

Framework for Apolipoprotein 1-Mediated Kidney Disease Classification



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Introduction

Black Americans have an increased risk of chronic kidney disease (CKD) compared with individuals without African ancestry. Variants designated G1 and G2 in the apolipoprotein L1 protein encoded by the *APOLI* gene are a major contributor to this increased risk.¹ These variants arose independently, rarely occur together on the same chromosome, and exist almost exclusively in individuals with recent African ancestry. The percentage of individuals with 1 risk variant is 33% to 37% (G1/G0 or G2/G0), whereas 13% to 15% individuals possess 2 variants (high-risk genotype- G1/G1, G2/G2, or G1/G2). This equates to 5.6 million Black Americans having 2 *APOLI* risk variants (based on the 2024 United States census data). The high variant frequency reflects positive selection for protection against the endemic *Trypanosoma brucei rhodesiense* infection, a parasite causing African sleeping sickness. Although these variants protect

against infection, they come with the risk of *APOLI*-mediated kidney disease (AMKD); 15% to 20% of individuals with high-risk genotype develop CKD and 40% to 60% of Black patients with focal segmental glomerulosclerosis carry 2 risk variants. High-risk genotype is also associated with more rapid failure of kidney transplants and elevated risk in Black American living kidney donors. The evolving understanding of genetic risk for AMKD impacts clinical diagnostic genetic reporting, patient counseling, research, and clinical trial design. We propose an updated classification scheme for reporting genetic test results for *APOLI* that incorporates current knowledge.

Evolution of Our Understanding

In the initial autosomal recessive model of AMKD, patients with 2 *APOLI* risk variants had a high-risk of kidney disease whereas the risk of 0 or 1 variant was not significantly elevated. Patients with high-risk genotypes showed incomplete penetrance with approximately 15% of patients developing kidney disease during their lifetime. The recent finding

that the *APOLI* p.N264K (M1) variant is protective against G2,^{2,3} and that individuals with a monoallelic variant in *APOLI* have intermediate-risk for AMKD,⁴ adds nuance regarding genetic risk.

M1 Variant

The *APOLI* modifier variant M1 located in the membrane-addressing domain is protective against the G2 when present on the same chromosome copy (*cis*).² This variant was co-inherited through a proximity recombination event between a G0-M1 non-risk haplotype and a G2 risk haplotype.⁵ It is seen in 3.2% to 6% of individuals with a high-risk genotype containing at least 1 G2 (overall prevalence of 0.4%).^{3,6-8} This combination is designated G2-M1. M1 is protective against the cytotoxicity and risk variant-mediated disease of G2. This highlights the necessity of viewing *APOLI* risk variants in their genetic context (haplotype).³ M1 has not been detected in *cis* with G1 (mutually exclusive). When present in *cis* with G0 it did not show protective effect for G2 on the opposite chromosome copy (*trans*). There is no protective effect for M1 in the absence of G2.² Testing for M1 is warranted in patients with high-risk genotypes that contain at least 1 G2, as G1/G2-M1 and G2/G2-M1 genotypes have lower AMKD risk, and G2-M1/G2-M1 has even lower risk.^{2,8} Testing of patients with monoallelic G2 (G2/G0 genotype) will require phasing to demonstrate whether the M1 variant is in *cis* with G2 versus G0 (Supplementary Text S1). Although the presence of M1 will impact only 4% to 5% of patients with G2 containing high-risk genotype, there is a large impact at a population level. Based

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on a population prevalence of 13% for Black Americans carrying 2 *APOL1* risk variants, this could account for the reclassification of between 103,000 to 137,000 patients from high-risk to nonhigh risk genotype based on M1 testing if all Black Americans have a known *APOL1* risk status.^{3,6-8}

Monoallelic Risk Variants and Other Risk Modifiers

A recent study of *APOL1* risk variants in individuals with CKD from Ghana and Nigeria showed a dose-relationship with the number of variants present. Monoallelic variants demonstrated intermediate risk of CKD and focal segmental glomerulosclerosis (18% and 61% higher odds) and increased likelihood of CKD progression compared with zero variants. Participants with 2 risk alleles showed higher risk of CKD and focal segmental glomerulosclerosis (25% and 84% respectively) compared with a single variant.⁴ This study did not include testing for M1, and as study participants were limited to 2 regions of West Africa (Ghana and Nigeria) the results may not be generalizable to other African and nonAfrican regions because of differences in risk variant allele frequencies, interacting genetic elements, and environmental triggers. However, there is emerging evidence that African Americans with single *APOL1* risk variants also have increased risk of kidney disease and that G1 and G2 effect size may not be equivalent (Supplementary Text S2 and S3). African Americans with diabetes and *APOL1* high-risk genotype show more rapid decline in kidney function and disease progression; however, the impact of monoallelic risk variants in the setting of diabetes and transplantation requires additional investigation (Supplementary Text S4 and S5).

