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Clinical significance of APOL1-mediated renal disease

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Abstract

APOL1-associated renal disease, also known as APOL1 renal risk variants or APOL1 nephropathy, represents a genetic kidney disorder associated with certain variants of the APOL1 gene. The APOL1 gene encodes a protein that plays a crucial role in the immune system's response to trypanosome infection, the cause of African sleeping sickness. However, two distinct genetic variants of the APOL1 gene, known as G1 and G2, have been conclusively associated with an elevated risk of renal disease in individuals of African descent. Recent research has demonstrated that carrying two copies of either the G1 or G2 variant significantly increases the risk of progressive kidney diseases, such as focal segmental glomerulosclerosis (FSGS) and hypertensive kidney disease. APOL1-associated kidney disease typically presents with features of chronic kidney disease, including proteinuria, hematuria, hypertension, and declining kidney function. Furthermore, hypertension and diabetes serve as additional risk factors for kidney disease, and individuals with both conditions and APOL1 gene variants may further elevate their risk of developing renal disorders. Obesity and smoking also contribute to the risk of kidney disease, particularly in cases with APOL1 gene variants. Moreover, various medical conditions, including lupus, HIV, and sickle cell disease, can exacerbate the likelihood of kidney disease in individuals with APOL1 gene variants. These conditions could lead to end-stage renal disease (ESRD) necessitating treatments such as dialysis or kidney transplantation.

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Introduction

Apolipoprotein L1 (APOL1) associated nephropathy or APOL1-associated renal disease refers to a genetic disorder that predominantly affects the kidneys of African Americans with high blood pressure or diabetes (1). It leads to chronic kidney failure in a subset of individuals who carry specific mutations in the APOL1 gene, which have been related to an increased risk for this condition (1,2). This hereditary form of kidney disease is more prevalent among people of West African descent and accounts for up to 2% of all cases of end-stage renal disease (ESRD) in the United States. The mechanism through which these mutations cause damage to the kidneys involves a cascade of inflammation and oxidative stress, leading to progressive deterioration of kidney function over time (2). In this comprehensive review, we sought to study the most recent findings on APOL1-associated renal disease and its impact on clinical investigations and patient management.

Key point

The presence of APOL1 risk variants increases the risk of developing kidney disease. APOL1 genetic variants show a higher prevalence among individuals of recent African descent. Carriers of these variants have an augmented predisposition to develop kidney diseases, including focal segmental glomerulosclerosis and chronic kidney disease. The risk factors for developing APOL1-associated kidney disease include having two copies of the APOL1 gene variant, African ancestry, family history of kidney disease, and other medical conditions such as hypertension and diabetes. Environmental factors such as exposure to toxins and infections may further elevate the risk.

Search strategy

For this review, we conducted searches on various academic databases, including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, We used a range of keywords to ensure comprehensive coverage, such as focal segmental glomerulosclerosis, chronic kidney disease, HIV-associated nephropathy, APOL1-associated kidney disease, African ancestry,

kidney disease, hypertension, end-stage renal disease and apolipoprotein L1 (APOL1) associated nephropathy.

APOL1-associated kidney disease

APOL1 represents a rather unique disease gene. APOL1-associated kidney disease defies typical disease-causing gene patterns, featuring common variants with large effect size, both recessive and gain-of-function, a broad spectrum of related phenotypes, unique genetic testing issues, and lack of a clearly defined role for APOL1 in normal renal physiology (3,4). APOL1 variants have been implicated in renal disease, particularly in populations of recent African descent. These variants are linked to a spectrum of chronic renal diseases, from renal arteriosclerosis to severe forms of focal segmental glomerulosclerosis (FSGS) (5,6). Prior research has shed light on several mechanisms responsible for APOL1-mediated cell toxicity, including lysosomal dysfunction and stimulation of cellular pathways. The initial sign of APOL1-mediated kidney injury often manifests as proteinuria resulting from podocyte damage (7,8). Additionally, APOL1-associated renal disease (APOL1-associated nephropathy) is among the most common contributors to chronic renal failure globally. It is not limited to specific regions and affects individuals of African ancestry globally (6,9). Despite significant advancement in comprehending APOL1-associated kidney disease, there is a pressing need for additional case-control and longitudinal studies, particularly Within the African diaspora and sub-Saharan Africa, to further explore the associations and mechanisms underlying this complex condition. Recent studies found that in cases with high-risk APOL1 genotypes, the lifetime risk of developing kidney failure is approximately 15% (10,11). To assess the prevalence and distribution of Mendelian renal diseases in individuals with these high-risk genotypes undergoing commercial genetic examination in the United States, da Silva Francisco et al analyzed clinical exome sequencing data from 15,181 individuals. Their study revealed that about 10% of individuals with high-risk APOL1 genotypes exhibited evidence of Mendelian renal disease (12).

