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Genetic risk of *APOL1* and kidney disease in children and young adults of African ancestry

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Structured Abstract

Purpose of review—Understanding the genetic risk of *APOL1* in children and young adults is important given the lifetime risk of hypertension and kidney disease among children of African descent. We review recent epidemiologic and biologic findings on the effects of *APOL1* and kidney disease.

Recent findings—*APOL1* in children and young adults is associated with hypertension, albuminuria, and more rapid decline in kidney function and progression to end stage kidney disease, especially among those with glomerular causes of kidney disease, and those affected by sickle cell disease or HIV. There is conflicting data on the *APOL1* association with cardiovascular disease in children and young adults. *APOL1* functions as part of the innate immune system. Podocyte expression of *APOL1* likely contributes to development of kidney disease. In cell culture and model organisms, *APOL1* expression disrupts autophagic and ion flux, leads to defects in mitochondrial respiration and induces cell death.

Summary—*APOL1* explains almost 70% of the excess risk of kidney disease in those of African descent, and is common in children with glomerular disease. Evolving understanding of the pathogenesis of *APOL1* mediated kidney damage may aid in personalized medicine approaches to *APOL1* attributable kidney disease.

Keywords

APOL1; genetics; kidney disease; end stage renal disease; focal segmental glomerulosclerosis; children

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Conflicts of interest

KR is site PI for a Questcor supported clinical trial with no relevance to the contents of this manuscript. The remaining authors have no conflicts of interest.

Introduction

Until 2008, genetic risk of kidney disease was underestimated in association with complex kidney phenotypes unlike Mendelian forms of kidney disease such as focal segmental glomerulosclerosis (FSGS) and IgA nephropathy. With identification of the chromosome 22q12 locus and the gene, *APOL1*, genetic risk now accounts for 70% of the excess risk for end stage renal disease (ESRD) and FSGS among African Americans^{1–3}. There are 3 single nucleotide polymorphisms (SNPs) in *APOL1*, that comprise the G1 (terminal exon with two SNPs: rs73885319 and rs609101) and G2 (six base pair deletion: rs71785313) haplotypes. The development of variants in *APOL1* are likely due to changes approximately 60,000 years ago for protection against trypanosomal infection (sleeping sickness) on the African continent. Carriers of 2 risk alleles are at high-risk of progression to ESRD in a recessive pattern. Among African Americans in the US, it is estimated that 12–14% carry 2 high-risk alleles, yet less than 15 out of 100 with high risk alleles are predicted to develop ESRD⁴. Moreover, *APOL1* high-risk variants are virtually nonexistent in other ethnicities⁵.

Unravelling the epidemiology and biology of *APOL1* is complex as the gene exists only in humans and higher order primates, penetrance is not 100%, and interaction with the genes and/or environment is necessary to develop kidney disease. In this review, we will highlight the specific studies focused on the epidemiology in children and young adults impacting lifetime risk, and the recent studies on the biology of *APOL1* leading to kidney disease.

Epidemiology of *APOL1*-related kidney disease (Figure 1)

Progressive kidney disease

Initial studies of *APOL1* were focused on studying progressive kidney disease with case-control studies of extreme phenotypes, which first identified the association of *APOL1* with ESRD in those with nondiabetic kidney disease and FSGS². Population based studies have subsequently demonstrated an association with progressive disease over years leading to end stage renal disease (ESRD). Middle aged African American adults have a 2 times greater risk of progression to ESRD or composite kidney outcomes compared to low-risk carriers or Whites^{6,7}. Risk was worse in those with proteinuria. Thus, *APOL1* is definitely considered a “progressor” gene but its role in inciting new kidney disease is less clear.

This has significant implications to children and young adults. In studies of young adults followed over decades, rates of ESRD are very low. Thus, *APOL1* may be associated with rapid declines to kidney failure only after decades and also require additional exposures to other factors (“second hits”) predisposing to kidney injury. Early kidney disease, however, manifested by albuminuria defined as greater than ACR > 30 mg/g, has a significantly higher incidence rate among high-risk carriers of *APOL1* at 15.6 (95% confidence interval [95% CI], 10.6–22.2) per 1000 person years, compared with 7.8 (6.4–9.4) for low-risk carriers and much lower among Whites at 3.9 (3.1–4.8) in a young adult population followed over 25 years⁸. Decline in kidney function measured by an estimated glomerular filtration rate (eGFR) using cystatin C demonstrated that after adjustment, high-risk carriers of *APOL1* had a 0.45% faster yearly decline in eGFR over 9 years compared with whites, and this decline was significantly steeper after development of albuminuria. In children with

glomerular disease, *APOL1* high-risk carriers had a 2–4 fold faster rate of glomerular filtration rate decline than low risk children⁹.

