What is the APOL1 gene and its association with kidney disease?

A mutation (variant or allele) in the APOL1 gene evolved to protect against the parasite trypanosomes that cause African sleeping sickness. However, the variant increases the risk for kidney damage.

APOL1 associated kidney disease has an **autosomal recessive** pattern of inheritance with incomplete penetrance (not everyone who has two copies of the mutant gene will develop kidney disease):

- Having **two copies of the APOL1 risk variant** is considered a risk factor for kidney disease
- **20% of people with two risk variants** will get kidney disease – people need a “second hit”, such as a viral infection (like HIV or COVID) or environmental factors, to get kidney disease. The nature of this “second hit” is unclear.

Impact of APOL1 on kidney disease

- Having two APOL1 risk variants can cause:
  - Focal segmental glomerulosclerosis (FSGS)
  - HIV associated kidney disease
  - Hypertension-induced kidney disease
  - Accelerated development of lupus nephritis
  - Accelerated development of diabetic or non-diabetic kidney disease

- Two APOL1 risk variants in patients with established kidney disease can accelerate progression to dialysis and poorer response to standard treatment, such as blood pressure control and ACE inhibitors.
Who is more likely to have two APOL1 risk variants?

Because the APOL1 risk variant evolved to fight trypanosomes, which are found in Africa, people who have Western and Central African ancestry are more likely to have two APOL1 risk variants. This includes people who identify as:

- Black
- African American
- Latina/Latino
- Afro-Caribbean
- Afro-Brazilians
- Afro-Caribbean

How does APOL1 affect kidney transplant?

Impact on kidney recipients

- Some people (20-25%) who received a kidney from a deceased donor with two APOL1 risk variants had a lower graft survival than those whose donors had one or no APOL1 risk variants
- More research is needed on whether the recipient’s APOL1 status affects graft survival

Impact on living kidney donors

- Two APOL1 risk variants in Black living kidney donors is related to lower pre- and post-donation eGFR
- After donation, some Black living kidney donors with two APOL1 risk variants had faster decline in eGFR and reached end-stage renal disease sooner
- Not all living donors with 2 APOL1 risk variants develop kidney disease

Action steps for providers

- **Educate patients about APOL1** – educate patients who self-report Western or Central African ancestry about the APOL1 gene and its association with kidney disease
- **Do genetic testing** – APOL1 genetic testing is appropriate in people of Western and Central African Ancestry who are either of these:
  - A patient with kidney disease symptoms, such as proteinuria
  - A possible living kidney donor who is young and has a family history of kidney disease
- **Use genetic counselors in APOL1 genetic testing** – people should see a genetic counselor before and after genetic testing to know all the knowns and unknowns about APOL1-mediated kidney disease
- **Educate patients and donors that researchers are currently investigating treatment options for APOL1-mediated kidney disease.** Read research articles about treatments being investigated at doi.org/10.1172/jci.insight.126124 and DOI: 10.1056/NEJMoa2202396.

Resources

If you don’t have a genetic counselor at your institution, The National Society of Genetic Counselors can help you learn more and find one.

- Visit their website at www.nsgc.org
- Visit their genetic counselor directory at findageneticcounselor.nsgc.org

Send your patients to the American Kidney Fund website to learn more about APOL1 at kidneyfund.org/apol1