Common APOL1 variants associated with kidney disease

The most common APOL1 variants associated with kidney disease are G1 and G2, which are exclusively found on African-derived chromosomes and absent on Asian or European chromosomes. The G1 and G2 variations developed separately in distinct episodes on two different haplotypes of chromosome 22 and have not undergone recombination events; consequently, G1 and G2 are not noted on the same haplotype (6,13). APOL1 kidney risk alleles have a profound impact on the spectrum of renal diseases in individuals of recent African descent throughout their life course. These variants significantly increase rates of hypertension-associated end-stage kidney failure, HIV-associated nephropathy, FSGS and other forms of non-diabetic renal disease. Having both risk variants result in an odds ratio of approximately 7–10 for hypertension-related end-stage kidney failure, around17 for FSGS and roughly 29–89 for HIV-associated nephropathy (6,14).

Mechanism of action of APOL1 variants in renal disease

The dominant perspective for variant APOL1-induced kidney injury proposes a gain-of-function mechanism whereby APOL1 risk variants form active ion channels, causing cytotoxicity and damage to kidney cells (3,15). Recent studies suggest that APOL1 risk variants may stimulate cytotoxicity and damage to kidney cells by depleting cellular potassium and inducing stress-activated protein kinases. Additionally, these variants exacerbate podocyte injury by intensifying inflammatory stress. Their presence in renal vascular cells and podocytes contributes further to renal disorders (16,17).

Difference between APOL1 G0 and G1/G2 variants regarding kidney injury

The difference between APOL1 G0 and G1/G2 variants in terms of kidney injury is as follows:

APOL1 G0 variant

The G0 variant is the reference variant and is considered non-risk. Individuals with the G0 variant have a lower risk of developing kidney disease compared to those with G1 or G2 variants. The G0 variant is not associated with an increased risk of idiopathic FSGS or other forms of kidney disease (5,18).

APOL1 G1/G2 variants

The G1 and G2 variants are considered renal-risk variants, associated with an increased risk of non-diabetic kidney diseases, such as FSGS and HIV-associated nephropathy (HIVAN). These variants have higher odds ratios for HIVAN and FSGS compared to the G0 variant. Notably, G1 and G2 variants are exclusive to African-derived chromosomes and are absent in Asian or European chromosomes (19,20). The G1 and G2 variations developed separately on distinct haplotypes of chromosome 22 without recombination, meaning they are not found on the same haplotype (6,13). APOL1 kidney risk variants are most strongly linked to HIV-associated nephropathy and FSGS, with odds ratios of 17 and 29, respectively. However, it's important to note that additional factors, such as sickle cell anemia, viral infections, autoimmune disorders, or glomerular hyperfiltration, are often required as "second hits" for kidney disease to manifest. Recently it was detected that the upregulation of APOL1 by various interferons can serve as a potent second hit. While FSGS and HIV-associated kidney disease are the most commonly associated diseases with APOL1 G1 and G2 variants, it is worth mentioning that APOL1 variants have also been linked to an increased risk of other forms

of nondiabetic chronic kidney disease. Nevertheless, FSGS and HIV-associated nephropathy remain the primary diseases associated with these variants (7,21).

