



Brigham and Women's Hospital
Founding Member, Mass General Brigham

APOL1 and Kidney Disease

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Clinical focus: Adult Nephrology

Research focus: APOL1-Mediate Kidney Disease



Disclosures

Advisor for Maze Therapeutics and Podium Bio
Received research funding from NIH and Icagen.



Objectives

- Understand the role of APOL1 variants in kidney disease epidemiology and pathogenesis
- Recognize the clinical spectrum of APOL1-mediated kidney diseases
- Apply knowledge of APOL1 to transplantation and donor counseling
- Discuss emerging therapies and clinical trial updates
- Highlight board-relevant diagnostic and management approaches



Case Vignette

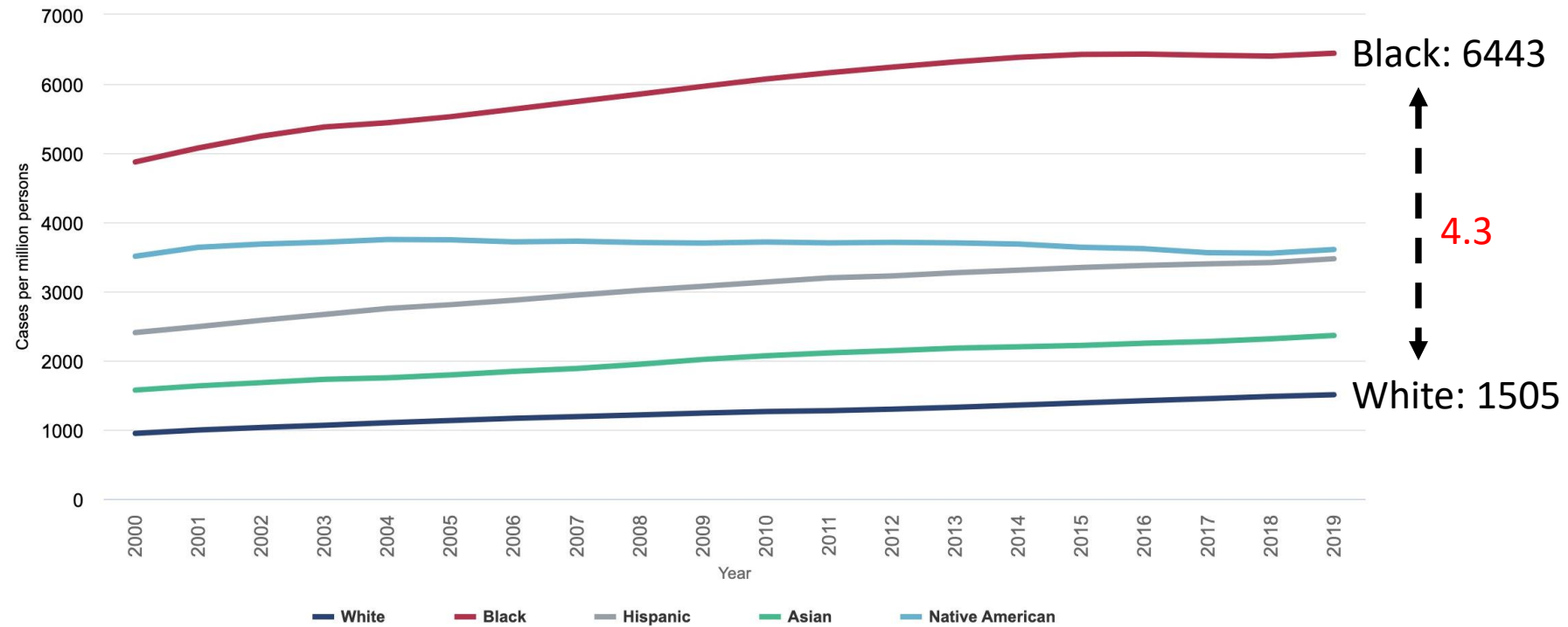
39 year old non-diabetic African American male with history of hypertension and FSGS presents for routine follow up visit. His proteinuria is stable at 0.8g/day. However, his eGFR has been declining over the past 3 years from 45 to 35 despite optimal BP management with lisinopril and chlorthalidone. He asked the following questions:

Questions:

- 1) What is the likelihood that he has high-risk APOL1 genotype?
- 2) Would you recommend APOL1 genetic testing for him?
- 3) If he carries high-risk APOL1 genotype, does it impact the progression of his CKD to ESKD?
- 4) Are there new interventions that could slow down the progression of his kidney disease?
- 5) What is the impact of donor APOL1 genotype on kidney allograft outcome?



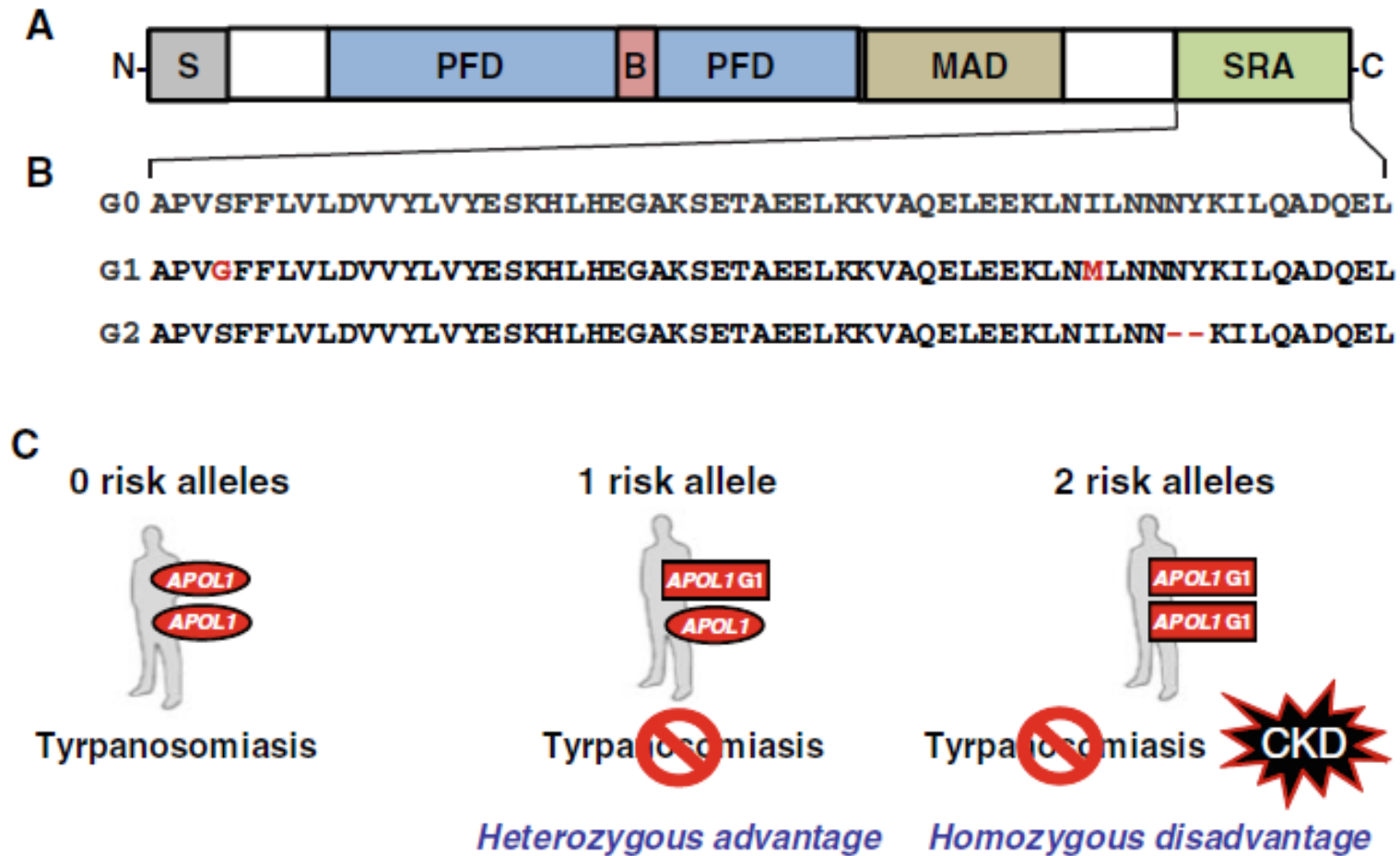
Black Americans are **4-times** more likely to develop kidney failure than White Americans



