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“Ten years in: *APOL1* reaches beyond the kidney”

Joshua S. Waitzman^a, Jennie Lin^{a,b,c}

^aDivision of Nephrology and Hypertension, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

^bFeinberg Cardiovascular and Renal Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

^cJesse Brown Veterans Affairs Medical Center, Chicago, IL, USA

Abstract

Purpose of review—*APOL1* nephropathy risk variants drive most of the excess risk of chronic kidney disease (CKD) seen in African Americans, but whether the same risk variants account for excess cardiovascular risk remains unclear. This mini-review highlights the controversies in the *APOL1* cardiovascular field.

Recent findings—In the past ten years, our understanding of how *APOL1* risk variants contribute to renal cytotoxicity has increased. Some of the proposed mechanisms for kidney disease are biologically plausible for cells and tissues relevant to cardiovascular disease (CVD), but cardiovascular studies published since 2014 have reported conflicting results regarding *APOL1* risk variant association with cardiovascular outcomes. In the past year, several studies have also contributed conflicting results from different types of study populations.

Summary—Heterogeneity in study population and study design has led to differing reports on the role of *APOL1* nephropathy risk variants in CVD. Without consistently validated associations between these risk variants and CVD, mechanistic studies for *APOL1*'s role in cardiovascular biology lag behind.

Keywords

APOL1; cardiovascular; genetics

Introduction

Approximately a decade ago, a cluster of genes on the long arm of chromosome 22 was discovered to account for a large portion of increased risk of non-diabetic chronic kidney disease (CKD) in African Americans [1,2]. Over the ensuing ten years, *APOL1*, encoding Apolipoprotein L1, has been identified as the causative gene, and tests for its nephropathy

Correspondence to: Jennie Lin, MD MTR, Division of Nephrology and Hypertension, Northwestern University Feinberg School of Medicine, 303 E Superior St, Lurie Research Building 10-109, Chicago, IL, 60611, USA, Tel: 312-503-1892, jennie.lin@northwestern.edu.

Conflicts of interest
None.

risk variants have entered the clinical practice of nephrology. However, the mechanisms underlying APOL1-associated kidney disease and the implications of genetic testing on patient management remain unclear. Even less clear is how APOL1, which circulates on high-density lipoprotein-3 (HDL3), modulates cardiovascular disease (CVD) among African Americans and how therapeutics currently being engineered to treat APOL1-associated kidney disease may alter cardiovascular risk. Here we briefly summarize what is known about high-risk *APOL1* genotype in CKD pathophysiology, discuss our current understanding of APOL1 in the context of CVD, and outline open questions for the field as it enters its second decade.

APOL1 in the kidney

APOL1 encodes a small, membrane-associated protein that enables the innate immune system to lyse the protozoan *Trypanosoma brucei*. APOL1 has multiple functional domains, including a signal peptide for secretion, pore-forming domain, and SRA-interacting domain that interacts with SRA produced by *Trypanosoma brucei rhodesiense* [3–5]. Individuals who carry a single copy of the common G1 or G2 coding variant in the *APOL1* gene have increased serum anti-trypanosome activity and thus are less susceptible to African sleeping sickness. However, those who carry two copies of these variants (G1/G1, G2/G2, or G1/G2), i.e., the high-risk *APOL1* genotype, are at significantly elevated risk of developing kidney disease [6,7]. In case-control studies, individuals with two risk alleles are at a tenfold increased risk of hypertension-associated CKD. The odds ratios for focal segmental glomerulosclerosis (FSGS) and HIV-associated nephropathy (HIVAN) are even higher at 17 and 29, respectively [8].

