Global Science. Local Change.

KDIGO Controversies Conference on *APOL1* Kidney Disease

April 25 – 28, 2024
Accra, Ghana

Scope of Work

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of people with kidney disease worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences to review the state of the art on a focused subject pertaining to kidney disease and set priorities for improving patient care and outcomes. In addition to highlighting areas for which additional research is needed, sometimes the conferences lead to KDIGO guideline development efforts.

CONFERENCE BACKGROUND AND RELEVANCE

Variants in the *apolipoprotein L1* (*APOL1*) gene are strongly associated with a high risk of chronic kidney disease (CKD) in people of African ancestry.[1, 2] Two amino acid substitutions and two deletions in the *APOL1* gene produce the G1 and G2 variants, respectively, which confer resistance to infection with certain subspecies of the trypanosome parasite. Having two *APOL1* risk variants (G1G1, G2G2, or G1G2) is referred to as a high-risk genotype for development or progression of CKD. Although the presence of one renal risk variant is referred to as a low-risk genotype, some evidence indicates having one variant alone increases risk of CKD or progression rates compared with individuals with neither variant.[3]

Frequencies of the G1 and G2 alleles are highest in Western Africa, with G1 >40% and G2 6%-24% in Ghana and Nigeria.[4] Among African Americans, estimated allelic frequency is 20% to 22% for G1 and 13% to 15% for G2, with approximately 10% to 15% of African Americans carrying 2 *APOL1* risk alleles.[4] Estimates of population-attributable risks suggest that the presence of two *APOL1* kidney risk variants results in the 7- to 30-

fold increased risk of kidney disease in segments of African Americans compared with non-Hispanic white Americans.[5] More than 100 million sub-Saharan Africans may have a lifetime increased risk of CKD or accelerated progression due to having two *APOL1* risk alleles, making the burden of *APOL1* kidney disease in sub-Saharan Africa catastrophically high.

Among African Americans, approximately 25% with two *APOL1* risk alleles develop CKD, and 40-60% with primary focal and segmental glomerulosclerosis (FSGS) have two *APOL1* risk alleles.[6-8] Because having two *APOL1* risk alleles does not necessarily lead to development of CKD, the prevailing hypothesis is that an additional stressor or "second hit" is necessary for CKD to develop in most individuals with the high-risk genotype. Although observational studies and posthoc analyses of clinical trial data show very strong associations between high-risk genotype status and higher risks of specific kidney diseases or etiologically non-specific CKD, it is not possible to predict which individuals with a high-risk genotype will develop CKD, idiopathic FSGS, hypertension-attributed kidney disease, HIV-1–associated nephropathy (HIVAN), or kidney transplant rejection. Having two *APOL1* risk variants has not been linked to the development of diabetic kidney disease, but some evidence suggests that two *APOL1* risk alleles can contribute to its progression.[9]

The typical clinical phenotype traits of *APOL1* kidney disease include recent (<10,000 years) African ancestry, high urinary protein loss, interstitial fluid accumulation, and reduced kidney function on a background of non-diabetic glomerular disease. Understanding how *APOL1* variants mediate kidney disease is crucial for developing therapeutic targets, yet molecular mechanisms involved in the pathophysiology of kidney disease due to *APOL1* variants are not fully understood. It is unclear whether the initiation and progression of kidney injury depends on the risk variants themselves or is due to variant-independent overexpression. However, clinical and histopathologic evidence strongly suggests that podocyte injury is central to *APOL1* nephropathy. Animal models of *APOL1* kidney disease have been developed,[10, 11] and other mechanisms of injury associated with *APOL1* risk variants are being elucidated.

Since the original findings in 2010,[1, 2] the field of *APOL1* and kidney disease has advanced dramatically, with significant progress both in understanding genetic, environmental, immunomodulatory, proinflammatory, and apoptotic signaling processes and ion channel pathways as well as in exploring novel therapeutic pathways.

APOL1 small molecule inhibitors, antisense oligonucleotides, and agents involving the JAK/STAT pathway blockade are being evaluated in Phase 1 or 2 trials.[12, 13]

Notwithstanding the burgeoning research on *APOL1* and kidney disease, with over 1,000 related publications in PubMed, there remain significant gaps in our knowledge of the genetics and clinical epidemiology of CKD caused by or attributable to *APOL1* risk variants, how the G1 and G2 variants mediate pathology, or what constitutes a "second hit." In addition, more needs to be learned regarding patient and community preferences in receiving *APOL1* results, who should give the results, where those results reside, and who or what entities have access to the results. Without more precise understanding of the central pathophysiology and contributory factors, novel testing, treatment, and policy approaches currently being implemented with the aim of benefiting patients could potentially cause significant harm in some populations.[14]

CONFERENCE OVERVIEW

Drs. Akinlolu ("Ojo") Ojo (University of Kansas School of Medicine, USA) and Ifeoma Ulasi (University of Nigeria College of Medicine, Nigeria) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. This highly interactive conference will invite key thought leaders and relevant stakeholders, including patients, and experts in nephrology and other related disciplines (nephropathology, genetics, epidemiologists, ethics, immunology, pharma, social work, etc) who will comprehensively review the literature and current state of understanding in this area and address clinical issues as outlined in the Appendix: Scope of Coverage. The conference output will include the publication of a position statement that will help guide KDIGO and others on the therapeutic management and future research in *APOL1* kidney disease.

APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: *APOL1* Kidney Disease: Pathogenesis/Pathophysiology and the Role of Modifiers

1. What is the appropriate terminology for *APOL1* kidney disease?
2. Which cell types (inside and outside of the kidney) express *APOL1* mRNA or protein under physiologic or pathologic conditions? What physiologic/pathologic conditions or environmental factors induce *APOL1* expression?
3. To what extent do available evidence support the paradigm that variants of *APOL1* cause kidney disease? Is there evidence indicating G0 *APOL1* is toxic?
4. What is the nature of kidney injury that results from variants of *APOL1*? How do we explain the spectrum of kidney diseases associated with the *APOL1* high-risk genotype?
5. What is the current state of knowledge about the pathomechanisms underlying *APOL1*-mediated cellular injury?
6. What are current gaps in experimental modeling of *APOL1* kidney disease? Which attributes of *APOL1* kidney disease do existing experimental models (animal and cell-based models) capture well, and which attributes are poorly captured by these models? What are promising strategies for modeling *APOL1*-associated, low-proteinuric kidney diseases such as hypertension-attributed CKD in experimental animals?
7. What is the current state of knowledge about genetic factors (modifiers and variants such as p.N264K) as well as environmental factors that contribute to *APOL1* kidney disease?

Breakout Group 2: Epidemiology of *APOL1* Kidney Disease: Characterization of Risk Phenotypes, Risk Factors, and Adverse Outcomes

1. What is the appropriate terminology for *APOL1* kidney disease?
2. What is the prevalence of the *APOL1* risk variants globally, and how does the prevalence vary across populations, especially in sub-Saharan Africa? Why does the *APOL1* high-risk variant frequency vary so much in different regions of Africa?
3. What is the difference in kidney failure and CKD progression in *APOL1* high-risk versus low-risk genotypes? Does the risk differ in adult populations compared with pediatric populations?
4. Are there phenotypic differences between G1 and G2 alleles? Are there differences in microalbuminuria and macroalbuminuria for individuals with G1 versus G2 alleles?
5. Does the risk of incident CKD or CKD progression or the rate of estimated glomerular filtration rate (eGFR) decline vary between individuals with the G1 versus G2 alleles?
6. Do high- and low-risk genotypes confer higher CVD risk in those with CKD?
7. Does the *APOL1* high-risk genotype confer a higher risk heart failure, atherosclerosis, mortality, acute coronary syndrome, or stroke compared with low-risk genotypes in those with CKD?
8. Do high- and low-risk genotypes confer higher complication risks (e.g., preeclampsia) among pregnant women and increased risk of intrauterine fetal growth restriction?
9. What is the significance of fetal or maternal discordance in genotype on the risk of preeclampsia?

10. Are babies with high-risk *APOL1* variants at increased risk of subsequent development of hypertension and CKD?

Breakout Group 3: Prognosis, Current Management, and Novel Therapeutic Approaches

1. What is the appropriate terminology for *APOL1* kidney disease?
2. Which biomarkers predict development and progression of *APOL1* kidney disease (e.g., soluble urokinase plasminogen activator receptor [suPAR], kidney injury molecule 1 [KIM-1], tumor necrosis factor receptor 1 [TNFR1], TNFR2, proteinuria)?
3. Which tools can be used for prognostication (e.g., risk equations such as those from the CKD Prognosis Consortium)?
4. Describe therapeutic targets in *APOL1* kidney disease: inhibition of channel function or APOL1 production (antisense, antibody-mediated), downstream inflammatory pathways, or agents targeting environmental and or genetic modifiers.
5. What is the approach to management (and how would it change) if multiple drivers of CKD coexist (e.g., *APOL1* kidney disease and either lupus, HIV or COVID, sickle cell disease, or collapsing glomerulopathy)?
6. What is the role of treatment targeting APOL1 in slowing the progression of kidney diseases that are not necessarily associated with *APOL1* kidney disease (e.g., non-*APOL1* associated FSGS, minimal change disease, membranous glomerulonephritis, IgA nephropathy, diabetic nephropathy)?
7. What is the role of treatment targeting APOL1 in patients who received a kidney transplant from donors with high-risk *APOL1* genotypes, or living related donors with high-risk *APOL1* genotypes?
8. How do potential treatments affect those in endemic areas of trypanosomiasis and other infectious diseases?

