Apolipoprotein L1 (APOL1) and Nephropathy

Articoli originali

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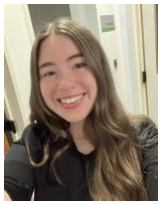
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ABSTRACT

Introduction. End-stage renal disease exhibits a disproportionate prevalence among Black individuals and older adults within the United States and worldwide. A significant genetic contributor to this disparity is the Apolipoprotein L1 (APOL1) gene, found exclusively in populations of African ancestry.
Materials and Method. We aim to perform a narrative review regarding the current understanding of APOL1 and its complex role in kidney disease pathogenesis.
Results. The G1 and G2 APOL1 risk alleles are strongly associated with an elevated risk for non-diabetic chronic kidney disease (CKD), including hypertensive nephropathy, focal segmental glomerulosclerosis, and HIV-associated nephropathy, in individuals who are homozygous or compound heterozygous for these variants. While 10-15% of African Americans carry two APOL1 risk alleles, approximately 80% remain disease-free, suggesting incomplete penetrance and the involvement of additional risk factors. In this condition, renal damage could be induced through different mechanisms such as altered cellular ion transport, mitochondrial dysfunction, and the requirement for additional stressors or "second hits".
Conclusion. The increased susceptibility to end-stage renal disease (ESRD) in individuals of African ancestry is influenced by variations in the APOL1 gene.

KEYWORDS: Apolipoprotein L1, kidney diseases, genetics

Introduction

Studies in the United States have revealed that the risk of developing end-stage renal disease (ESRD) is significantly higher in Black individuals and older adults. Specifically, Black individuals are almost three times more likely to develop this condition compared to White individuals, and those aged 75 and older are almost three times more likely to develop it compared to those aged 45 to 64 [1, 2].

Apolipoprotein L1 (APOL1) is a gene observed exclusively within populations of African ancestry. The APOL1 risk alleles, G1 and G2, which are characterized by two linked single nucleotide polymorphisms (G1) and a deletion (G2), respectively, are strongly associated with an elevated risk for non-diabetic chronic kidney disease in homozygous or compound heterozygous individuals, following an autosomal recessive inheritance pattern [3–12].

In African Americans, 50% carry at least one G1 or G2 allele, while 10-15% are homozygous or compound heterozygous for these risk alleles. Despite a significant risk of chronic kidney disease associated with G1 and G2 APOL1 variants, approximately 80% of individuals with two risk alleles will remain disease-free [8].

It is worth mentioning that Chen et al. found that even though the prevalence of hypertension, coronary heart disease, atrial fibrillation/flutter, stroke, and heart failure was similar between Black individuals with high-risk and low-risk APOL1 genotypes, significant disparities emerged when comparing Black and White participants. Black participants, regardless of APOL1 genotype (high or low risk), exhibited a higher prevalence of hypertension, diabetes mellitus, and overall cardiovascular disease compared to White participants. Moreover, APOL1 risk variants were identified as risk factors for end-stage renal disease, but not for mortality, and this association remained consistent across different age groups [1].

APOL1

APOL1, a recently evolved gene present only in humans and certain primates, circulates as part of high-density lipoprotein and protects against *Trypanosoma brucei rhodesiense*, the causative agent of African sleeping sickness, by inducing lysosomal swelling and lysis of the parasite [8].

The APOL1 gene is located at chromosome 22, and encodes apolipoprotein L1, a protein expressed across a range of tissues and cell types [1, 3, 10]. The APOL1 messenger RNA is expressed in various tissues, including liver, lung, placenta, and endothelial cells, with weaker expression in heart and pancreas, and potential expression in macrophages [4]. The majority of APOL1 present in human plasma is secreted by the liver, and circulates as part of high-density lipoprotein class 3, specifically the dense subclass 3a, and is largely absent from other HDL classes [5, 8]. Beyond its well-established association with kidney disease, APOL1 plays a key role in lipid metabolism, particularly as a structural component of high-density lipoprotein (HDL) particles. APOL1 is primarily secreted by the liver and circulates in HDL subclass 3a, where it participates in the reverse cholesterol transport (RCT) pathway, promoting cholesterol efflux from macrophages and peripheral tissues toward the liver for excretion. Variants in APOL1 (G1 and G2), although evolutionarily selected for their protective role against Trypanosoma brucei rhodesiense, may alter HDL composition and function, leading to reduced anti-atherogenic capacity.