Despite strong genetic association with CKD, the mechanisms by which APOL1 induces kidney injury remain an area of active investigation with unresolved controversies potentially relevant to mechanisms of APOL1-mediated disease in other organ systems. Current mainstream hypotheses have been carefully outlined in prior reviews by Beckerman and Susztak, and by Kruzel-Davila and Skorecki [9,10]. Based on previously published reports, hypotheses for APOL1-mediated renal pathophysiology include impaired podocyte autophagy [11,12], activation of focal adhesion signaling in the podocyte in complex with suPAR [13], impaired mitochondrial metabolism [14], and depletion of intracellular potassium and signaling via stress-activated protein kinases [15]. However, several major questions remain and may be applicable in the context of CVD, discussed below. First, why does only a subset of individuals with the high-risk *APOL1* genotype develop CKD? Investigators allude to a “second hit” as being necessary to induce APOL1-associated kidney disease [9,10]; would the same second hit be required for APOL1-mediated cardiovascular traits to develop? This leads to the next question of which genetic and environmental factors contribute to CKD risk. Prior genetic analyses reported conflicting results in terms of interacting genomic loci and variants [16–18], although these were performed prior to the recent identification of approximately 300 million base pairs present in African ancestry genomes but missing from the most current human reference genome build [19]. Furthermore, we have not yet determined which environmental factors contribute to disease risk. Finally, is APOL1-associated kidney disease exclusively a cell-autonomous phenomenon in podocytes? The *APOL1* gene is expressed in multiple tissues, as seen in

publicly available GTEx bulk RNA-sequencing data [20] (Figure 1A). It is also expressed in multiple cell types within the kidney, as demonstrated by recently published single cell RNA-sequencing data generated from human kidney biopsy samples [21,22] (Figure 1B). Although these dot plots do not represent direct statistically tested comparisons of gene expression across samples, they do suggest that *APOL1* expression may shift in a cell-specific manner, with prominent endothelial expression under injury conditions. Potential endothelial involvement in systemic APOL1-mediated cell and tissue injury may need to be considered in future studies in the kidney and other organs.

APOL1 beyond the kidney: causality in cardiovascular risk?

Identifying and understanding the genetic determinants of CVD have been a prioritized area of investigation for the past decade [23–25]. Because African Americans are at increased risk of developing CVD [26], multiple groups have leveraged pre-existing genetic cohorts to evaluate whether *APOL1* nephropathy risk variants contribute to this excess cardiovascular risk. The initial observational study on APOL1 and cardiovascular outcomes included participants from the Jackson Heart Study (JHS) and Women's Health Initiative (WHI) and identified a twofold increased risk of CVD, defined as myocardial infarction, stroke, and surgical and endovascular interventions [27]. However, subsequent conflicting studies differ due to heterogeneity in cohort design, demographics, comorbidities of the enrolled participants, and composite outcomes. In Table 1, we provide a summary of these studies and their key findings. Examining key differences among conflicting studies may suggest strategies for moving forward in interrogating the question of APOL1's potential link to CVD.

Sample size

Although many cardiovascular cohorts tend to have large numbers of participants, they have significantly fewer African-ancestry individuals enrolled compared to European-ancestry individuals. Among the African-ancestry participants, even fewer have the high-risk *APOL1* genotype, so some of these studies may not be adequately powered to detect a causal association between *APOL1* risk variants and CVD. For example, the negative results from the Systolic Blood Pressure Intervention Trial (SPRINT) study, which recruited higher numbers of participants with two *APOL1* risk alleles, had 80% power to detect an odds ratio (OR) of 1.53, assuming the appropriate recessive model [28]. This OR threshold is higher than some of the significant ORs ranging from 1.28 to 1.92 for the association between causal *LPA* variants and coronary heart disease [41], raising the possibility that a significant association exists between APOL1 and CVD, but at a more modest OR.

Defining the composite cardiovascular outcome

Out of the 14 studies listed in Table 1, five reported a positive association between high-risk *APOL1* genotype and CVD. However, each study defined the cardiovascular composite outcome differently, and these differences in composite outcome may account for some of the conflicting conclusions drawn by investigators. Some studies included stroke and heart failure as part of the composite outcome, while others did not. Some measured subclinical atherosclerosis, while others focused on myocardial infarction. Some measured incident

disease while others focused on prevalent disease. Uniformity in study design and measured outcomes across future cohort studies and trial groups may provide improved clarity on whether *APOL1* nephropathy risk variants associate negatively with cardiovascular health.

