;22:2129–2137. doi: 10.1681/ASN.2011040388.
11. Kasembeli AN, Duarte R, Ramsay M, Mosiane P, Dickens C, Dix-Peek T, Limou S, Sezgin E, Nelson GW, Fogo AB, Goetsch S, Kopp JB, Winkler CA, Naicker S. APOL1 risk variants are strongly associated with HIV-associated nephropathy in black South Africans. *J Am Soc Nephrol*. 2015;26:2882–2890. doi: 10.1681/ASN.2014050469.
12. Foster MC, Coresh J, Fornage M, Astor BC, Grams M, Franceschini N, Boerwinkle E, Parekh RS, Kao WH. APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol*. 2013;24:1484–1491. doi: 10.1681/ASN.2013010113.
13. Friedman DJ, Kozlitina J, Genovese G, Jog P, Pollak MR. Population-based risk assessment of APOL1 on renal disease. *J Am Soc Nephrol*. 2011;22:2098–2105. doi: 10.1681/ASN.2011050519.
14. Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR. APOL1 localization in normal kidney and nondiabetic kidney disease. *J Am Soc Nephrol*. 2011;22:2119–2128. doi: 10.1681/ASN.2011010069.
15. Beckerman P, Bi-Karchin J, Park AS, et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med*. 2017;23:429–438. doi: 10.1038/nm.4287.
16. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol*. 2004;15:1307–1315.
17. Chen TK, Appel LJ, Grams ME, Tin A, Choi MJ, Lipkowitz MS, Winkler CA, Estrella MM. *APOL1* risk variants and cardiovascular disease: results from the AASK (African American Study of Kidney Disease and Hypertension). *Arterioscler Thromb Vasc Biol*. 2017;37:1765–1769. doi:10.1161/ATVBAHA.117.309384.
18. Ito K, Bick AG, Flannick J, et al. Increased burden of cardiovascular disease in carriers of APOL1 genetic variants. *Circ Res*. 2014;114:845–850. doi: 10.1161/CIRCRESAHA.114.302347.
19. Mukamal KJ, Tremaglio J, Friedman DJ, Ix JH, Kuller LH, Tracy RP, Pollak MR. APOL1 genotype, kidney and cardiovascular disease, and death in older adults. *Arterioscler Thromb Vasc Biol*. 2016;36:398–403. doi: 10.1161/ATVBAHA.115.305970.
20. Langefeld CD, Divers J, Pajewski NM, Hawfield AT, Reboussin DM, Bild DE, Kaysen GA, Kimmel PL, Raj DS, Ricardo AC, Wright JT Jr, Sedor JR, Rocco MV, Freedman BI; Systolic Blood Pressure Intervention Trial (SPRINT). Apolipoprotein L1 gene variants associate with prevalent kidney but not prevalent cardiovascular disease in the Systolic Blood Pressure Intervention Trial. *Kidney Int*. 2015;87:169–175. doi: 10.1038/ki.2014.254.
21. Grams ME, Rebholz CM, Chen Y, Rawlings AM, Estrella MM, Selvin E, Appel LJ, Tin A, Coresh J. Race, APOL1 risk, and eGFR decline in the general population. *J Am Soc Nephrol*. 2016;27:2842–2850. doi: 10.1681/ASN.2015070763.
22. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. *J Clin Epidemiol*. 2016;70:214–223. doi: 10.1016/j.jclinepi.2015.09.016.
23. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372:793–795. doi: 10.1056/NEJMp1500523.

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

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

APOL1 and Cardiovascular Disease: A Story in Evolution

Archna Bajaj, Katalin Susztak and Scott M. Damrauer

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

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