This dysfunction could contribute to endothelial injury, vascular inflammation, and accelerated atherosclerosis in carriers of APOL1 risk alleles, potentially linking renal and cardiovascular pathogenesis within the same genetic framework. While findings remain partially inconsistent – some studies not demonstrating a direct causal link – emerging evidence supports that APOL1

variants may impair HDL-mediated cholesterol trafficking and anti-inflammatory functions, offering a unifying explanation for the increased cardiovascular and renal risk in individuals of African ancestry. Understanding this dual role of APOL1 in both lipid handling and kidney injury may help nephrologists interpret the broader systemic implications of APOL1 genotypes and design integrated approaches to patient care (Figure 1) [15].

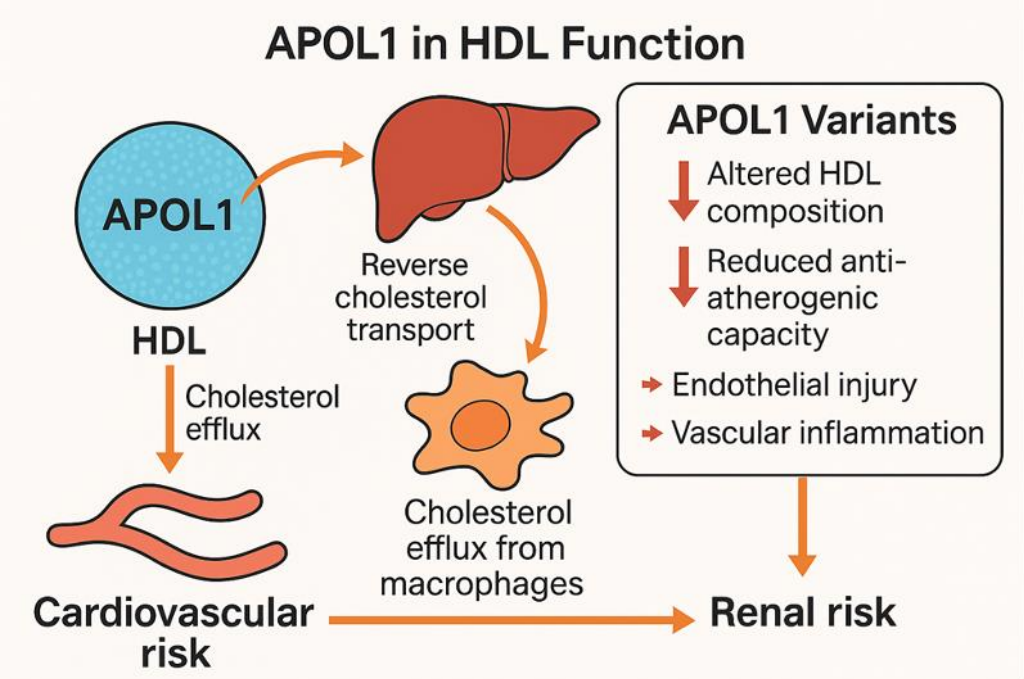

Figure 1. Schematic representation of the role of APOL1 in high-density lipoprotein (HDL) metabolism and reverse cholesterol transport. APOL1, primarily secreted by the liver, is incorporated into HDL3a particles that mediate cholesterol efflux from macrophages to the liver. APOL1 risk variants (G1, G2) may alter HDL composition, impair cholesterol trafficking, and reduce its anti-atherogenic capacity, contributing to endothelial injury, vascular inflammation, and increased cardio-renal risk.

The APOL1 protective effect against *Trypanosoma brucei rhodesiense* explains the high frequency of APOL1 risk variants in sub-Saharan Africa [4, 8, 10]. Thomson et al. found that the G1 variant of the APOL1 gene was most prevalent in West Africa, while the G2 variant was distributed more evenly across the globe [3, 5]. Genetic variation in the APOL1 gene is a major contributor to the disparity in non-diabetic kidney disease rates between African Americans and European Americans. Approximately 30% of African Americans chromosomes carry either the G1 or G2 APOL1 allele, which are mutually exclusive on single chromosomes. Around 10-12% of African Americans inherit two APOL1 risk alleles, while 49% lack any risk variants. In contrast, these risk variants are infrequent in European Americans, with roughly 0.3% carrying the G1 allele and 0.1% carrying the G2 allele [4].