Sweetening the inclusion criteria: participants with diabetes

Although *APOL1*-associated kidney disease has been described primarily in patients without diabetes, the directionality of *APOL1*'s effect on CVD in the setting of diabetes conflicts between studies [27, 29, 35]. For example, two large studies, SPRINT and AASK [28,32], did not find an association between high-risk *APOL1* genotype and CVD, but they also did not include participants with diabetes. Ito et al. did include diabetic patients from JHS and WHI in their positive study [27]. However, Freedman et al. found that in the African American-Diabetes Heart Study (AA-DHS), *APOL1* risk variants associated with lower levels of subclinical atherosclerosis and decreased all-cause mortality [29]. Diabetes is a well-known strong risk factor for CVD [42], so these different results may seem surprising. However, the AA-DHS cohort consisted of participants with very mild or no renal disease; the nature of the interaction between diabetes and CKD in the setting of *APOL1* cardiovascular biology still remains unclear.

Heart the kidneys

SPRINT and population cohorts such as Atherosclerosis Risk in Communities (ARIC) had high mean estimated glomerular filtration rates (eGFR) across the board, even among participants with two *APOL1* risk alleles. Without much CKD represented in these studies, there may be some selection bias. When the investigators of the REGARDS study attempted to address this by stratifying their analyses by CKD status, they did not find a positive association between high-risk *APOL1* genotype and CVD in individuals with CKD [38], although this could be due to some degree of survivor bias, which will be discussed below. Also worth considering is whether albuminuria is a covariate for which *APOL1* genetic CVD analyses should be adjusted using standard regression. *APOL1*-associated kidney disease may increase the risk for CVD not only through traditional CKD-mediated pathways (e.g., hypertension and vascular calcification) but potentially through *APOL1*-specific pathways acting in multiple cell types and tissues (Figure 1A). If *APOL1* nephropathy risk variants are pleiotropic (causal for multiple traits), regressing out albuminuria could introduce severe bias and mask a significant causal CVD relationship [43,44]. Indeed, albuminuria has recently been identified as a causal risk factor for hypertension through a large-scale Mendelian randomization study of novel albuminuria genomic loci [45]. In a more focused population albuminuria may be found to be causal in *APOL1*-mediated cardiovascular pathophysiology. One example of how Mendelian randomization deconvoluted a complex “cardio-renal” causal relationship is a recent Chronic Renal Insufficiency Cohort (CRIC) study interrogating the relationship between lipoprotein(a) [Lp(a)] and CVD in the setting of CKD [46]. Although Lp(a) was previously established as a causal risk factor for coronary heart disease in individuals carrying risk alleles at the *LPA* locus [41], Lp(a) is also elevated in the setting of CKD due to decreased clearance. Through Mendelian randomization, investigators were able to establish that genetically elevated Lp(a) independently associates with increased incidence of myocardial infarction and mortality in the CKD population. Combining CRIC with other CKD cohorts to increase power, a similar

analysis with albuminuria as an instrumental variable may be informative for APOL1's role in cardiovascular health.

Survivor bias: age is not just a number

In half of the 14 studies listed in Table 1, the high-risk *APOL1* genotype group was significantly younger than their low-risk and the European-ancestry counterparts. Most of the studies with age differences had negative results in the APOL1 CVD context, raising the question of whether high-risk *APOL1* genotype individuals died of cardiovascular causes before potential study recruitment and thus introduced survivor bias into negative studies. Interestingly, Hughson et al. explored this in a small autopsy cohort of younger adults and found a significant association between younger age and cardiovascular death among individuals with the high-risk *APOL1* genotype [40].

Quantifying and analyzing the role of percent African ancestry

One major limitation of multiple large cohorts is the use of self-reported race and the absence of quantified percent African ancestry data. Modifiers of *APOL1* risk variant toxicity may directly correlate with markers of recent African ancestry, and this was most recently demonstrated by a study of the *UBD* locus and APOL1-associated kidney disease [47]. We may also be under-recognizing the effect of *APOL1* risk variants both in CKD and CVD by not incorporating participants with Caribbean, Central American, and South American background who may not always self-identify as black but by genetics do have high African ancestry percentage and high-risk *APOL1* genotype [48].