Data Source: 2021 United States Renal Data System Annual Data Report



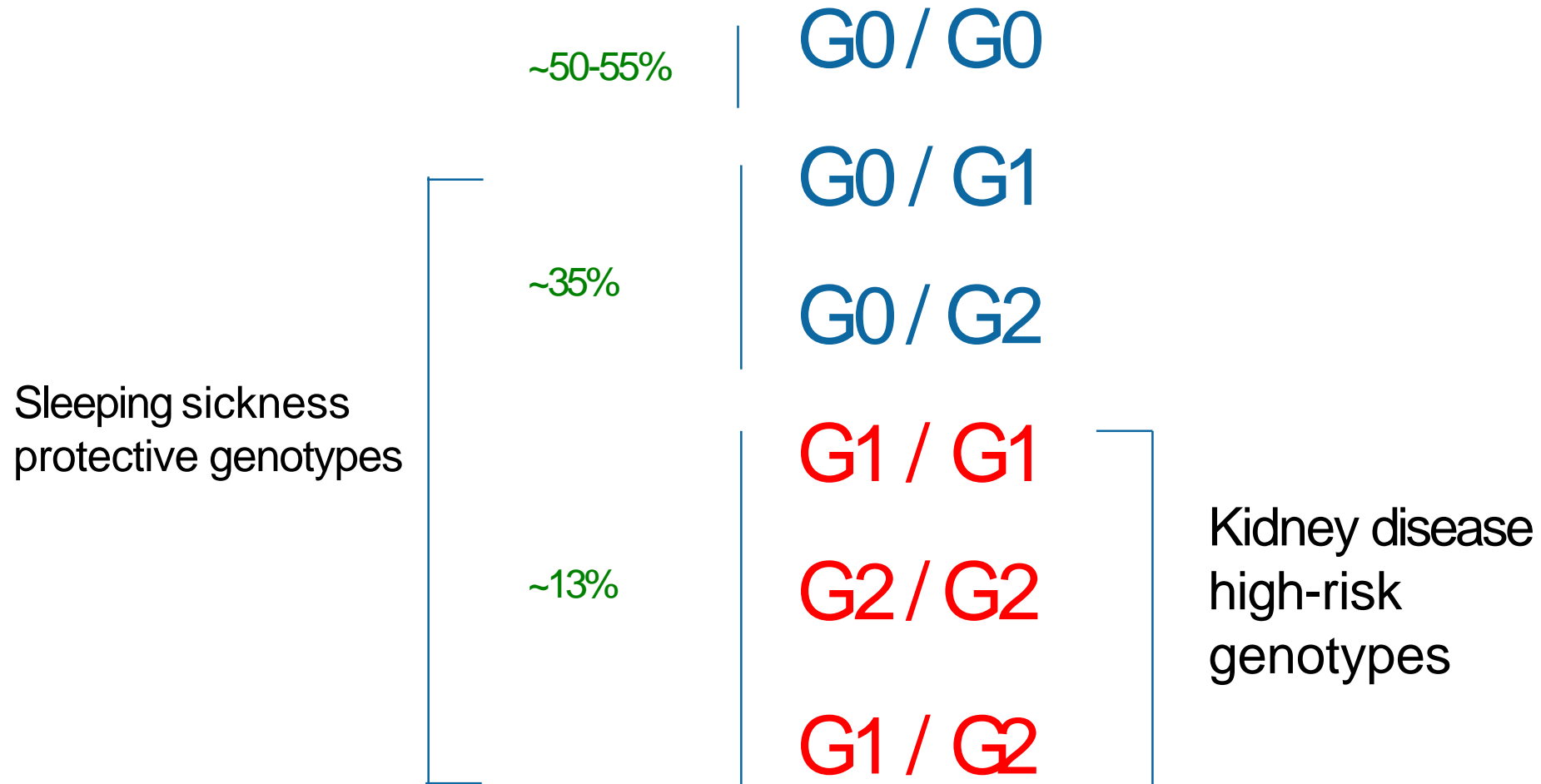
Two coding variants (G1, G2) in *APOL1* explain much of the excess risk of kidney disease



Only individuals with recent sub-Saharan African ancestry carry *APOL1* risk variants



13% of Black Americans Have High-Risk *APOL1* genotypes



Question #1:

Which of the following forms is NOT associated with APOL1 high-risk genotype?

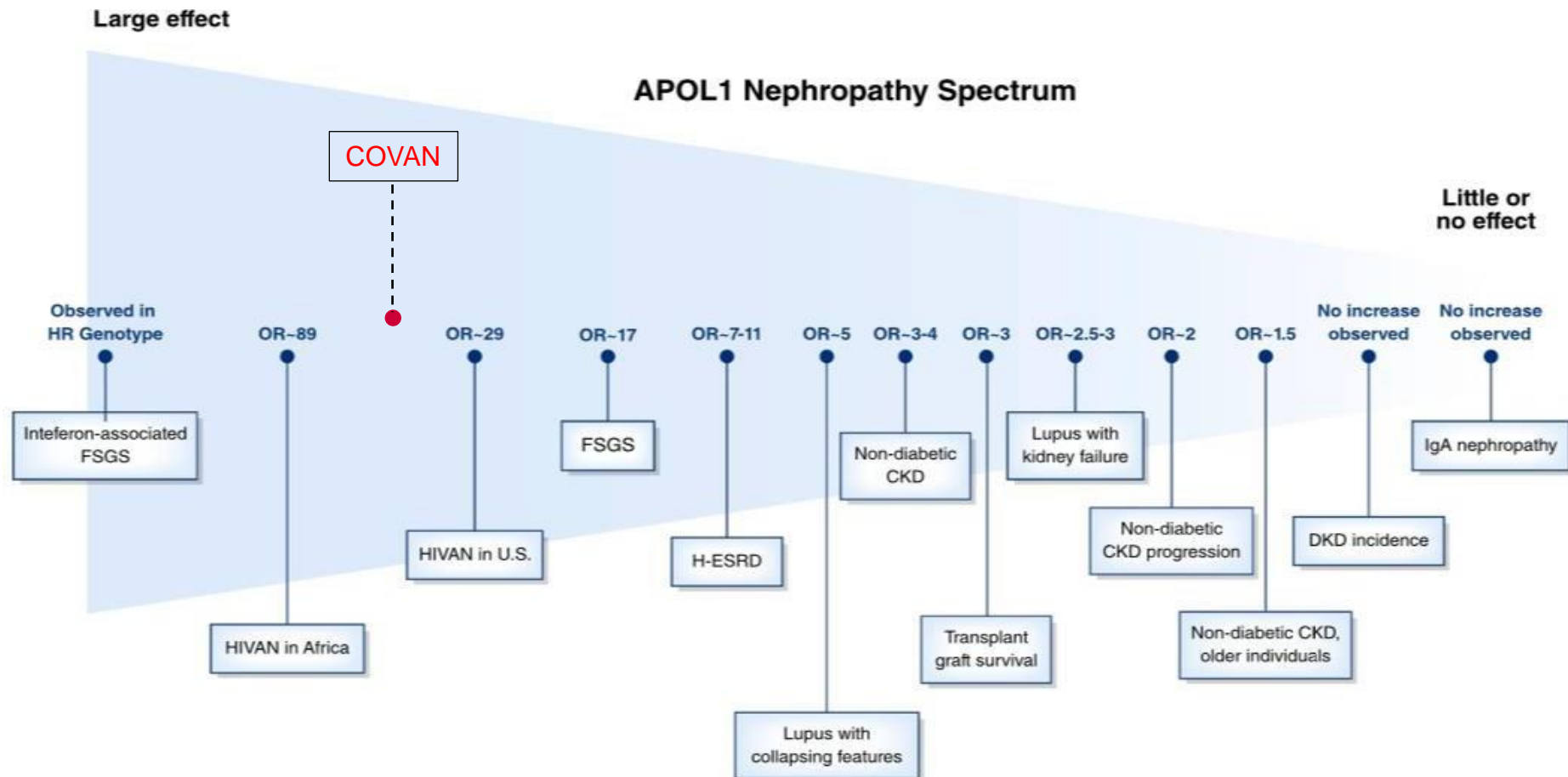
- A. Hypertension-attributed kidney disease
- B. Increased incidence of diabetic kidney disease
- C. COVID-19 associated collapsing nephropathy
- D. HIV associated collapsing nephropathy
- E. Lupus associated collapsing nephropathy