The G1 allele was found in approximately 40% of Yoruba (West Africa) chromosomes but was absent in European, Japanese, and Chinese individuals. Similarly, G2 was detected in only three Yoruba subjects and not in the other groups [6]. North American studies have reported APOL1 allele frequencies between 20% and 39%, while Asian and some Latin American studies have shown considerably lower frequencies, ranging from 1.9% to 9.4% (Figure 2) [3].

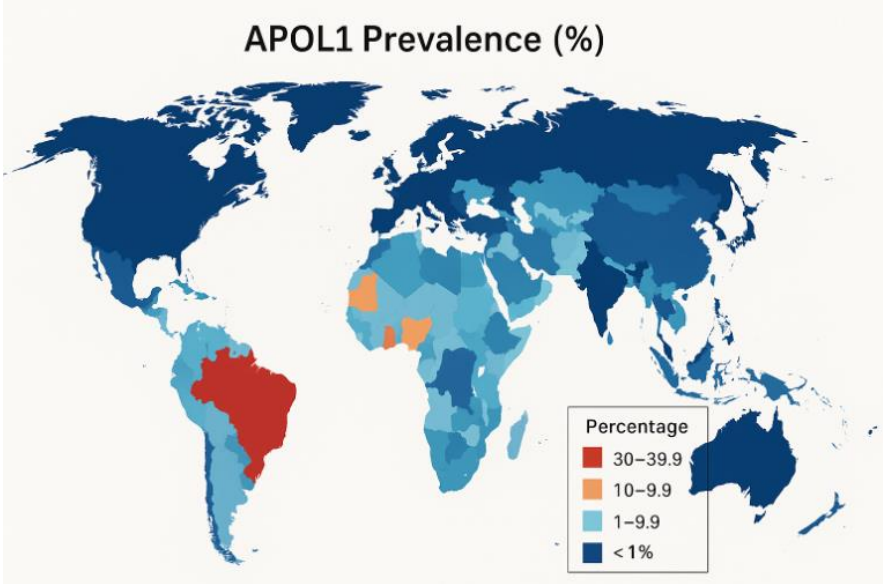

Figure 2. Global prevalence of APOL1 risk variants (G1 and G2). The map illustrates regional differences in APOL1 allele frequencies: dark red (>30%) in Sub-Saharan Africa, orange (10-30%) in North America and Afro-descendant regions, yellow (1-9%) in some Latin American populations, and light grey (<1%) in Europe, Asia, and Oceania. This distribution reflects the evolutionary pressure exerted by Trypanosoma brucei rhodesiense exposure.

APOL1 and kidney disease

APOL1 gene variants in African Americans significantly increase the risk of hypertensive kidney disease, lupus nephritis, sickle cell nephropathy, focal segmental and global glomerulosclerosis, characterized by interstitial scarring and arteriolar changes, and HIV-associated collapsing glomerulosclerosis [3–12]. In Afro-descendant patients with chronic kidney disease, the prevalence of APOL1 gene mutations is 20-22% for the G1 variant and 13-15% for the G2 variant [3].

In the population-based Dallas Heart Study, APOL1 risk variants were associated with an increased prevalence of microalbuminuria and a decreased glomerular filtration rate among African American participants. However, no statistically significant difference in proteinuria or estimated glomerular filtration rate was observed between individuals with two APOL1 nephropathy risk variants and those with less than two [7].

In kidney transplant patients, no significant difference in renal allograft survival was observed between recipients of kidneys from donors carrying one APOL1 nephropathy risk variant and those receiving kidneys from donors without such variants, while it was found significantly reduced renal allograft survival in recipients of deceased donor kidneys from African Americans with two APOL1 nephropathy risk variants compared to those receiving kidneys from African American donors with fewer than two risk variants [4]. Additionally, it has been suggested that APOL1 expression across podocytes, endothelial cells, and immune cells may independently or synergistically contribute to the complex pathogenic processes affecting renal allograft survival [12]. Recent evidence also suggests that APOL1 variants may influence cardiovascular risk beyond their established renal effects. As a structural component of high-density lipoproteins (HDL), APOL1 participates in reverse cholesterol transport, facilitating cholesterol efflux from peripheral macrophages to the liver. Alterations in APOL1 structure or expression could impair HDL function, potentially reducing its anti-atherogenic capacity. This dysfunctional HDL phenotype may contribute to endothelial injury, vascular inflammation, and accelerated atherosclerosis in APOL1 risk allele carriers. Although the

literature remains inconsistent – some studies failing to confirm a direct causal relationship – the possibility of a link between APOL1 variants, altered lipid metabolism, and cardiovascular disease warrants further investigation [13].