Ongoing clinical trials for APOL1-associated kidney disease

Small molecule inhibitors and antisense oligonucleotides that target APOL1 (APOL1 inhibitors) are under study as potential therapies for APOL1-associated kidney disease (22).

Vertex Pharmaceuticals is conducting a phase II study of an oral small molecule inhibitor of APOL1 activity, VX-147, in cases of APOL1-associated FSGS (23).

Maze Therapeutics is developing an APOL1 inhibitor program for the treatment of chronic kidney disease (24,25). A phase IIa clinical trial of inaxaplin, an APOL1 inhibitor, has shown promising results in reducing proteinuria in cases with APOL1-mediated FSGS (26). This study showed that inaxaplin significantly reduced proteinuria, demonstrating a mean reduction of 47.6% from baseline at week 13. This finding suggests that inhibiting APOL1 may help mitigate kidney damage associated with these variants (26).

Individuals with APOL1-associated kidney disease have the opportunity to participate in a clinical trial for potential cures conducted by Duke Clinical Research Study (27,28).

These ongoing clinical trials aim to assess the effectiveness, safety, and pharmacokinetics of potential therapies for APOL1-associated kidney disease.

Clinical implications in pediatrics

Children with high-risk APOL1 genotypes often present with kidney disease at an older age compared to those with non-APOL1 causes. However, the disease tends to progress more aggressively, leading to lower estimated glomerular filtration rates (eGFR) at diagnosis and rapid annual declines in kidney function (29,30). This disease is particularly prevalent among children with conditions such as sickle cell disease, since increased rates of albuminuria and lower eGFR have been observed in this group. Meanwhile, children with HIV and APOL1 high-risk genotypes show significantly elevated risks for proteinuric kidney disease (1,30,31). Diagnosis of APOL1-mediated kidney disease is typically established when a child with a high-risk genotype develops nondiabetic kidney disease. Genetic testing can confirm the presence of APOL1 variants, which is essential for understanding individual risk profiles (32,33).

Treatment options for APOL1-associated nephropathy

Currently, there are no approved treatments designed to directly target the underlying cause of APOL1-associated kidney disease. However, ongoing research efforts and potential treatment options are under investigation. APOL1 inhibitors are small molecule inhibitors, and antisense oligonucleotides that target APOL1 are being investigated as potential therapies for APOL1-associated kidney disease. These inhibitors aim to reduce the expression or activity of APOL1, potentially mitigating the cytotoxicity and damage caused by APOL1 risk variants (22,34). In some cases, high-dose steroids may be used for a short period to manage symptoms and reduce inflammation in APOL1-associated kidney disease (1,8,30). These treatment options are still in the early stages of development and clinical trials and further research is needed to determine their efficacy, safety, and long-term effects. Meanwhile, innovative therapies targeting APOL1 mRNA and small molecules that inhibit its function are undergoing clinical trials. These approaches aim to reduce APOL1-related kidney injury and hold promise for patients at high genetic risk (35). Other risk factors such as hypertension, diabetes, and viral infections is also vital for the overall management of APOL1-associated renal disorders (8).

Conclusion

APOL1-associated nephropathy is a significant health challenge that requires ongoing research endeavors to enhance its diagnosis, management, and outcomes. While there are currently no known treatment specific to APOL1- related renal disease, emerging therapeutics like APOL1 inhibitors and antisense oligonucleotides provide hope for the future.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the author thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Friedman DJ, Pollak MR. APOL1 Nephropathy: From Genetics to Clinical Applications. Clin J Am Soc Nephrol. 2021;16:294-