Other AMKD disease risk modifiers have been reported, and in the context of the “omnigenic model of disease” it is likely that other positive and negative risk modifiers will be identified. The omnigenic model would also encompass population-based genetic differences (e.g., ancestry specific background *APOL1* haplotypes) and could be extended to environmental effects (Supplementary Text S6 and S7).

A Proposed Classification Scheme with Implications for Practice and Policy

The classification scheme we propose arose from practical necessity to report results of clinically validated M1 genotyping as reflex testing for patients with G1/G2 or G2/G2 genotypes. From this perspective, the historic 2-tier risk classification does not adequately communicate current understanding regarding AMKD risk. We believe a 4-tiered risk classification scheme best reflects our current understanding. However, input from basic researchers, epidemiologists, nephrologists, patients, laboratory diagnosticians, and pharmaceutical scientists is needed to produce a consensus scheme to communicate *APOL1* genotyping results and AMKD risk.

Our proposed scheme retains the original high-risk category for 2 *APOL1* risk variants without the M1 protective variant. Individuals with G0/G0 genotype are classified as nonrisk; single G1 or single G2 without M1 as indeterminate-risk; and G2-M1/G0 or G2-M1/G2-M1 as low-risk. To communicate that the testing for the M1 was performed and that it was not detected, we propose the designation of “G2-M0”. The indeterminate-risk categorization communicates that individuals with a monoallelic risk variant (G1/G0, G2-M0/G0, or G2-M0/G2-M1) have a low-to-

intermediate risk of kidney disease compared with those with 0 variants, but less risk than individuals with 2 variants (G1/G1, G1/G2-M0 or G2-M0/G2-M0) and avoids giving false reassurance implied by the previous “low-risk” term. Individuals with an indeterminate-risk genotype would benefit from monitoring of kidney function. Although the risk of kidney disease in the low-risk group is likely very low, it is not conclusively known to be zero. We believe this 4-tiered classification scheme would more clearly communicate current knowledge regarding *APOL1* genotyping and AMKD risk (Figure 1 and Table 1) but will require periodic updates to incorporate new knowledge (Supplementary Text S8). Updated diagnostic criteria for AMKD will require further development and integration of genetic risk classification with clinical features. Such a scheme will have to consider regional and population effects on disease risk, and individual clinical context, such as diabetes and kidney transplantation.

Call to Action

Attention to AMKD offers hope for addressing the disproportionate burden of kidney disease in individuals with at-risk African ancestry. However, the complexity of determining which individuals with *APOL1* risk variants are truly at elevated risk requires focused effort to address critical research questions and diagnostic challenges.

Biomarkers

Biomarkers to enable a more definitive AMKD diagnosis are critical. Historically, a diagnosis of AMKD has been made in patients with nondiabetic CKD patients with a high-risk *APOL1* genotype. This is problematic given that