Spectrum of kidney diseases

Among African Americans, *APOL1* is associated with increased risk of hypertensive disease, lupus, diabetic and HIV-related kidney disease^{2,10,11}. Risk varies depending on selected population with early or advanced kidney disease, and study design and risk ranges from 2 to as high as 89 times greater odds or relative risk of ESRD. Risk is significantly higher in case-control studies of extreme phenotype such as end stage renal disease vs. healthy controls and is significantly attenuated in the longitudinal studies of the general population. Risk is also consistently highest for those with HIV disease, which reflects a possible association of viral infection, innate immunity, and potentially gene-environment interaction. Among African children with perinatal HIV infection, there is a 3.5 increased odds of chronic kidney disease, about 1 case per 100 person years, which is important to consider in long-term risk as these children age¹². With the reduction of perinatal HIV transmission globally, the burden may diminish over time. Sickle cell nephropathy may be impacted by *APOL1* risk alleles. In two studies (one of over 400 African adolescents and young adults and another of 152 young adults with African ancestry in France with sickle cell disease)¹³, *APOL1* was associated with albuminuria¹⁴ and lower eGFR. The spectrum of involvement further highlights the association with progressive kidney disease (Figure 1).

Focal segmental glomerulosclerosis (FSGS)

In children and young adults with African ancestry, the prevalence of *APOL1* risk carriers is similar at 67–78% in those with glomerular disease enrolled in the FSGS trial and also prospective cohorts of Chronic Kidney Disease in Children (CKID) or biopsy proven FSGS (Neptune)^{9,15}. Interestingly, age at presentation of FSGS among *APOL1* high-risk carriers is older with a mean age of 12 years, as compared to 5 years for low-risk carriers⁹. Findings from the FSGS trial revealed that there was no difference in treatment response by *APOL1* high-risk carrier status, however, this may have been due to limited power with only 94 children in the trial with available DNA and only 27 carried high-risk *APOL1* variants. In kidney biopsies of children and adults, coexpression of *APOL1* mRNA levels with a group of intrarenal transcripts associated with increased interstitial fibrosis and tubular atrophy in kidney biopsies, support the role of *APOL1* in progressive kidney disease phenotypes¹⁶.

Gene and environmental interaction with APOL1

Given the incomplete penetrance of *APOL1*, environmental and genetic interactions may contribute to development of kidney disease. While often underpowered, the majority of studies have demonstrated modest or little association of gene-gene interactions or environmental modifications. HIV remains one of the most important environmental factors. It is not clear if HIV's impact is related to viral load or the immune response. A circulated protein, suPAR, also shows that among high-risk carriers with elevated suPAR the decline in kidney function is steeper compared to low-risk carriers; although statistically different, this difference in slopes is not clinically significant¹⁷. Also, gene-gene interaction with GSTM-1, a gene related to oxidative stress, has demonstrated that carriage of GSTM-1 null allele in the setting of *APOL1* high-risk alleles further increased risk from 2 (*APOL1* high risk alone)

to 3 fold as compared to GSTM-1 active/APOL1 low risk patients) for development of kidney composite outcomes (ESRD and decreased GFR) among 682 African Americans¹⁸. This interaction has not yet been tested in children.