Getting to the heart of mechanism via lipids

While the jury is still out on whether *APOL1* nephropathy risk variants are causal in CVD, the rationale for studying APOL1 in a cardiovascular context has been rooted in biological plausibility. First, APOL1 circulates bound to HDL3, a subfraction of HDL that has been inversely correlated with myocardial infarction among populations of mostly European-ancestry individuals [49–51]. While HDL3 circulates in higher concentrations in African-ancestry compared to European-ancestry individuals [52], individuals with at least one *APOL1* risk allele also have higher levels of total HDL and small HDL compared to those without any risk alleles in one study [53]. Interestingly, a DNA variant at the *HPR* locus associates with circulating APOL1 levels [54], which is congruent with other data showing that APOL1 complexes with HPR in HDL3 [55]. However, whether plasma APOL1 levels drive CVD remains unclear as they do not associate with APOL1-associated kidney disease [54]. Because dysfunctional HDL rather than total HDL-C levels is increasingly gaining traction in CVD pathophysiology [56], how risk-variant APOL1 alters HDL subfractions and lipid biology may inform its role in atherosclerosis.

Getting to the heart of mechanism via vasculature

APOL1 is expressed in cells relevant to atherosclerosis, including endothelial cells [57–58], vascular smooth muscle cells [59], and macrophages [60–61]. Whether APOL1 in vascular and immune cells causes atherosclerosis has not been reported, but the potential role of risk-variant APOL1 in endoplasmic reticulum (ER) stress [62] may be a promising avenue of

investigation given the established role of ER stress in the pathogenesis of atherosclerosis [63–64]. Because *APOL1* risk variants do not associate with longitudinal blood pressure [36], their contribution to the hypertension driving putative CVD risk remains unclear. However, fetal high-risk *APOL1* genotype has been linked to maternal preeclampsia (established CVD risk factor) and hypothesized to be due to placental dysfunction [65]. This finding is consistent with a published transgenic *APOL1* mouse model, which did not exhibit significant podocyte loss but did have more preeclampsia events [66], providing some evidence for vascular APOL1's role in CVD.

New insights needed from prospective studies

More prospective data on *APOL1* genotype and outcomes are needed to address previously unmeasured confounders. The APOL1 Long Term Kidney Transplantation Outcomes Network (APOLLO) study will follow kidney donors and recipients who have been genotyped, allowing for structured follow-up over time [67]. This information will be of significant value as providers counsel organ donors and recipients on their renal and cardiovascular risks. GENE-FORECAST, sponsored by the National Human Genome Resource Institute, aims to identify novel predictors of cardiovascular risk in African Americans, including the role of degree of genetic African ancestry in CVD and the interplay between genetic variation and the environmental “exposome” [68]. As part of the study, investigators will perform a focused and deep genotype-to-phenotype analysis of patients with high-risk *APOL1* alleles that will likely, if adequately powered, resolve some of the conflicting cardiovascular data in the APOL1 field.

Conclusion

The APOL1 story has been ten years in the making and still evolving, with questions remaining not only regarding the mechanisms by which *APOL1* risk variants drive CKD, but also whether these same variants are truly causal in CVD. Additional large prospective genetic studies are needed to validate whether the high-risk *APOL1* genotype associates with specific types of CVD, and mechanistic studies are also needed to elucidate APOL1's role in cardiovascular pathophysiology.

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Key Points

- Disease modifiers that drive APOL1-associated kidney disease have not been completely elucidated, and even less is known about APOL1's role in cardiovascular pathophysiology.
- Human genetic studies interrogating the association between high-risk *APOL1* genotype and different cardiovascular outcomes have been conflicting due to study design differences.
- More prospective clinical genetic studies and mechanistic studies are needed to elucidate the role of APOL1 risk variants, if any, in the pathogenesis of CVD.

Figure 1. *APOL1* mRNA expression across tissue and cell type. A) Normalized *APOL1* expression by RNA sequencing of different human tissues. **Denotes kidney expression. Adapted from gtexportal.org. The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. The data used for the analyses described in this manuscript were obtained from: the GTEx Portal on 01/15/19 B) Single-cell RNA sequencing dot plots representing relative *APOL1* expression in different cell types of the kidney, adapted from online database curated at humphreyslab.com., originally from <https://www.ncbi.nlm.nih.gov/pubmed/29980650>. Abbreviations: EC endothelial cell PC principal cell PT proximal tubule LH or LOH Loop of Henle DCT distal convoluted tubule IC intercalated cell CD collecting duct Mono monocytes.