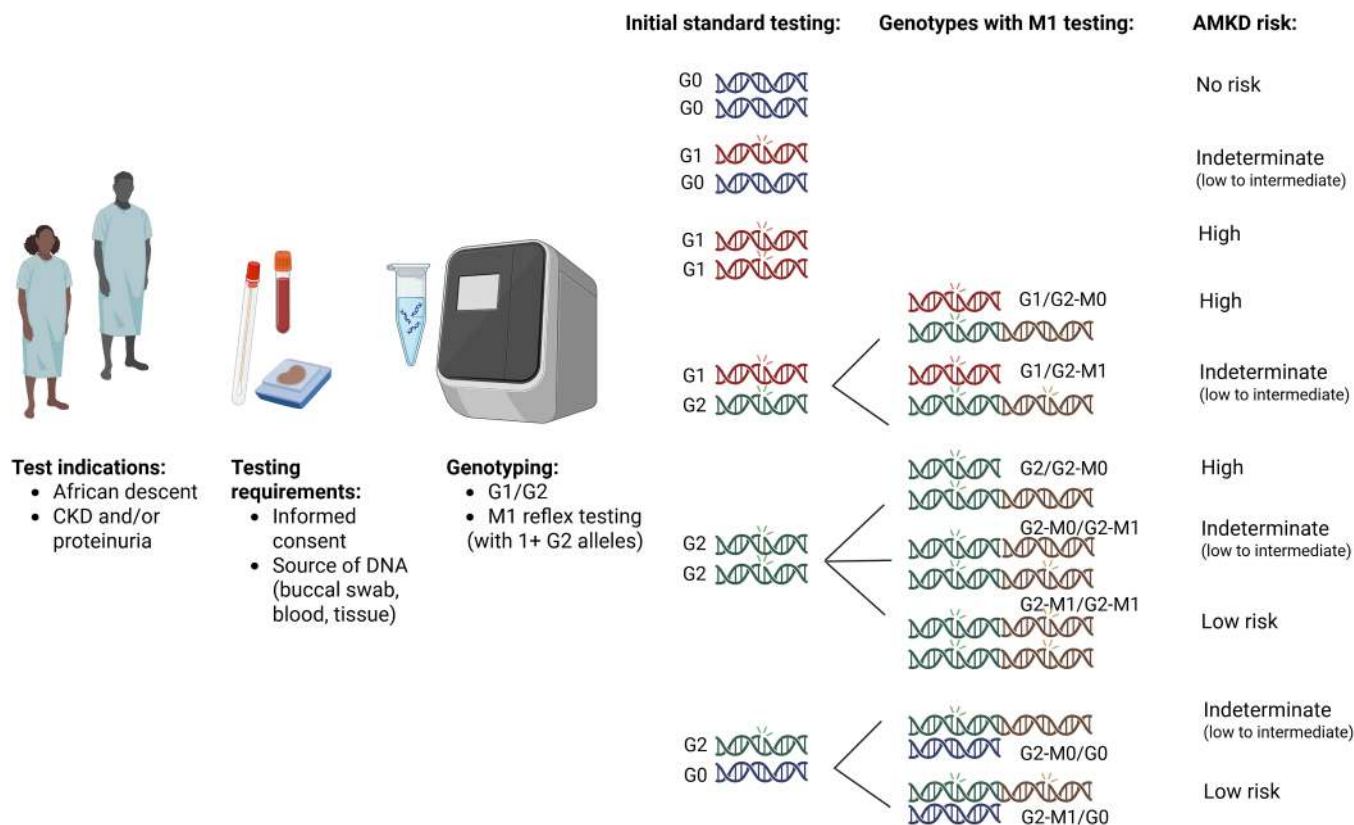


Figure 1. *APOL1* testing workflow. *APOL1* genetic testing is indicated for Black Americans with CKD and/or proteinuria. Patient consent is required, as well as a DNA sample (such as from buccal cells, blood, and frozen or formalin-fixed paraffin tissue). Genotyping is performed by polymerase chain reaction for G1 and G2 alleles. For cases with a G2 allele, M1 variant testing can be performed for improved assessment of genetic risk status. CKD, chronic kidney disease; AMKD, *APOL1*-mediated kidney disease.

most individuals with high-risk genotypes will not develop kidney disease (incomplete penetrance) and risk variants may accelerate disease progression in patients with pre-existing diabetic kidney disease. There is currently no definitive way to know if such patients truly have CKD resulting from AMKD. Although the

histopathologic spectrum on kidney biopsy includes focal segmental glomerulosclerosis or nephrosclerosis, these can also be attributed to other etiologies. These issues highlight the urgent need for blood, urine, and/or tissue biomarkers to determine which patients may benefit from *APOL1* targeted therapy.

into future trials. Large studies are needed to better understand AMKD risk in patients with low and indeterminate-risk genotypes when they have known potential secondary “triggers,” such as viral infections or autoimmune diseases. Improved risk stratification would also be useful in Black American prospective living kidney donors. Such information could inform clinical decisions regarding therapeutic interferon for conditions such as multiple sclerosis or viral hepatitis.