APOL1 variants increase the risk of many different forms of kidney disease

Histopathology :

- Podocytopathy: FSGS and collapsing glomerulopathy → rapid progression
- Vascular nephropathy: HTN-attributed CKD → slow progresses



Question #1:

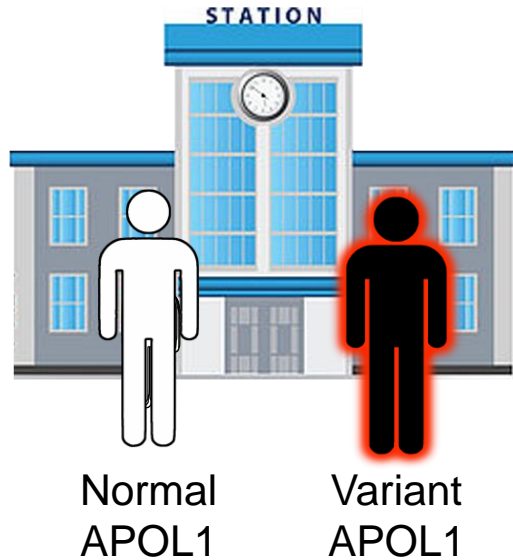
Which of the following forms is NOT associated with high-risk APOL1 genotype?

- A. Hypertension-attributed kidney disease
- B. Increased incidence of diabetic kidney disease
- C. COVID-19 associated collapsing nephropathy
- D. HIV associated collapsing nephropathy
- E. Lupus associated collapsing nephropathy

Note: While high-risk APOL1 genotype does not increase the incidence of DKD, it accelerates progression of established DKD



High Risk APOL1 Causes Various Forms of Kidney Disease (It makes it more likely to get on the kidney disease train)



Focal segmental glomerulosclerosis



Frequency of HR APOL1: **70%**

Hypertension-associated CKD



Frequency of HR APOL1: **40%**

COVID-associated nephropathy



Frequency of HR APOL1: **90%**

HIV-associated nephropathy

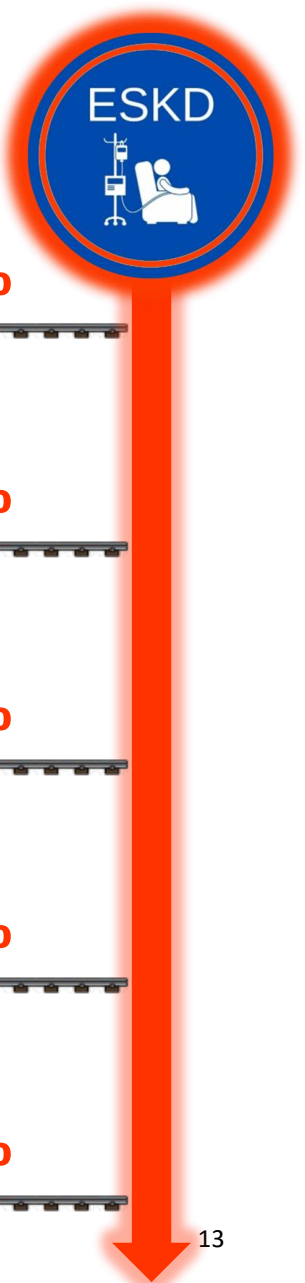


Frequency of HR APOL1: **90%**

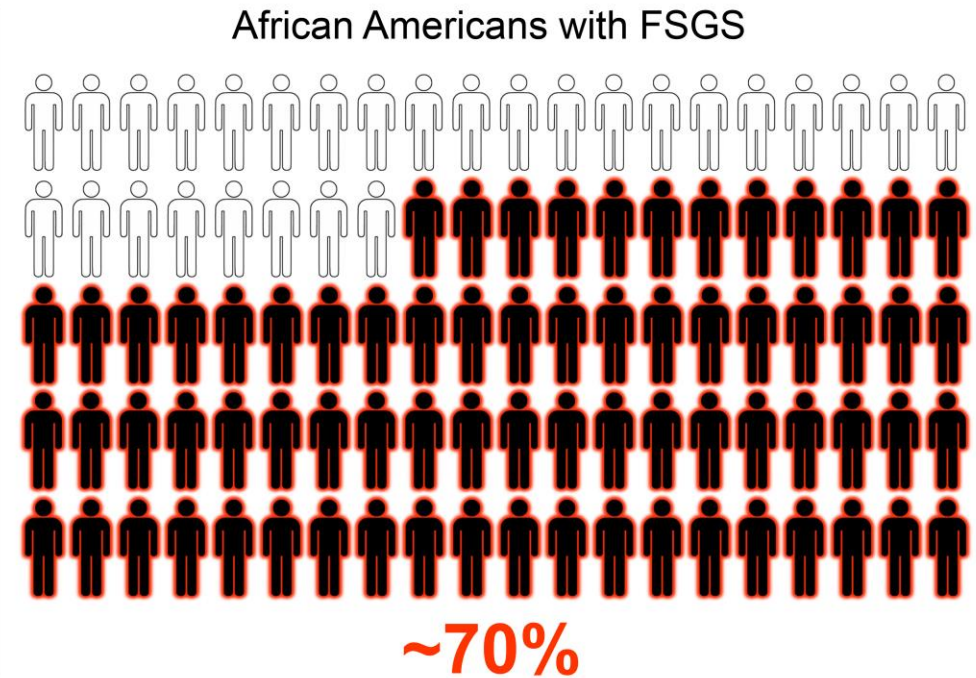
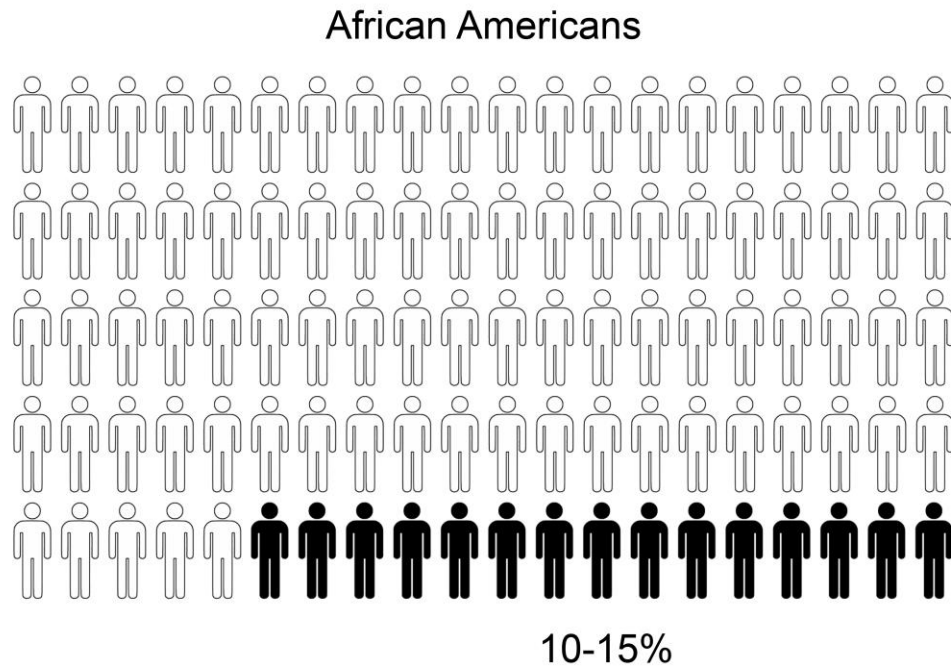
Lupus nephritis