APOL1 damaging mechanisms

It has been hypothesized several potential mechanisms by which APOL1 variants may induce nephropathy in native kidneys:

- The APOL1 protein present in individuals homozygous for APOL1 risk alleles, may exhibit reduced HDL binding, leading to its filtration and reabsorption within the proximal nephron, culminating in kidney damage. In this sense, circulating APOL1 has been implicated in recurrent focal segmental glomerulosclerosis post-transplantation, a condition responsive to plasmapheresis [4].
- Abnormal HDL levels may contribute to renal microvascular disease, frequently observed in focal segmental glomerulosclerosis and hypertension-attributed end-stage renal disease [4].
- The requirement of two APOL1 risk alleles for phenotype development may be explained by a multimerization model. This model proposes that wild-type APOL1 interacts with an unknown factor to antagonize APOL1 toxicity. In the presence of a single APOL1 risk allele, the formation of APOL1 multimers containing at least one wild-type subunit is sufficient to maintain the inhibitory binding of the toxicity-blocking factor. Conversely, when two risk alleles are present, multimers predominantly lack wild-type APOL1, leading to the manifestation of toxicity [8].
- APOL1 podocyte expression may result in cellular dysfunction or injury. Given APOL1 structural and functional similarities to the Bcl2 family of apoptosis-related proteins, APOL1-induced podocyte apoptosis could lead to glomerulosclerosis. These pathways could contribute to subclinical APOL1-associated kidney disease in native kidneys, as well as to graft dysfunction post-donation in the context of cold ischemia and nephrotoxic agents, such as calcineurin inhibitors [4].
- Since nephropathy does not manifest in all individuals who present two APOL1 risk variants inheritance, this suggests that additional genetic and/or environmental factors (second hit) are necessary for developing this disease. This ‘second hit’ may interact with APOL1 risk variants, resulting in renal damage. For example, the presence of HIV infection (60-70% HIV-associated collapsing focal segmental glomerulosclerosis carry the high-risk APOL1 genotype) or variations within the podocin gene (NPHS2) may represent second hits [7]. Another potential ‘second hit’ is serum suPAR, a predictive biomarker for kidney disease in individuals with the high-risk APOL1 genotype, which could bind podocyte integrins and APOL1, potentially leading to renal damage [8].
- Interferon treatment in some individuals with this genotype has induced proteinuria and focal segmental glomerulosclerosis. These findings strongly suggest that viral infections, by an interferon-mediated mechanism, are a crucial second hit for kidney disease development. Interferon strongly induces APOL1 RNA and protein expression in cultured human podocytes and endothelial cells, due to multiple STAT-binding sites on APOL1 regulatory regions [8].
- It has been proposed that risk variant APOL1-induced toxicity is mediated by impaired late endosome-lysosome fusion (a VAMP8-mediated process), and subsequent disruption of autophagy flux [8].

- APOL1 variants mediate kidney disease pathogenesis by exerting ion channel activity, consequently resulting in the NLRP3 upregulated activation as cytotoxicity mediator and STING function as immune mediators inducer, both of which are nephropathy determinants (Figure 3) [12].