APOL1 associated with cardiovascular disease

Among high-risk carriers of *APOL1*, incidence of cardiovascular disease is significantly higher compared to low-risk carrier. Cardiovascular events such as coronary disease, stroke, heart failure, peripheral vascular disease, and mortality have been implicated as potentially pleiotropic effects of *APOL1*. Yet, the findings are inconsistent as the focus has been on various types of cardiovascular disease including atherosclerosis, heart failure, and calcification, which differ in pathogenesis especially in those with underlying kidney disease. In young adults and children, there is risk of hypertension and left ventricular hypertrophy (LVH). In a cross sectional analysis of clinic participants from a single medical system, about 5000 participants had genotyping for *APOL1* with replication in an additional 5000 individuals from other centers. Among the 20–39 year old heterozygotes for *APOL1*, there was a 1.4–1.6 mm Hg higher systolic blood pressure and among homozygotes for *APOL1* risk alleles, there was a 2.5–2.9 mm Hg increase in systolic blood pressure. In a prospective cohort of 480 young adults followed over two decades, there was a higher risk of hypertension among African Americans compared to European American children, however, by *APOL1* risk status, there was no difference in risk. In the same cohort of young adults, there was also no evidence of subclinical atherosclerosis or left ventricular hypertrophy by *APOL1* risk status. In a study of 140 children with underlying chronic kidney disease, there was a borderline association with LVH¹⁹ and uncontrolled blood pressure. Dissecting the causal pathway of hypertension and kidney disease among children and young adults is complex. It is not clear if cardiovascular disease is a result of pleiotropic effects of *APOL1* or increased cardiovascular events due to underlying kidney disease (Figure 2)²⁰. These associations are further confounded by additional risk factors that accumulate with age such as poor nutrition, obesity and inactivity. Larger studies are need to address genetic screening of children and adolescents and the potential clinical utility in this high-risk African ancestry population.

Implications

In children with hypertensive disease or FSGS, there was a higher proportion of *APOL1* risk alleles among those with a family history of ESRD. Highlighting that, irrespective of genetic testing, family history is a potential useful screening test²¹.

Recent studies have highlighted that recipients of donors with high-risk kidney are at greater risk for graft loss. This is particularly controversial as the absolute risk overtime is low for potential donors, however, the risk to recipients could result in a loss of a kidney 2 times greater risk of kidney allograft failure²². A consortium, APOLLO, funded by the NIDDK will seek to study this question prospectively to study the implications of a kidney transplant with *APOL1* high- risk alleles.

There are implications to children and young adults as parents may still want to donate regardless of their own *APOL1* risk status. This raises a number of ethical concerns as

APOL1 is not routinely screened as risk to the donor and/or the recipient needs to further tested. A study of 3483 young African American adults aged 18–30 years determined the risk scores for transplantation²³. It is estimated that the 25 year risk of CKD for an 18 year old with *APOL1* high-risk carrier status was significantly increased among women and men with and without baseline clinical characteristics compared to those with low-risk status or White. The absolute risk of CKD was projected to be as high as 6% in women and 11% in men²³. Nonetheless, parents may also wish to donate regardless of personal risk as they recognizing that living kidney donation is better for the child. The implications to transplantation are potentially significant since the recipient pool keeps increasing with a diminishing donor pool. Moreover, the competing risk of surviving with end organ kidney disease to reach even wait listing for an organ is a real issue confronting children that may not receive preferential listing after age 18. In pediatric transplantation, the goal is also to provide the best organ for the first transplant as most children with require a second transplant. Until we have further data, it is important to screen all potential donors with a family history before embarking on widespread *APOL1* genetic testing.

Potential mechanisms of *APOL1* action leading to kidney disease

Recent studies have elucidated mechanisms by which *APOL1* functions in both health and disease (Figure 3). *APOL1* is among a family of six highly homologous lipoproteins (*APOL1-6*). *APOL1* is the only one that is secreted and exists in a circulating form bound to high density lipoproteins (HDLs). Activation of toll like receptor 3 (TLR3) and cytokines such as interferon gamma and tumor necrosis factor up-regulate *APOL1* expression^{24–27}. *APOL1* is protective in HIV by blocking HIV-1 transcription and by degradation of HIV-1 Gag via activation of the transcription factor EB (TFEB)²⁸. *APOL1* mRNA expression is also increased in skin lesions from patients with self limited (vs. disseminated) leprosy²⁹. These findings are consistent with the concept that the primary function of *APOL1* is in innate immunity.