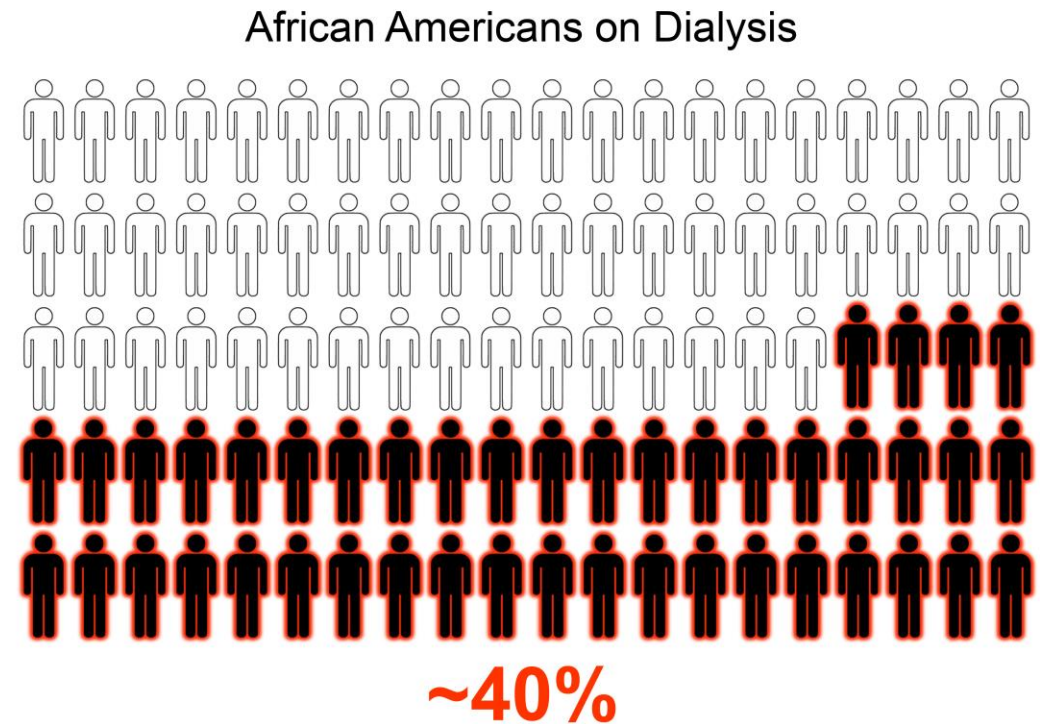
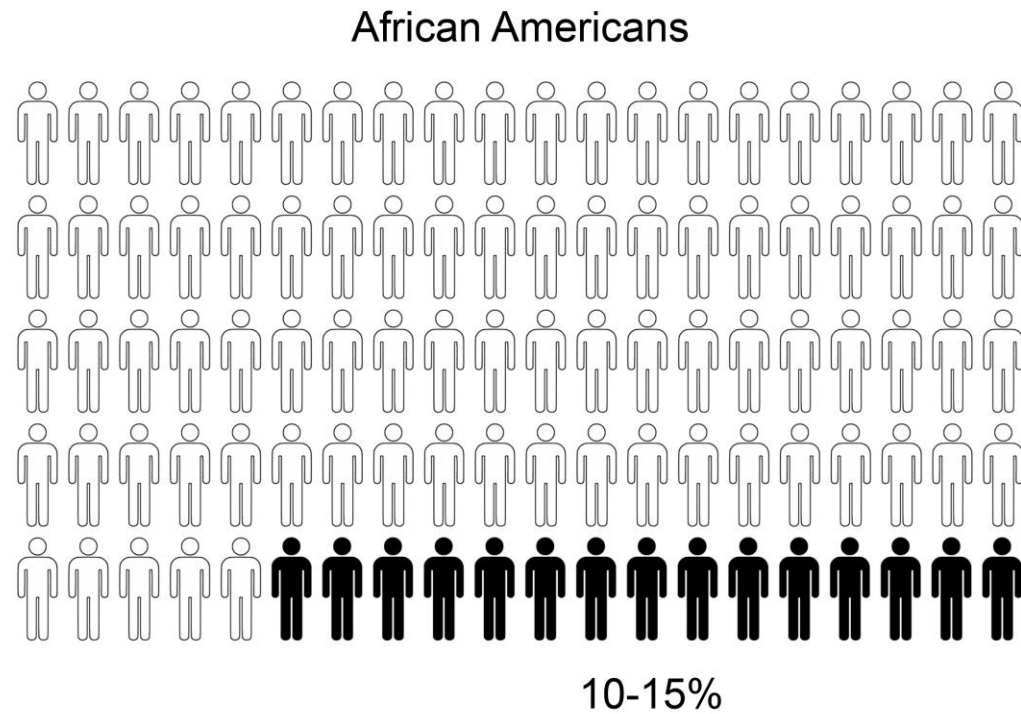
Frequency of HR APOL1: **25%**



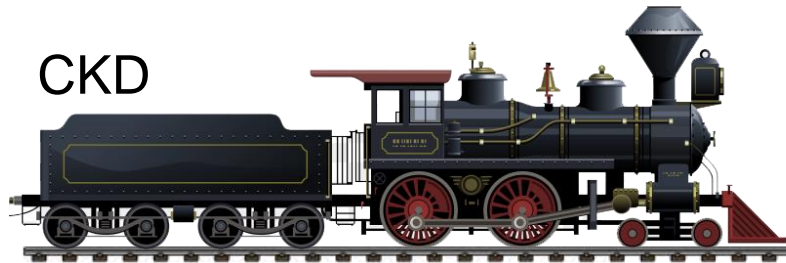
Approximately **7 in 10** Black Americans with FSGS
have kidney failure caused by APOL1



Approximately **4 in 10** Black Americans on dialysis
have kidney failure caused by APOL1



High Risk APOL1 Accelerates Progression of Kidney Disease to Dialysis (It speeds up the train)



APOL1 CKD



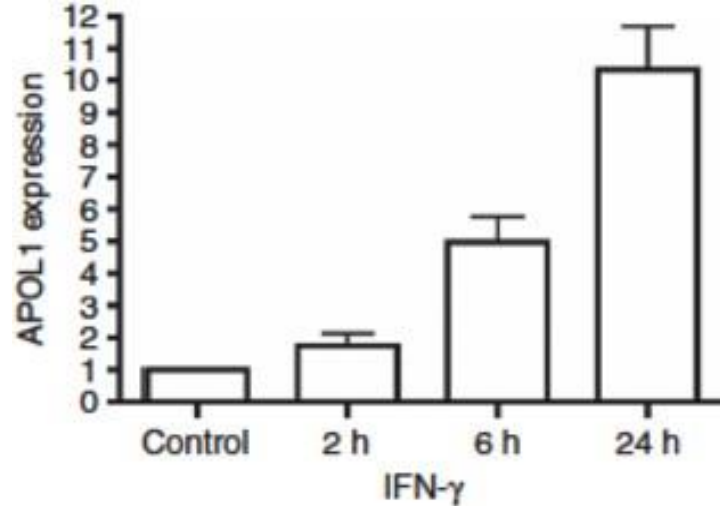
No Known Intervention That Slows This CKD Progression

Why do only some people with high-risk genotype get disease?