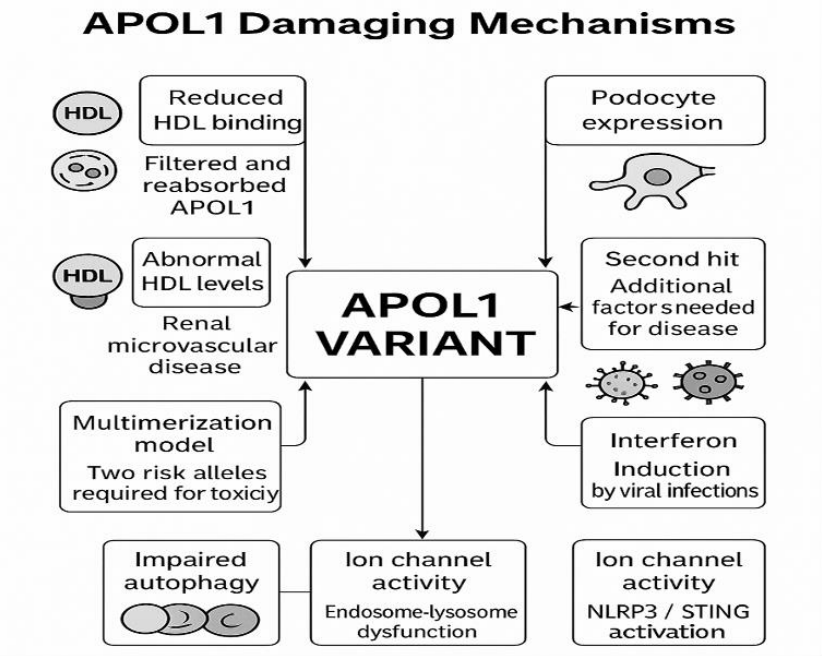

Figure 3. APOL1 Damaging Mechanisms.

APOL1 and pre-eclampsia

The life course of APOL1-related disease may begin in utero. In the CKiD and NEPTUNE cohorts, children carrying APOL1 risk variants (RVs) showed a higher likelihood of preterm birth. Although population studies do not confirm a general association between APOL1 and preterm delivery, fetal APOL1 RVs have been linked to an increased maternal risk of pre-eclampsia, particularly among U.S.-born women, suggesting that environmental factors may modulate this risk. Some evidence indicates an additive effect, where even a single maternal APOL1 RV increases susceptibility, but the highest risk occurs when the fetus carries a high-risk APOL1 genotype; mismatches between maternal and fetal genotypes may further influence outcomes. This association likely reflects the high placental expression of APOL1, as demonstrated in transgenic mice, where APOL1 expression in the placenta induced a pre-eclampsia-like phenotype – even in wild-type dams carrying APOL1-positive fetuses. Additionally, fetal APOL1 RVs have been associated with small-for-gestational-age infants in pre-eclamptic pregnancies. Collectively, these findings suggest that APOL1 genotyping could serve as a risk-stratification tool for pregnant women of African ancestry, and that pre-eclampsia or preterm birth might act as second hits predisposing to early-onset kidney disease in childhood [14].

APOL1 treatment

The growing understanding of the molecular basis of APOL1-mediated nephropathy has fostered the development of several targeted therapeutic strategies aimed at reducing APOL1 expression, inhibiting its cytotoxic function, and modulating downstream inflammatory pathways [10]. These interventions are grounded in the observation that APOL1-induced injury is driven by elevated

expression and aberrant channel activity of the high-risk G1 and G2 variants, which promote podocyte dysfunction, inflammation, and cell death. Therefore, reducing APOL1 levels or blocking its pore-forming activity is hypothesized to attenuate the initial pathogenic cascade. Among the most advanced compounds is Inaxaplin (VX-147), a small-molecule inhibitor designed to block APOL1 pore function and prevent cationic dysregulation within podocytes. In a Phase 2 study [15] treatment with Inaxaplin in patients carrying two APOL1 risk variants and focal segmental glomerulosclerosis resulted in a clinically meaningful reduction in proteinuria after 13 weeks, suggesting that selective inhibition of APOL1 function may slow the progression of nephropathy and potentially redefine the therapeutic approach for genetically determined glomerular disease. In parallel, antisense oligonucleotides (ASOs) targeting APOL1 mRNA have demonstrated preclinical efficacy by silencing APOL1 gene expression, thereby reducing the accumulation of toxic protein in podocytes and mitigating kidney injury [16]. This gene-specific strategy directly addresses the pathogenic source and may complement small-molecule inhibitors in patients with high-risk genotypes. Beyond direct APOL1 modulation, recent findings highlight the potential of downstream pathway inhibition. Wu et al. identified both the NLRP3 inflammasome and the STING (stimulator of interferon genes) signaling pathway as critical effectors operating downstream of APOL1 channel activity within podocytes. Inhibiting STING may represent a particularly promising strategy, given its role in amplifying interferon production, which in turn induces APOL1 overexpression and perpetuates cellular toxicity. STING blockade, therefore, could interrupt this pathogenic feedback loop and limit the inflammatory milieu driving APOL1-associated renal damage. Similarly, pharmacologic inhibition of NLRP3 inflammasome activation may attenuate pyroptosis and inflammatory cytokine release, thereby preserving podocyte viability [17].