9. What barriers and opportunities exist for advancing the diagnosis and treatment of *APOL1* kidney disease?

Breakout Group 4: Practical Issues Related to *APOL1* Screening and Diagnosis, and Ethical Issues Related to *APOL1* Genetic Testing

1. What is the appropriate terminology for *APOL1* kidney disease?
2. When is it most appropriate to perform *APOL1* genetic testing? Who has access to those data? Where do those data reside in the clinical system?
    a. Who should be tested for *APOL1* (self-identified African ancestry, admixture population, uncertain cause of CKD)?
    b. What is the extent of testing for family members, and how should family members be approached and by whom?
3. What is the best way to operationalize *APOL1* genetic testing, and how are the results communicated to the patient and clinical team?
    a. What are the benefits and pitfalls of *APOL1* testing?
    b. How do you give informed consent for *APOL1* testing?
    c. What is the best way to educate about *APOL1*?
    d. What about pediatric populations and screening for *APOL1*?
4. What are the social implications and or consequences of *APOL1* testing?
    a. What are the psychological complications of knowing one is *APOL1* positive?
    b. What are the potential effects of *APOL1* testing on health disparities?
    c. What are potential implications for patients—stigmatization, family planning, life insurance, discrimination?
5. What are the implications of *APOL1* in the transplant setting for potential kidney donors who have *APOL1*?
    a. What are the implications of *APOL1* testing for potential transplant donors in respect to long-term prognosis and kidney disease risk?
    b. Is there a way to stratify risk of kidney disease development in donors who are *APOL1* positive?

c. Should potential donors be given the right to donate a kidney even in setting of having high-risk *APOL1* phenotypes?

6. What are the implications of *APOL1* in the transplant setting for potential kidney recipients?
   a. What is the effect of donor *APOL1* status on graft survival?
   b. What are the tradeoffs between accepting a kidney with *APOL1* risk allele(s) versus waitlisting?

References

1. Genovese G, Friedman DJ, Ross MD*, et al.* Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329:** 841-845.

2. Freedman BI, Kopp JB, Langefeld CD*, et al.* The apolipoprotein L1 (APOL1) gene and nondiabetic nephropathy in African Americans. *J Am Soc Nephrol* 2010; **21:** 1422-1426.

3. Kasembeli AN, Duarte R, Ramsay M*, et al.* APOL1 risk variants are strongly associated with HIV-associated nephropathy in black South Africans. *J Am Soc Nephrol* 2015; **26:** 2882-2890.

4. Limou S, Nelson GW, Kopp JB, Winkler CA. APOL1 kidney risk alleles: Population genetics and disease associations. *Adv Chronic Kidney Dis* 2014; **21:** 426-433.

5. Friedman DJ, Pollak MR. Genetics of kidney failure and the evolving story of APOL1. *J Clin Invest* 2011; **121:** 3367-3374.

6. Kopp JB, Nelson GW, Sampath K*, et al.* APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 2011; **22:** 2129-2137.

7. Kopp JB, Winkler CA, Zhao X*, et al.* Clinical features and histology of apolipoprotein L1-associated nephropathy in the FSGS Clinical Trial. *J Am Soc Nephrol* 2015; **26:** 1443-1448.

8. Ng DK, Robertson CC, Woroniecki RP*, et al.* APOL1-associated glomerular disease among African-American children: A collaboration of the Chronic Kidney Disease in Children (CKiD) and Nephrotic Syndrome Study Network (NEPTUNE) cohorts. *Nephrol Dial Transplant* 2017; **32:** 983-990.

9. Parsa A, Kao WH, Xie D*, et al.* APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013; **369:** 2183-2196.

10. McCarthy GM, Blasio A, Donovan OG*, et al.* Recessive, gain-of-function toxicity in an APOL1 BAC transgenic mouse model mirrors human APOL1 kidney disease. *Dis Model Mech* 2021; **14**.

11. Yoshida T, Latt KZ, Heymann J, Kopp JB. Lessons from APOL1 animal models. *Front Med* 2021; **8:** 762901.

12. Friedman DJ, Ma L, Freedman BI. Treatment potential in APOL1-associated nephropathy. *Curr Opin Nephrol Hypertens* 2022; **31:** 442-448.

13. Egbuna O, Zimmerman B, Manos G*, et al.* Inaxaplin for proteinuric kidney disease in persons with two APOL1 variants. *N Engl J Med* 2023; **388:** 969-979.

14. Freedman BI, Kopp JB, Sampson MG, Susztak K. APOL1 at 10 years: Progress and next steps. *Kidney Int* 2021; **99:** 1296-1302.