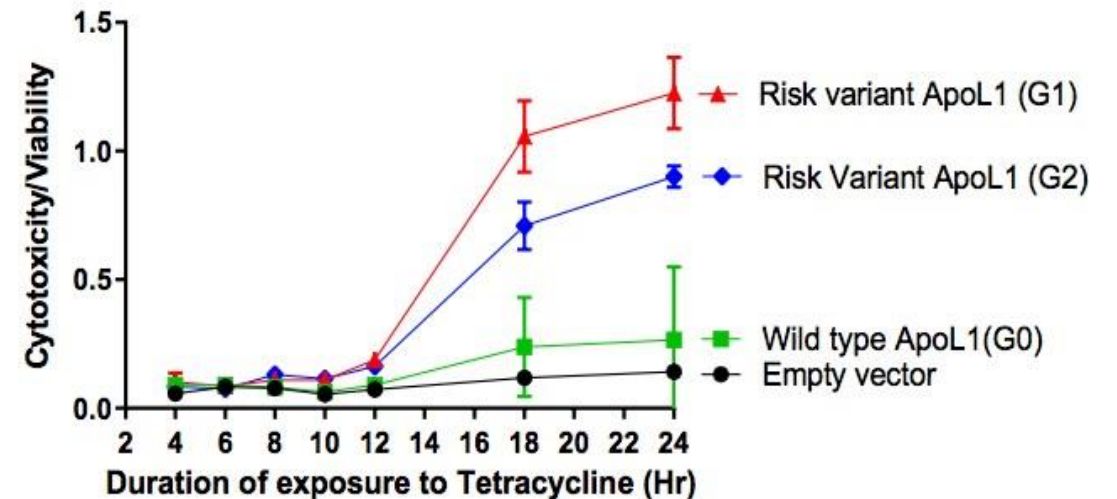
One possible mechanism: expression plus toxicity

- Two-hit hypothesis: Genetic susceptibility + environmental/immune triggers
- Interferons (e.g., during infections) upregulate APOL1 expression → podocyte injury

IFN γ upregulates APOL1



Variant APOL1 is toxic to cells



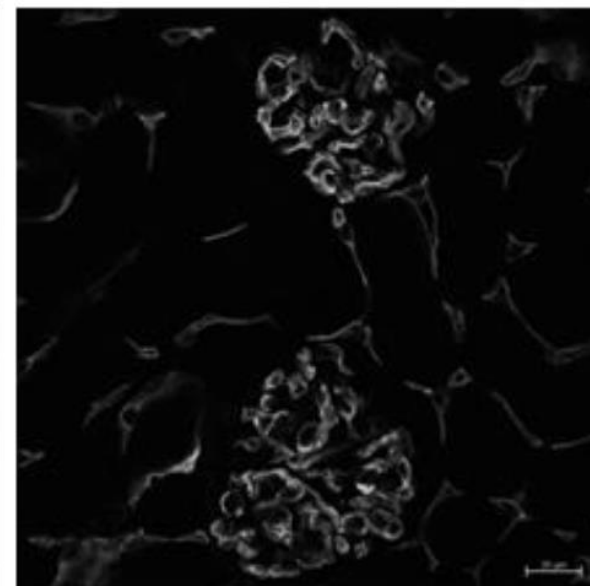
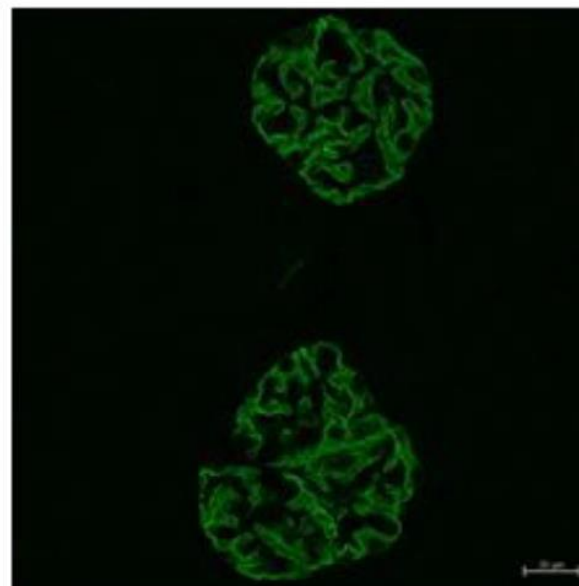
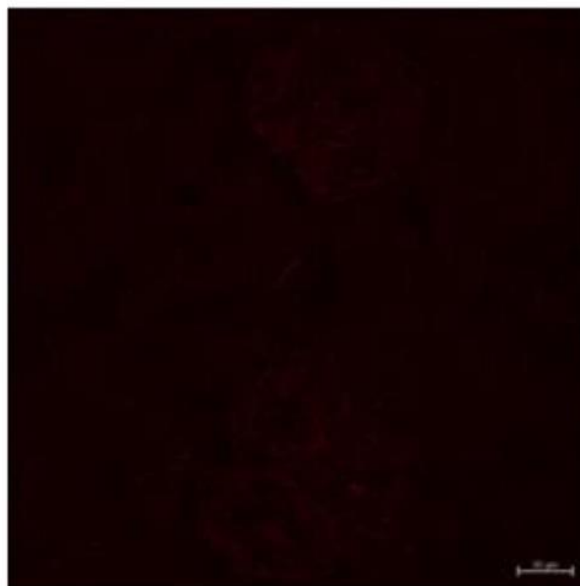
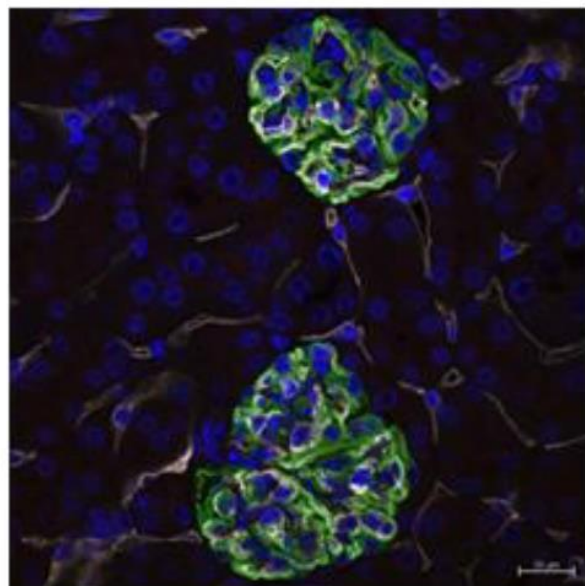
Overlay