The most well understood role for *APOL1* in innate immunity is as a circulating defense factor against Trypanosoma species *T.b. brucei* and *T. evansi*^{30–35}. Trypanosoma are flagellate parasites transmitted by Tsetse flies that cause African sleeping sickness (trypanosomiasis). *T.b. rhodesiense* express a serum resistance factor that binds *APOL1* and prevents the parasite lysis. *T.b. gambiense* is also resistant to *APOL1* mediated cell lysis, but due to different and not fully understood mechanisms. *APOL1* has 3 protein domains: a membrane addressing domain, a pore forming domain and serum resistance associated protein binding domain. *APOL1* high-risk haplotypes evolved in the binding domain for the serum resistance factor, and *in vitro* both lyse *T.b. rhodesiense*². The presence of at least one copy of G2 variant results in a 5-fold decreased risk of *T.b. rhodesiense* infection, however, G1 was not protective among infected participants from endemic regions of sleeping sickness³¹. Instead having one or two G1 variants was protective against symptomatic *T.b. gambiense* infection, while having either one or two G2 variants was associated with higher risk of symptomatic *T.b. gambiense* infections³¹. These findings suggest that G1 and G2 may have differential functions in protection against infection but carriage of any 2 risk alleles (either G1 and/or G2) increases risk of kidney disease.

The current understanding of the trypanolytic function of *APOL1* involves endocytosis of *APOL1*, with insertion of *APOL1* into endosome membranes. Once inside the Trypanosome, the low pH alters *APOL1* conformation and induces pore formation. The pore forming domain of *APOL1* is homologous to pore forming domains of colicin A (a peptide toxin released by E.Coli) and has a BH3 binding domain. *APOL1*'s BH3 binding domain contributes to alterations in autophagic cell flux and is required to induce cell death²⁶.

Pore formation in lysosomes and mitochondria results in lysosomal swelling, mitochondrial membrane depolarization and fenestration, and ultimately parasite cell death³³. The pore forming domain of *APOL1* requires an acidic environment for membrane insertion and trypanolytic activity^{30,36}. In addition, the characteristics of *APOL1* pores vary with pH³⁶. Modification of the pore forming domain to overcome pH dependence in recombinant *APOL1* improved its trypanolytic activity and may lead to new treatments for trypanosomiasis. Despite the importance of pore formation to *APOL1*'s innate immune function, the precise contribution of pore formation and subsequent ion transport to *APOL1* attributable kidney disease is debated³⁷.

Several lines of evidence suggest that the intracellular form of *APOL1* leads to increased risk for kidney disease. First, donor kidneys with *APOL1* high-risk genotypes had higher risk of graft failure, while recipients (with circulating *APOL1* high risk variants) had no increased risk of graft failure^{22,38–41}. Second, circulating *APOL1* levels are not associated with kidney disease⁴². Furthermore, rare humans with loss of *APOL1* function (a functional knockout human) do not develop kidney disease⁴³. Thus, there appears to be a change in *APOL1* function that results in kidney pathology.

One of the challenges in understanding mechanisms by which *APOL1* contributes to kidney disease is that its subcellular localization is not fully understood, with localization reported in plasma membrane⁴⁴, endoplasmic reticulum⁴⁵, endosomes^{46,47}, and mitochondria³³. Another major challenge is that *APOL1* evolved only in primates, and thus all experimental models of *APOL1* rely on expression of exogenous *APOL1* variants in model organ systems.

Several mouse models have been generated to examine *APOL1* function. Inducible transgenic podocyte expression of *APOL1* G0, G1, and G2 variants showed that the highest expressing G1 and G2 transgenic mice developed proteinuria and glomerulosclerosis lesions similar to human disease⁴⁷. Additionally, it was reversible when induction of the *APOL1* expression was removed. This is consistent with a concept that stimuli (such as inflammatory signals of interferons) that increase *APOL1* expression may lead to manifestation of disease²⁷. Impaired autophagic flux as well as inflammasome activation and cell death by pyroptosis was induced in transgenic *APOL1*, suggesting that these pathways may mediate podocyte damage in *APOL1* related kidney disease.

Other have developed alternative organ systems and cellular culture approaches to investigate *APOL1* function. Expression of the *APOL1* G1 and G2 alleles in *Drosophila* disrupted endocytic trafficking and induced hypertrophy and cell death of the “nephrocyte” (*Drosophila* analogue to the podocyte)^{48,49}. Two independent groups identified mitochondrial dysfunction in cells overexpressing the *APOL1* G1 and G2 constructs^{45,50,51}.