Other approaches under investigation include JAK-STAT pathway inhibitors, such as baricitinib, which suppress cytokine-driven APOL1 transcription and have shown beneficial effects in experimental models of inflammatory podocytopathy. Collectively, these strategies reflect a multifaceted therapeutic paradigm – ranging from direct genetic and molecular inhibition of APOL1 to modulation of its downstream signaling effectors [18]. While most agents remain in early clinical or preclinical phases, these emerging data collectively underscore a paradigm shift in the management of APOL1-associated kidney diseases – from non-specific immunosuppression toward precision nephrology, grounded in genetic stratification and mechanistic understanding (Table 1). The integration of APOL1 genotyping into clinical practice will be crucial for patient selection and for guiding the application of these novel therapies, ultimately improving renal outcomes and addressing long-standing health disparities in populations of African ancestry.

Agent	Mechanism/Target	Development Phase	Key Reference(s)
Inaxaplin (VX-147)	Small-molecule APOL1 function/pore inhibitor; reduces proteinuria	Phase 2/3	Egbuna et al., N Engl J Med 2023
APOL1 Antisense Oligonucleotide	APOL1 mRNA silencing (reduces APOL1 expression)	Preclinical/early clinical	Aghajan et al., JCI Insight 2019
Baricitinib (JAK inhibitor)	Blocks cytokine-induced JAK-STAT signaling and APOL1 upregulation	Experimental/repurposing	Nystrom et al., JCI Insight 2022
STING pathway inhibitors	Attenuate interferon-stimulated APOL1 expression and inflammatory signaling	Preclinical	Wu et al., Immunity 2021
NLRP3 inflammasome blockers	Inhibit inflammasome activation/pyroptosis downstream of APOL1	Preclinical	Wu et al., J Clin Invest 2021

Table 1. Drugs under investigation for APOL1-mediated kidney disease.

Transplant implications

In the context of kidney transplantation, donor APOL1 genotype has emerged as a more consistent predictor of allograft outcomes than recipient genotype, particularly with respect to long-term graft survival. Several cohorts have shown that kidneys procured from deceased African American donors who carry two APOL1 renal-risk alleles display a significantly shorter allograft survival, even after adjusting for donor age, cold ischemia time, and HLA matching [19]. In contrast, the recipient's APOL1 risk status has not reliably correlated with five-year graft loss in most studies, suggesting that the intrinsic "health" of the graft – shaped by donor APOL1 expression – is the critical determinant. Case reports further support the donor-risk paradigm: Chang et al. described instances of de novo collapsing focal segmental glomerulosclerosis (FSGS) occurring in recipients of kidneys from donors later found to harbor two high-risk APOL1 alleles. In several of those cases, viral infections (e.g. CMV or BK viremia) served as plausible "second hits", triggering glomerular injury in a graft already genetically predisposed. These findings reinforce a "two-hit" model of APOL1 injury, wherein a high-risk donor background requires additional stressors to precipitate overt graft disease [20]. Because of this evidence, transplant programs increasingly consider APOL1 genotyping in donor evaluation, especially among donors of African ancestry. Some guidelines recommend counseling recipients about the increased graft risk when the donor carries a high-risk genotype [21]. However, the use of APOL1 genotyping in recipient decision-making remains controversial: the presence of the risk alleles in recipients has not consistently translated into worse short- or intermediate-term allograft survival across studies. Going forward, large-scale prospective studies (such as the APOLLO (APOL1 Long-term Kidney Transplantation Outcomes) study) are poised to clarify the magnitude of risk conferred by donor APOL1 status and to refine allocation strategies that balance graft utility with equity [22]. Meanwhile, the evidence supports that donor high-risk APOL1 genotype should be considered a relevant risk factor in transplant planning, while recipient genotyping must be interpreted with caution and in the context of broader immunologic, hemodynamic, and environmental influences.