APOL1

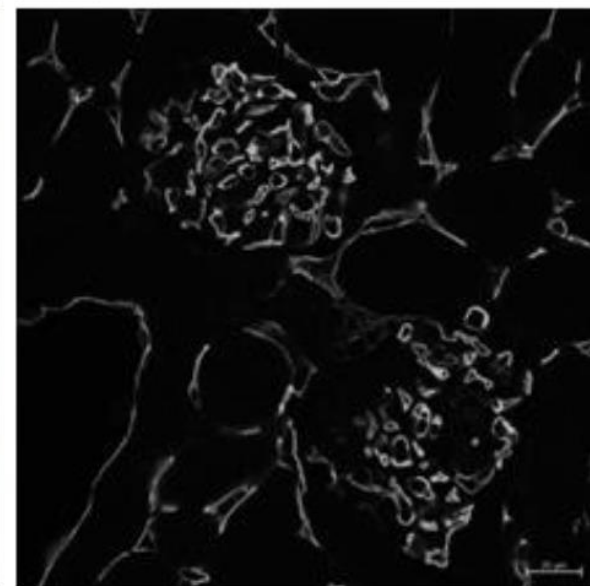
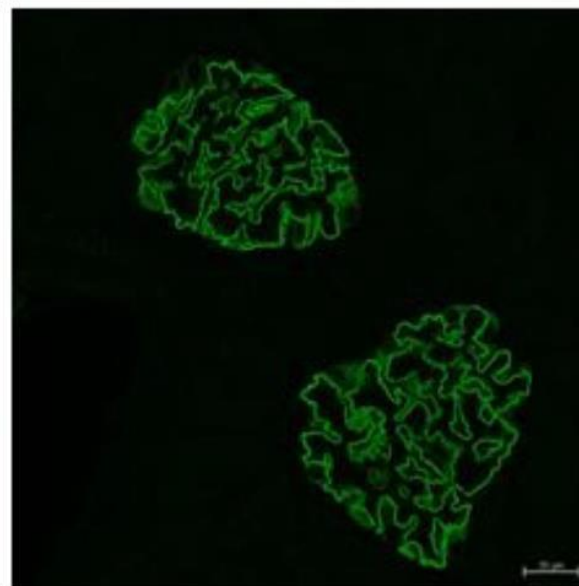
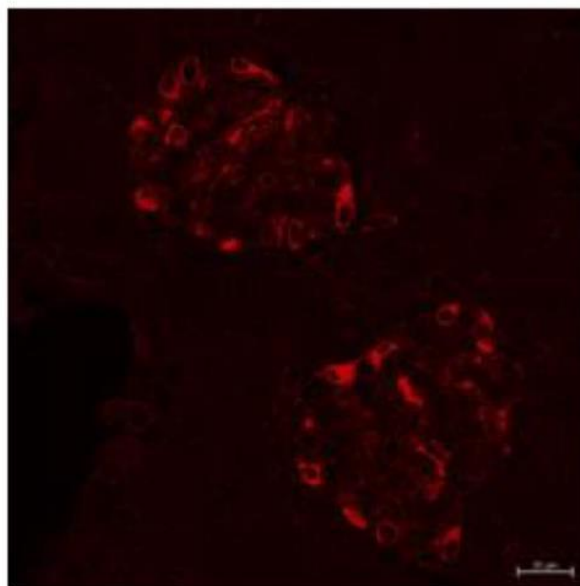
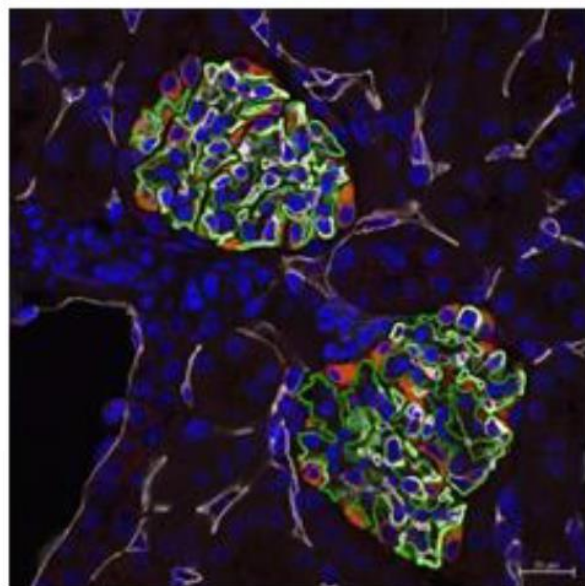
Nephrin