303. doi: 10.2215/CJN.15161219.
2. Friedman DJ, Pollak MR. Apolipoprotein L1 and Kidney Disease in African Americans. Trends Endocrinol Metab. 2016;27:204-215. doi: 10.1016/j.tem.2016.02.002.
3. Pollak MR, Friedman DJ. APOL1 and APOL1-Associated Kidney Disease: A Common Disease, an Unusual Disease Gene - Proceedings of the Henry Shavelle Professorship. Glomerular Dis. 2023;3:75-87. doi: 10.1159/000529227.
4. Giudicelli GC, De Souza CMB, Veronese FV, Pereira LV, Hünemeier T, Vianna FSL. Precision medicine implementation challenges for *APOL1* testing in chronic kidney disease in admixed populations. Front Genet. 2022;13:1016341. doi: 10.3389/fgene.2022.1016341.
5. Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol. 2011;22:2129-37. doi: 10.1681/ASN.2011040388.
6. Yusuf AA, Govender MA, Brandenburg JT, Winkler CA. Kidney disease and APOL1. Hum Mol Genet. 2021 Apr 26;30:R129-R137. doi: 10.1093/hmg/ddab024.
7. Daneshpajouhnejad P, Kopp JB, Winkler CA, Rosenberg AZ. The evolving story of apolipoprotein L1 nephropathy: the end of the beginning. Nat Rev Nephrol. 2022;18:307-320. doi: 10.1038/s41581-022-00538-3.
8. Ma L, Divers J, Freedman BI. Mechanisms of Injury in APOL1-associated Kidney Disease. Transplantation. 2019;103:487-492. doi: 10.1097/TP.0000000000002509.
9. Freedman BI, Limou S, Ma L, Kopp JB. APOL1-Associated Nephropathy: A Key Contributor to Racial Disparities in CKD. Am J Kidney Dis. 2018;72:S8-S16. doi: 10.1053/j.ajkd.2018.06.020.
10. Foster MC, Coresh J, Fornage M, Astor BC, Grams M, Franceschini N, et al. APOL1 variants associate with increased risk of CKD among African Americans. J Am Soc Nephrol. 2013;24:1484-91. doi: 10.1681/ASN.2013010113.
11. Elliott MD, Marasa M, Cocchi E, Vena N, Zhang JY, Khan A, et al. Clinical and Genetic Characteristics of CKD Patients with High-Risk APOL1 Genotypes. J Am Soc Nephrol. 2023;34:909-919. doi: 10.1681/ASN.0000000000000094.
12. da Silva Francisco R Jr, Punj S, Vincent L, Sanapareddy N, Bhalla V, Chertow GM, et al. Prevalence of Mendelian Kidney Disease Among Patients With High-Risk *APOL1* Genotypes Undergoing Commercial Genetic Testing in the United States. Kidney Int Rep. 2024 Jun 22;9:2667-2676. doi: 10.1016/j.ekir.2024.06.028.
13. Limou S, Nelson GW, Kopp JB, Winkler CA. APOL1 kidney risk alleles: population genetics and disease associations. Adv Chronic Kidney Dis. 2014;21:426-33. doi: 10.1053/j.ackd.2014.06.005.
14. Dummer PD, Limou S, Rosenberg AZ, Heymann J, Nelson G, Winkler CA, et al. APOL1 Kidney Disease Risk Variants: An Evolving Landscape. Semin Nephrol. 2015;35:222-36. doi: 10.1016/j.semnephrol.2015.04.008.
15. Bruggeman LA, Sedor JR, O'Toole JF. Apolipoprotein L1 and mechanisms of kidney disease susceptibility. Curr Opin Nephrol Hypertens. 2021;30:317-323. doi: 10.1097/MNH.0000000000000704.
16. Olabisi OA, Zhang JY, VerPlank L, Zahler N, DiBartolo S 3rd, Heneghan JF, et al. APOL1 kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases. Proc Natl Acad Sci U S A. 2016;113:830-7. doi: 10.1073/pnas.1522913113.
17. Giovinazzo JA, Thomson RP, Khalizova N, Zager PJ, Malani N, Rodriguez-Boulan E, et al. Apolipoprotein L-1 renal risk variants form active channels at the plasma membrane driving cytotoxicity. Elife. 2020;9:e51185. doi: 10.7554/eLife.51185.