Discussion

Testing for APOL1 genetic variants is recommended in selected clinical scenarios where the results may clarify diagnosis, prognosis, or influence management decisions. The strongest indications include unexplained non-diabetic proteinuric chronic kidney disease (CKD), particularly in patients of African ancestry with focal segmental glomerulosclerosis (FSGS) or glomerulosclerosis on biopsy without another clear etiology; HIV-associated nephropathy (HIVAN) or other forms of collapsing glomerulopathy, in which APOL1 high-risk genotypes markedly increase disease susceptibility and accelerate progression; early-onset CKD or a family history of ESRD in individuals of African or Afro-Caribbean descent, where APOL1 testing can assist in genetic counseling and risk stratification; and evaluation of living kidney donors of African ancestry, as donor – but not recipient – APOL1 genotype has been linked to long-term allograft survival. Routine population screening is not currently recommended, as the majority of individuals carrying two risk alleles do not develop kidney disease, highlighting the influence of "second-hit" factors such as viral infections, interferon exposure, or inflammatory stressors. Nonetheless, APOL1 testing is increasingly integrated into precision nephrology programs, helping clinicians tailor surveillance, manage secondary risk factors, and inform transplant counseling [23]. Interpretation of APOL1 genotyping requires a nuanced understanding of its probabilistic – not deterministic – nature. The presence of a high-risk genotype, defined by two risk alleles (G1/G1, G2/G2, or G1/G2), substantially increases the probability and rate of CKD progression, particularly in non-diabetic etiologies such as focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, and HIV-associated nephropathy.

However, penetrance is incomplete: only a fraction (≈15-20%) of high-risk individuals develop clinically evident kidney disease, underscoring the importance of environmental and inflammatory "second hits" – for instance, viral infections, interferon exposure, or ischemic injury – that interact with the genetic background to precipitate renal damage. APOL1 results must always be interpreted in conjunction with histopathologic findings, clinical phenotype, and comorbid conditions. A biopsy can delineate specific glomerular lesions (e.g., collapsing FSGS, microvascular changes) that support APOL1-mediated pathology, while clinical context – such as hypertension, diabetes, or viral infection – helps differentiate genetic susceptibility from acquired injury. In transplant settings, donor high-risk status predicts reduced allograft survival, whereas recipient genotype alone does not consistently correlate with five-year graft outcomes. APOL1 genotyping refines risk stratification rather than providing a binary diagnosis. Its optimal use lies in integrated interpretation, combining genetic, histologic, and clinical dimensions to inform prognosis, surveillance intensity, and therapeutic decision-making – especially within precision nephrology and transplant counseling frameworks [24]. Genetic counseling for individuals tested for APOL1 risk variants should emphasize that the high-risk genotype confers susceptibility but not certainty of disease. Incomplete penetrance must be clearly explained to avoid undue anxiety or stigma. Counseling should also address ethical and psychosocial implications, including potential effects on insurability, employability, and family planning, which vary across jurisdictions and regulatory frameworks. Importantly, patients should be encouraged to focus on modifiable risk factors that can mitigate disease expression, such as optimal blood pressure control, renin-angiotensin-aldosterone system (RAAS) inhibition, and dietary sodium and protein moderation. Incorporating APOL1 education into broader CKD prevention programs can foster informed decision-making while minimizing genetic discrimination and promoting equitable access to testing and follow-up care [25].

In addition, we have reviewed the most recent literature on genetic testing in CKD and glomerular disease [26]. On this basis, we now propose a set of clear indications for practicing nephrologists facing isolated patients affected by CKD or specific nephropathies, which we have summarized in Box 1. This recommendation is based on the following factors, Prognosis / risk stratification**,** In Elliott et al. 2024 [26], both monogenic diagnoses (6.5% of patients) and high-risk APOL1 genotypes (5.5%) independently predicted faster eGFR decline and higher kidney failure risk [26]. Actionability, NKF 2024 consensus says nephrologists should actively integrate genetic testing into routine evaluation of suspected hereditary nephropathies, into donor assessment, and into longitudinal care planning, and provide algorithms for symptomatic and at-risk individuals [27]. Clinical utility in real-world CKD: A large prospective CKD panel study (>1,600 adults; RenaCARE) showed that ~21% had a positive genetic finding; in ~49% of those, the genetic result *replaced or reclassified* the working diagnosis, and physicians reported it changed management in >90% [28].

BOX 1. When should a clinical nephrologist order genetic testing?