Endomucin

No IFN

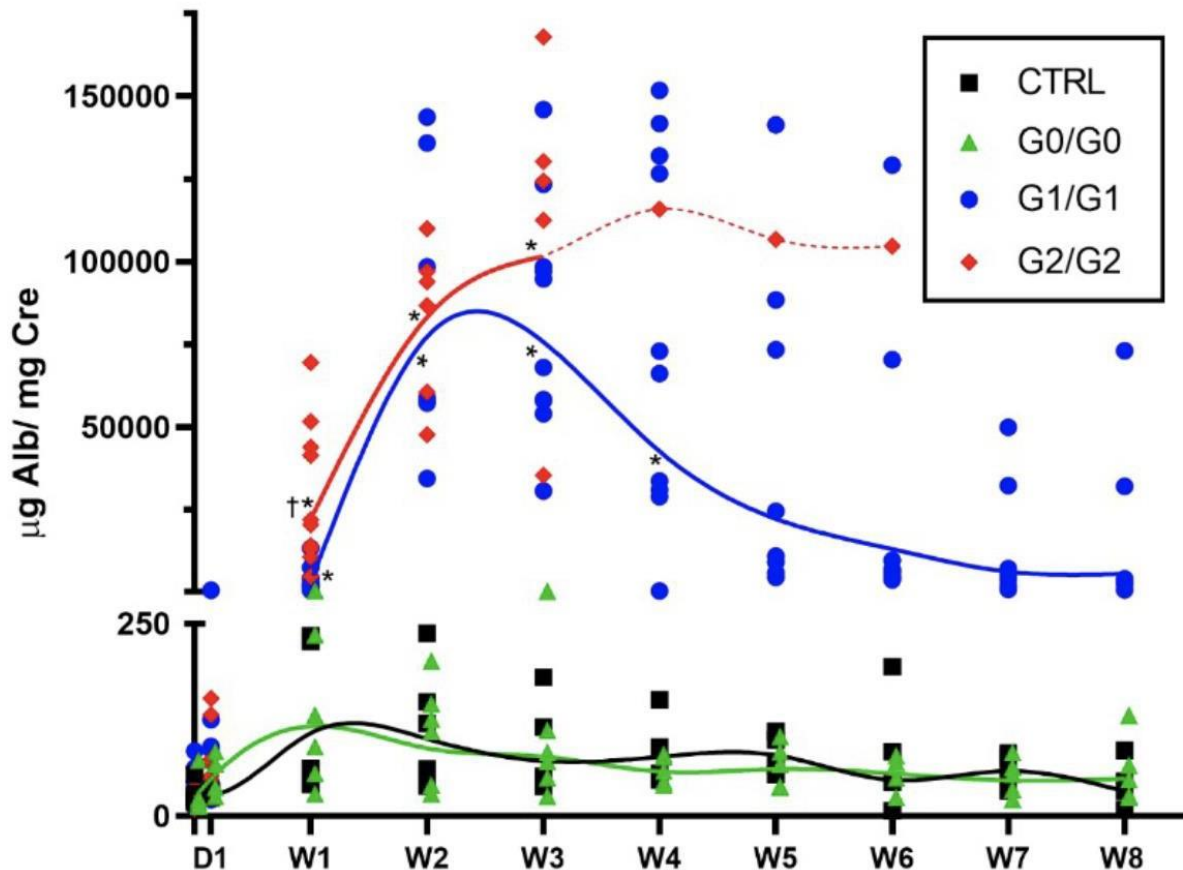


IFN γ

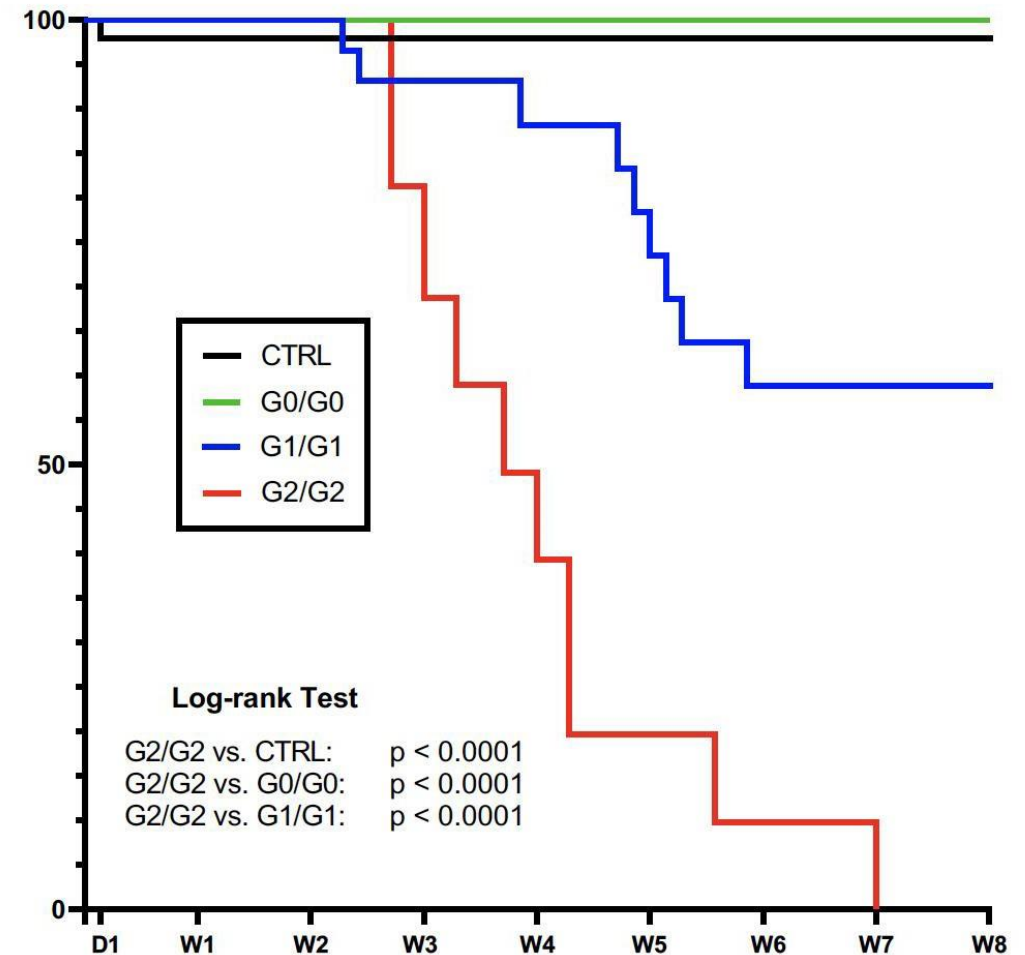


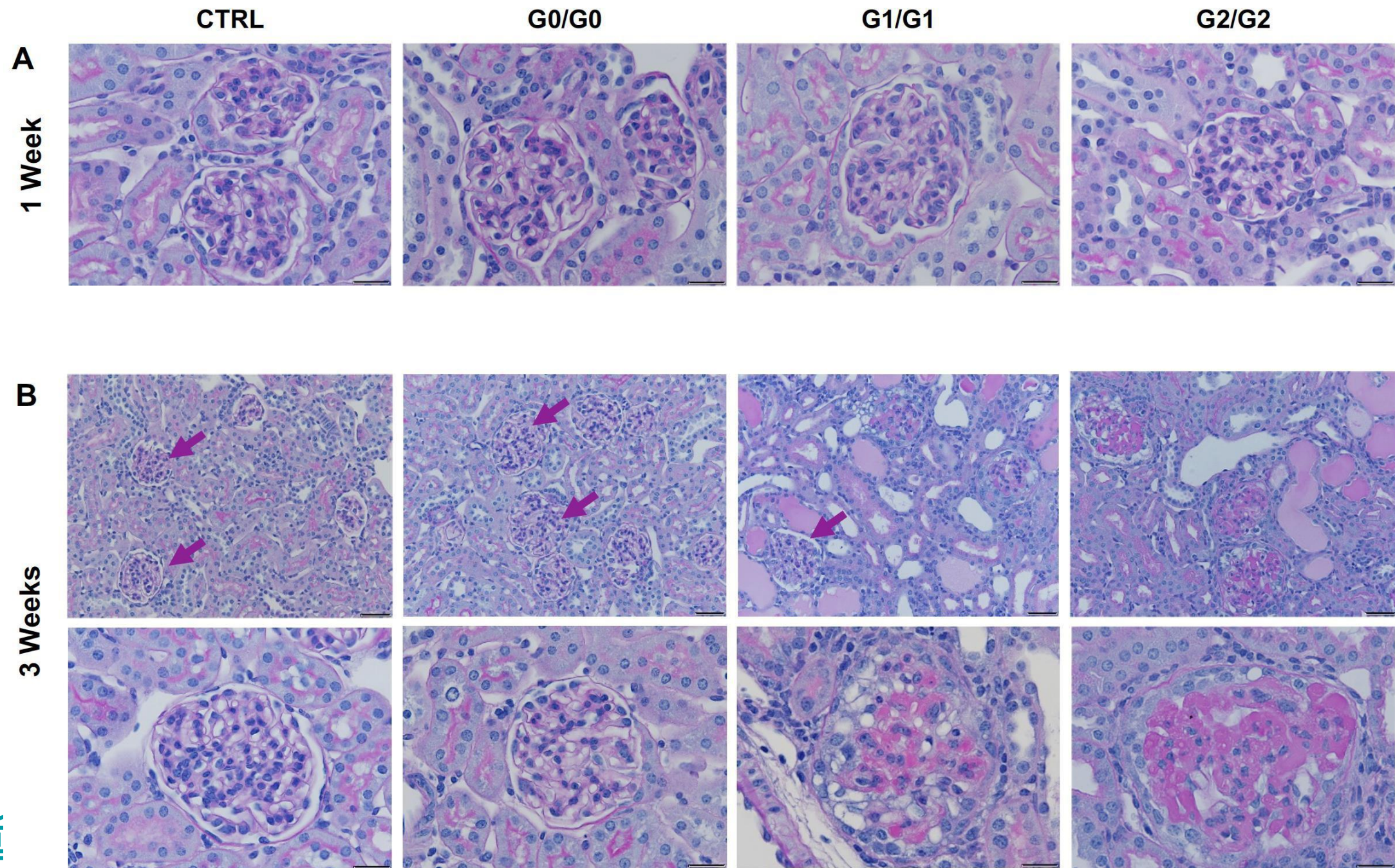
Transgenic Expression of G1 or G2 APOL1 is Sufficient to Cause Glomerulosclerosis, proteinuria and Kidney Failure in Mice