Table 1. Studies examining the association between high-risk *APOL1* genotype and cardiovascular disease (CVD)

Study	Database Used	Number of participants with high-risk <i>APOL1</i> genotype	Association between high-risk <i>APOL1</i> genotype and composite CVD outcome?	Significant difference in age between low and high-risk <i>APOL1</i> genotypes?	Participants with diabetes mellitus included?	Participants with moderate to advanced CKD included?
Ito et al. <i>Circ Res</i> , 2014 ²⁷	JHS, WHI	381	Yes	No	Yes	Yes
Langeveld et al. <i>Kidney Int</i> , 2015 ²⁸	SPRINT	361	No	Yes: high-risk younger, $P = 0.0325$	No	Yes: proteinuria > 1 g per day and eGFR < 20 mL/min excluded
Freedman et al. <i>Kidney Int</i> , 2015 ²⁹	AA-DHS	91	No: negative association with subclinical atherosclerosis	No	Yes	Yes: mean eGFR in high-risk group 85.8 mL/min and not statistically different from low-risk group
Mukamal et al. <i>Arterioscler Thromb Vasc Biol</i> , 2016 ³⁰	CHS	91	Yes	No: All participants > 65 years old	Yes	Yes
Grams et al. <i>J Am Soc Nephrol</i> , 2016 ³¹	ARIC	470	No	No	Yes	Yes: mean baseline eGFR in high risk group 110.4 mL/min
Chen et al. <i>Arterioscler Thromb Vasc Biol</i> , 2017 ³²	AASK	160	No: except for in additive genetic model HR per risk allele 1.74, $P = 0.04$	Yes: high-risk younger, $P < 0.01$	No	Yes
Chen et al. <i>J Am Heart Assoc</i> , 2017 ³³	MESA	213	No: except for higher risk of incident heart failure HR 1.84 (CI 1.02–3.32)	No	Yes	Yes
Blazer et al. <i>PLoS One</i> , 2017 ³⁴	New York University's SLE cohort	15	Yes: atherosclerotic disease only, no signal for heart failure	No	Yes	Yes
Wang H et al. <i>Cardiorenal Med</i> , 2017 ³⁵	CATHGEN	231	No	Yes: high-risk younger, $P = 0.01$	Yes	Yes
Chen et al. <i>Kidney Int</i> , 2017 ³⁶	CARDIA	176	No: hypertension as outcome	Yes: high-risk younger, $P = 0.01$	Yes	Yes (not excluded)
Gutiérrez et al. <i>Kidney Int</i> , 2018 ³⁷	CARDIA	159	No: subclinical atherosclerosis and LVH as outcomes	Yes: high-risk younger, $P = 0.02$	Yes	Yes (not excluded)
Gutiérrez et al. <i>Circ Genom Precis Med</i> , 2018 ³⁸	REGARDS	1346	Yes: driven by ischemic stroke	Yes: high-risk younger, $P = 0.02$	Yes	Yes
Franceschini et al. <i>JAMA Cardiol</i> , 2018 ³⁹	WHI	1370	No: reported increased risk of HFpEF hospitalization	No	Yes	Yes

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Study	Database Used	Number of participants with high-risk <i>APOL1</i> genotype	Association between high-risk <i>APOL1</i> genotype and composite CVD outcome?	Significant difference in age between low and high-risk <i>APOL1</i> genotypes?	Participants with diabetes mellitus included?	Participants with moderate to advanced CKD included?
Hughson et al. <i>KJ Reports</i> , 2018 ⁴⁰	University of Mississippi	3	Yes; more CVD on autopsy	Yes	Yes	Yes

Abbreviations: JHS Jackson Heart Study, WHI Women's Health Initiative, SPRINT Systolic Blood Pressure Intervention Trial, AA-DHS African American-Diabetes Heart Study, CHS Cardiovascular Health Study, ARIC Atherosclerosis Risk in Communities, AASK African American Study of Kidney Disease and Hypertension, HR hazard ratio, MESA Multi-Ethnic Study of Atherosclerosis, CI confidence interval, CATHGEN Catheterization Genetics, CARDIA Coronary Artery Risk Development in Young Adults Study, LVH left ventricular hypertrophy, REGARDS Reasons for Geographic and Racial Differences in Stroke, HFpEF heart failure with preserved ejection fraction