18. Datta S, Kataria R, Zhang JY, Moore S, Petitpas K, Mohamed A, et al. Kidney Disease-Associated *APOL1* Variants Have Dose-Dependent, Dominant Toxic Gain-of-Function. J Am Soc Nephrol. 2020;31:2083-2096. doi: 10.1681/ASN.2020010079.
19. Papeta N, Kiryluk K, Patel A, Sterken R, Kacak N, Snyder HJ, et al. APOL1 variants increase risk for FSGS and HIVAN but not IgA nephropathy. J Am Soc Nephrol. 2011;22:1991-6. doi: 10.1681/ASN.2011040434.
20. Kasembeli AN, Duarte R, Ramsay M, Mosiane P, Dickens C, Dix-Peek T, et al. APOL1 Risk Variants Are Strongly Associated with HIV-Associated Nephropathy in Black South Africans. J Am Soc Nephrol. 2015;26:2882-90. doi: 10.1681/ASN.2014050469.
21. Siemens TA, Riella MC, Moraes TP, Riella CV. APOL1 risk variants and kidney disease: what we know so far. J Bras Nefrol. 2018;40:388-402. doi: 10.1590/2175-8239-JBN-2017-0033.
22. Friedman DJ, Ma L, Freedman BI. Treatment potential in APOL1-associated nephropathy. Curr Opin Nephrol Hypertens. 2022;31:442-448. doi: 10.1097/MNH.0000000000000816.
23. Phase 2/3 Adaptive Study of VX-147 in Adult and Pediatric Participa nts With APOL1- Mediated Proteinuric Kidney Disease (AMPLITUDE). https://classic.clinicaltrials.gov/ct2/show/NCT05312879
24. Freedman BI, Kopp JB, Sampson MG, Susztak K. APOL1 at 10 years: progress and next steps. Kidney Int. 2021;99:1296-1302. doi: 10.1016/j.kint.2021.03.013.
25. Maze Therapeutics discloses new APOL1 inhibitors. Sep. 14, 2022. https://www.bioworld.com/articles/689644-maze-therapeutics-discloses-new-apol1-inhibitors?v=preview.
26. Egbuna O, Zimmerman B, Manos G, Fortier A, Chirieac MC, Dakin LA, et al; VX19-147-101 Study Group. Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants. N Engl J Med. 2023;388:969-979. doi: 10.1056/NEJMoa2202396.
27. Duke APOL1 Research Biorepository (DARB). https://classic.clinicaltrials.gov/ct2/show/NCT04160507.
28. Nephrology Clinical Trials and Other Human Subject Research Seeking Enrollment at Duke. https://medicine.duke.edu/divisions/nephrology/research/clinical-trials.
29. Ekulu PM, Nkoy AB, Adebayo OC, Kazadi OK, Aloni MN, Arcolino FO, et al. A focus on the association of Apol1 with kidney disease in children. Pediatr Nephrol. 2021;36:777-788. doi: 10.1007/s00467-020-04553-z.
30. Hilliard CB. APOL1 Variant and Kidney Disease. JAMA. 2024;332:1020. doi: 10.1001/jama.2024.14358.
31. Reidy KJ, Hjorten R, Parekh RS. Genetic risk of APOL1 and kidney disease in children and young adults of African ancestry. Curr Opin Pediatr. 2018;30:252-259. doi: 10.1097/MOP.0000000000000603.
32. Hopper T, Olabisi OA. APOL1-Mediated Kidney Disease. JAMA. 2024;331:1668-1669. doi: 10.1001/jama.2024.2667.
33. Kopp JB, Winkler CA. Genetic Testing for *APOL1* Genetic Variants in Clinical Practice: Finally Starting to Arrive. Clin J Am Soc Nephrol. 2020;15:126-128. doi: 10.2215/CJN.01810219.
34. Yang YW, Poudel B, Frederick J, Dhillon P, Shrestha R, Ma Z, et al. Antisense oligonucleotides ameliorate kidney dysfunction in podocyte-specific APOL1 risk variant mice. Mol Ther. 2022;30:2491-2504. doi: 10.1016/j.ymthe.2022.04.007.
35. Tabachnikov O, Skorecki K, Kruzel-Davila E. APOL1 nephropathy - a population genetics success story. Curr Opin Nephrol Hypertens. 2024;33:447-455. doi: 10.1097/MNH.0000000000000977.