APOL1 G1 and G2 expression led to impaired mitochondrial respiration, intracellular ATP depletion and activation of stress kinases (JNK/SAPK and p38). The two studies had conflicting data as to whether alterations of K efflux contributed to, or was caused by, mitochondrial dysfunction. Higher expression is consistently associated with cellular toxicity; but the manner of cell death remains under question, with apoptosis, necrosis, impaired autophagy and pyrophagy- all implicated as mechanisms of cellular death with *APOL1* expression.

In addition to the *APOL1* mouse model described above, a second mouse model was reported by Bruggeman et al. whereby the *APOL1* G0 and G2 variants were constitutively (rather than inducibly) expressed under the control of the nephrin promoter⁵². The constitutive expression resulted in phenotype during fetal development: pregnant mice in this model unexpectedly manifested a preeclampsia like phenotype, with hypertension, proteinuria and seizures. Further investigation demonstrated that *APOL1* expression was present in mice placentas and the mice had elevated soluble Flt1 (VEGFR1), a known circulating factor associated with preeclampsia in humans. In contrast to the inducible model, adult mice exhibited only a mild glomerular phenotype, with podocyte effacement with no evidence of glomerulosclerosis.

Interestingly, the *APOL1* transgenic mice had smaller litter sizes and increased fetal and perinatal loss. Children with FSGS who are carriers of *APOL1* high-risk alleles with FSGS had a 4.6 fold increase in preterm birth compared to low-risk carriers⁵³. A subsequent study of prematurity did not identify an increased prevalence of *APOL1* high risk alleles in mothers or infants in 2 studies of premature infants; however, further study of the impact of *APOL1* on birth outcomes is ongoing⁵³.

Conclusion

Risk alleles of the gene, *APOL1*, confer increased risk of hypertension and early markers of kidney dysfunction in young adults, but the lifetime risk for children is less certain. Ongoing work to understand the clinical implications for genetic screening will be important for children and young adults as risk for progressive kidney disease increases with age. Questions remain about which populations are at greatest risk and what are the additional genetic and environmental exposures need to develop kidney disease. Recent advances in biology highlight the relevance of *APOL1* to innate immunity. Podocyte over expression of *APOL1* results in human-like disease, and these and other models can provide insight into targetable pathways that contribute to *APOL1*-attributable disease.

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Summary

- *APOL1* gene variants account for the majority of excess risk of kidney disease in people of African descent.
- *APOL1* gene variants are common in children of African descent with glomerular disease and are associated with faster progression of kidney disease.
- Gene-gene or environmental “second hits” such as HIV contribute to development of *APOL1* attributed kidney disease.
- Understanding the mechanisms by which *APOL1* variants result in kidney disease provides an opportunity to develop new therapeutics and personalized medicine approaches in the future.

Figure 1.

Possible association of blood pressure, CKD and *APOL1*

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Figure 2. Possible pathways for *APOL1* risk alleles leading to the development of hypertension and chronic kidney disease. Reprinted with approval received from *Kidney International*.²⁰

a Innate immunity: *Trypanosoma* lysis **b Kidney disease** **Figure 3. Biologic function of APOL1**

Left: APOL1 contributes to innate immunity. Secreted APOL1 (depicted in red) circulates in a lipoprotein complex with high density lipoprotein (HDL). The complex is endocytosed by *Trypanosoma*, whereby APOL1 inserts into membranes and forms pores, leading to lysis of the parasite.

Depicted is APOL1 insertion in lysosomes; APOL1 induced mitochondrial dysfunction may also contribute to trypanosomal death. *APOL1* genetic variant G2 overcomes *T.b. rhodesiense*'s serum resistance factor and G1 protects against symptomatic *T.b. gambiense* infection.

Right: APOL1 (depicted in red) localization in the kidney is debated, with different studies identifying plasma membrane, endoplasmic reticulum (ER), endosomal and mitochondrial localization. Expression of APOL1 G1 and G2 variants in cell and animal models has been shown to: 1) disrupt autophagic flux, 2) induce mitochondrial respiration defects with ATP depletion, 3) induce K efflux and stress response pathways (p38 kinase/stat 3). Expression of the variants are cytotoxic, and cell death variably induced by apoptosis, necrosis and inflammatory cell death (pyroptosis). An inducible transgenic mouse model expressing the APOL1 gene variants in podocytes exhibited cell death by pyroptosis, with increased IL-1 β expression and caspase 1 mediated activation of IL-1 β .