The emerging understanding of AMKD highlights the need for additional research. We propose a classification schema for communicating current understanding of *APOL1* risk genotypes. Such a scheme will evolve as our knowledge of AMKD progresses. In the era of precision medicine, a clear

Table 1. Summary of descriptive AMKD risk attributed to results of G1, G2, and M1 *APOL1* variant genotyping

Genotype	G1	G2	M1	Risk of AMKD
G0/G0	0	0	N/A	Non risk
G1/G0	1	0	N/A	Indeterminate risk
G2-M0/G0	0	1	0	Indeterminate risk
G2-M1/G0	0	1	1	Low risk
G1/G1	2	0	N/A	High risk
G1/G2-M0	1	1	0	High risk
G1/G2-M1	1	1	1	Indeterminate risk
G2-M0/G2-M0	0	2	0	High risk
G2-M0/G2-M1	0	2	1	Indeterminate risk
G2-M1/G2-M1	0	2	2	Low risk

AMKD, *APOL1*-mediated kidney disease.

Risk Stratification

APOL1 risk stratification will soon have treatment implications. Although no FDA-approved therapies currently exist, multiple active clinical trials for AMKD (clinicaltrials.gov identifiers NCT05312879, NCT06824987, NCT05237388), are currently enrolling patients with high-risk genotypes. The impact of G2-M1 haplotype and monoallelic *APOL1* variant risk also needs to be incorporated

and adaptive classification system for *APOL1* genotyping is essential.

DISCLOSURE

APOL1 genotyping at Arkana is supported by a sponsored testing program with Vertex Pharmaceuticals to offer *APOL1* genotyping of G1 and G2 risk alleles at no cost to patients. However, the authors have no direct conflicts of interest to disclose in relation to this work.

AUTHOR CONTRIBUTIONS

JDW had full access to the data in the study and final responsibility for the decision to submit for publication. JDW designed the work that led to submission, participated in drafting and revising the manuscript, and approved the final version. TNC designed the work that led to submission, participated in drafting and revising the manuscript, and approved the final version. RSH designed the work that led to submission, participated in drafting and revising the manuscript, and approved the final version. CPL conceived and designed the work that led to the submission, participated in drafting and revising the manuscript, and approved the final version.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Text S1. AMKD testing and diagnostic criteria considerations.

Text S2. Monoallelic G1 and G2: effect size and region/population variability.

Text S3. Animal and experimental models.

Text S4. AMKD in the setting of diabetes.

Text S5. Monoallelic variants in the kidney transplant setting.

Text S6. Other known AMKD risk modifiers.

Text S7. Omnigenic model.

Text S8. Example test reporting results.

REFERENCES

- Ojo AO, Adu D, Bramham K, et al. APOL1 kidney disease: conclusions from a Kidney Disease: improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2025;108:763–779. <https://doi.org/10.1016/j.kint.2025.05.017>
- Gupta Y, Friedman DJ, McNulty MT, et al. Strong protective effect of the APOL1 p.N264K variant against G2-associated focal segmental glomerulosclerosis and kidney disease. *Nat Commun.* 2023;14:7836. <https://doi.org/10.1038/s41467-023-43020-9>
- Hung AM, Assimon VA, Chen HC, et al. Genetic inhibition of APOL1 pore-forming function prevents APOL1-mediated kidney disease. *J Am Soc Nephrol.* 2023;34:1889–1899. <https://doi.org/10.1681/ASN.00000000000002194>
- Gbadegesin RA, Ulasi I, Ajayi S, et al. *APOL1* bi- and monoallelic variants and chronic kidney disease in West Africans. *N Engl J Med.* 2025;392:228–238. <https://doi.org/10.1056/NEJMoa24042115>
- Simeone CA, McNulty MT, Gupta Y, et al. The APOL1 p.N264K variant is co-inherited with the G2 kidney disease risk variant through a proximity recombination event. *G3 (Bethesda).* 2025;15:jkae290. <https://doi.org/10.1093/g3journal/jkae290>
- Narjuz C, Vinh-Hoang-Lan Julie Tran, Rabant M, Karras A, Pallet N. Diagnostic yield of *APOL1* p.N264K variant screening in daily practice. *Kidney Int Rep.* 2024;9:1916–1918. <https://doi.org/10.1016/j.ekir.2024.04.008>
- da Silva Francisco R Jr., Punj S, Vincent L, et al. Prevalence of the M1 modifier p.N264K in APOL1 among individuals with kidney disease undergoing commercial genetic testing in the United States. *Am J Kidney Dis.* 2025;86:715–718. <https://doi.org/10.1053/j.ajkd.2025.07.004>
- Gbadegesin R, Martinelli E, Gupta Y, et al. *APOL1* genotyping is incomplete without testing for the protective M1 modifier. *Glomerular Dis.* 2024;4:43–48. <https://doi.org/10.1159/000537948>