1. CKD with unclear or atypical etiology (test broadly).

- Adults or children whose routine clinical, serologic and imaging work-up does not yield a clear cause ("CKD of unknown etiology").
- Includes patients with descriptive biopsy labels only (e.g. "FSGS", "interstitial nephritis", "nephrosclerosis") without an upstream driver.
- In the 5,727-patient cohort of Elliott et al. [26], a monogenic kidney disorder was found in 6.5% and a high-risk APOL1 genotype in 5.5%, and both were independently associated with higher kidney-failure risk (HR 1.72 and 1.67, respectively). Early genetic diagnosis therefore refines prognosis and therapy [29].

2. When a monogenic kidney phenotype is suspected.

2a. Stereotyped phenotypes with well-defined genes

- Persistent hematuria ± deafness/ocular signs → suspect COL4A3–COL4A5 (Alport spectrum).
- Steroid-resistant, collapsing or recurrent FSGS (child or young adult).
- Cystic kidney disease not fully compatible with "typical" late-onset ADPKD.
- CAKUT, especially bilateral or syndromic in pediatrics [27].

2b. Early-onset disease

- CKD/proteinuria/hematuria/HTA before 30-40 yrs without another explanation, higher monogenic yield across all 3 JCI 2024 cohorts and in 2025 frameworks [29].

2c. Kidney-plus presentations

- Kidney disease plus neurosensory, skeletal, endocrine, metabolic, neurologic, ocular or developmental features, think single-gene or ciliopathy [30].

3. Positive family history.

- ≥1 first or second degree relative with CKD, ESKD or transplant [29].

4. APOL1 testing in ancestry or phenotype appropriate patients.

- West African, Afro-Caribbean, African-American, Afro-Latin ancestry and collapsing FSGS or FSGS-like lesions, disproportionately aggressive "hypertensive" CKD or rapid eGFR loss.
- In living donor evaluation in these ancestries, as recommended by the NKF working group (2024) and reiterated in 2025 updates and the KDIGO APOL1 conference report [27].

5. Before accepting a related living kidney donor when hereditary disease is suspected.

- Donors biologically related to a recipient with proven or suspected COL4A, UMOD, PKD, or APOL1 mediated kidney disease should do targeted testing (familial variant or APOL1). This is now part of responsible donor evaluation in NKF 2024/2025 and in recent donor-genetics reviews [31].

6. When the molecular result changes management.

- To start a gene- or pathway-directed therapy (complement, CoQ10, RNAi, upcoming APOL1 drugs).
- To stop futile immunosuppression in monogenic podocytopathies
- To anticipate recurrence post-transplant and to organize cascade testing in the family [29].

7. Pediatric CKD

- In children 30-50% of CKD can be genetic (CAKUT, podocyte, ciliopathy, metabolic), so a broad exome is recommended [32].

Note: The most recent evidence (KDIGO 2024 on CKD evaluation, the NKF 2024/2025 report on genetics in nephrology, and 2025 studies combining exome sequencing with polygenic risk scores, PRS) shows that even in "unselected" CKD cohorts clinically actionable genetic findings are identified in ≈20% of patients. Together with the ongoing reduction in sequencing costs and the emergence of targeted mechanism based therapies (APOL1 inhibitors, complement directed drugs, CoQ10 pathway defects, etc), this strongly suggests that the threshold for ordering genetic studies will decrease in the near future.

Conclusion

The increased susceptibility to end-stage renal disease (ESRD) in individuals of African ancestry is influenced by variations in the APOL1 gene. While the precise molecular pathways leading to renal damage are still being investigated, current theories suggest that these variants may exert their effects through mechanisms such as altered cellular ion transport, mitochondrial dysfunction, and the requirement for additional stressors or “second hits”. The ongoing investigation into these complex mechanisms is crucial, as it directly informs the development of targeted therapies. Promising interventions, including agents that directly modulate APOL1 protein activity or inhibit downstream inflammatory cascades, offer the potential to mitigate disease progression and address the significant health disparities observed in APOL1-associated kidney disease. APOL1 genotyping represents a pivotal step toward precision nephrology, linking genetic risk with targeted prevention and emerging therapies. While a high-risk genotype increases susceptibility to kidney injury, its expression depends on environmental and clinical modifiers, underscoring the need for integrated interpretation and personalized management. Ongoing translational research and clinical trials promise to transform APOL1 from a genetic marker of risk into a therapeutic target, bridging discovery and clinical care for populations most affected by kidney disease.

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