Albuminuria after IFNgamma treatment



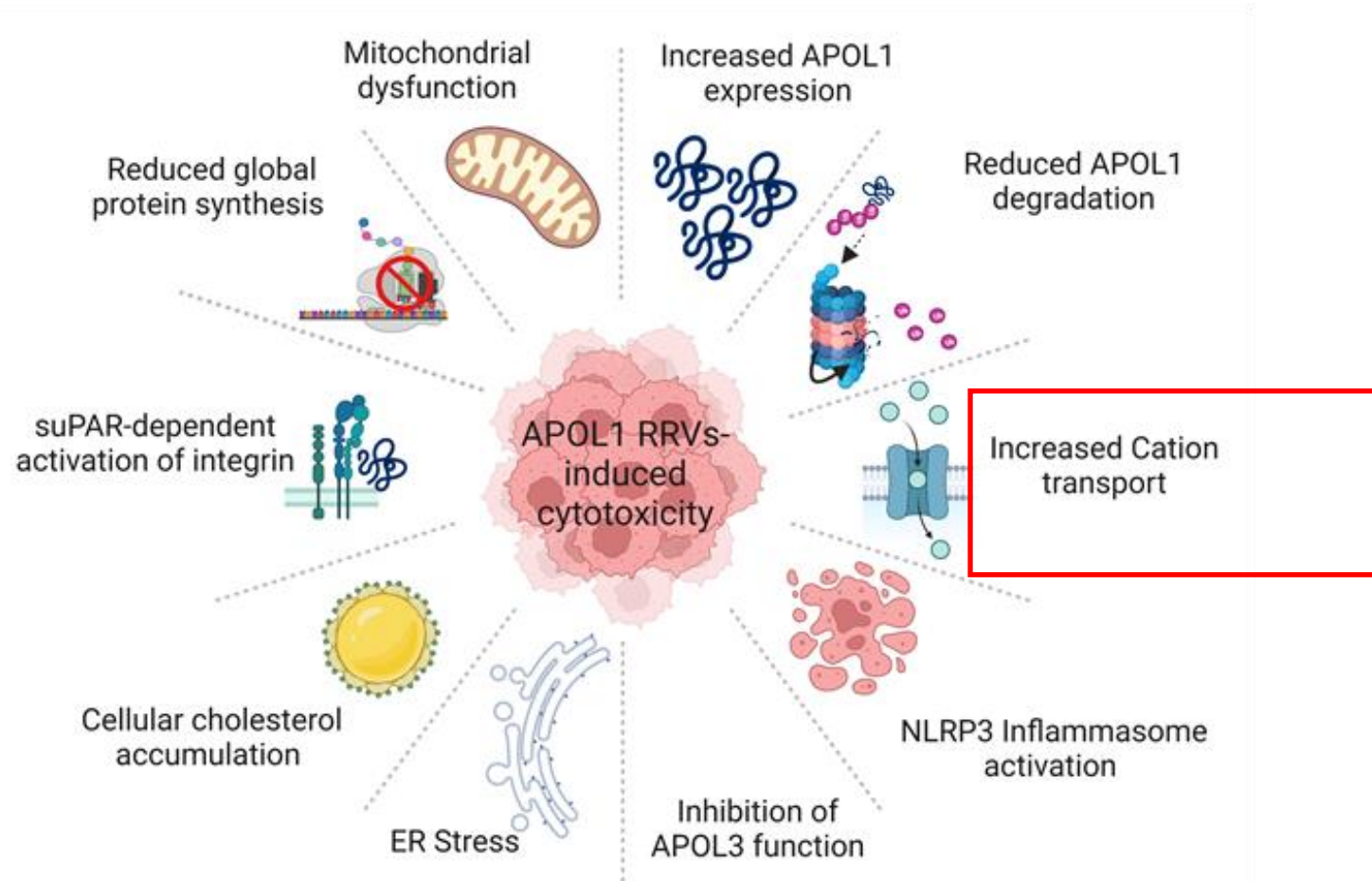
Survival after IFNgamma treatment





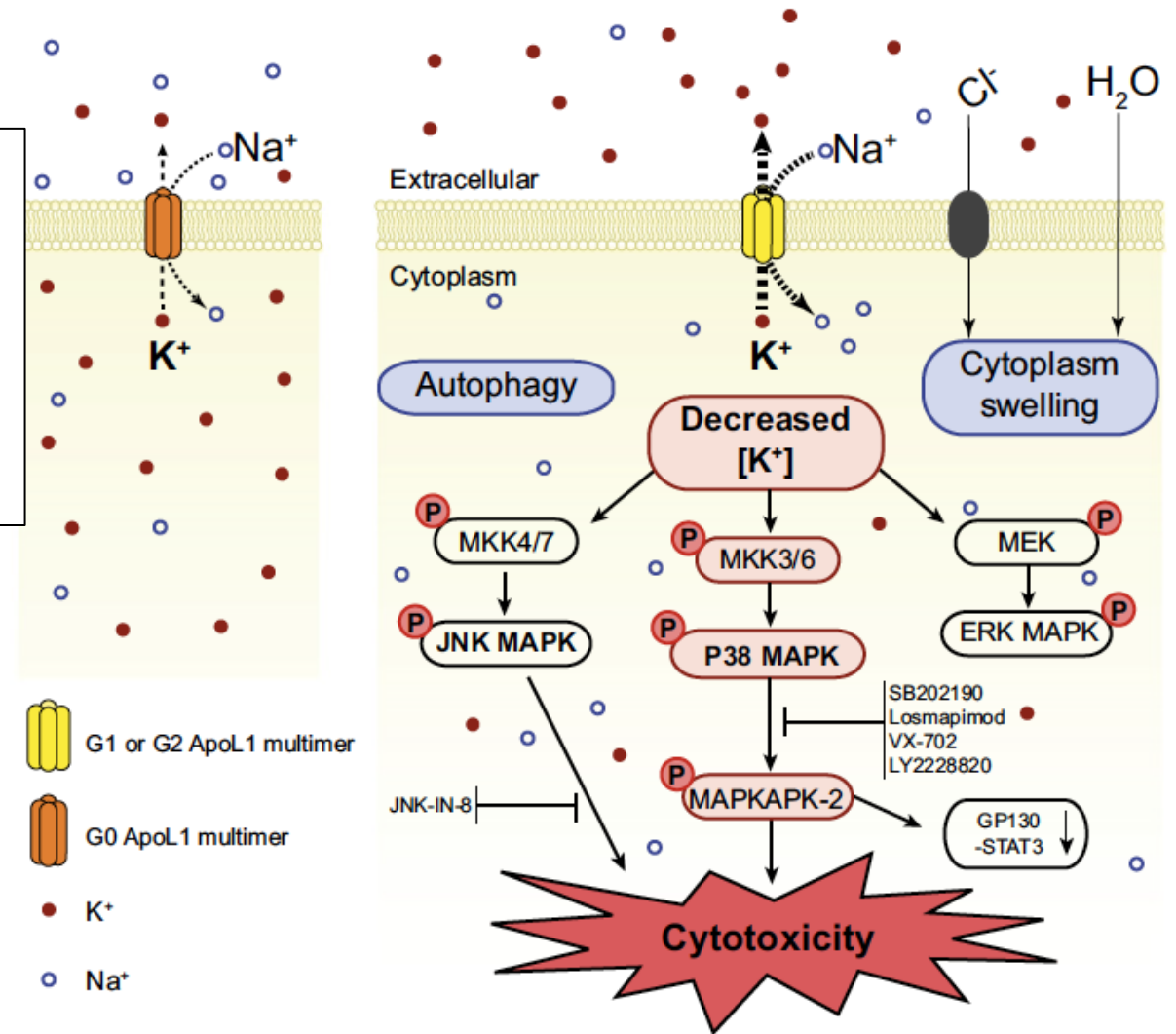
Proposed Mechanisms of APOL1-induced Cytotoxicity

Current theories of the mechanisms of APOL1-induced cytotoxicity

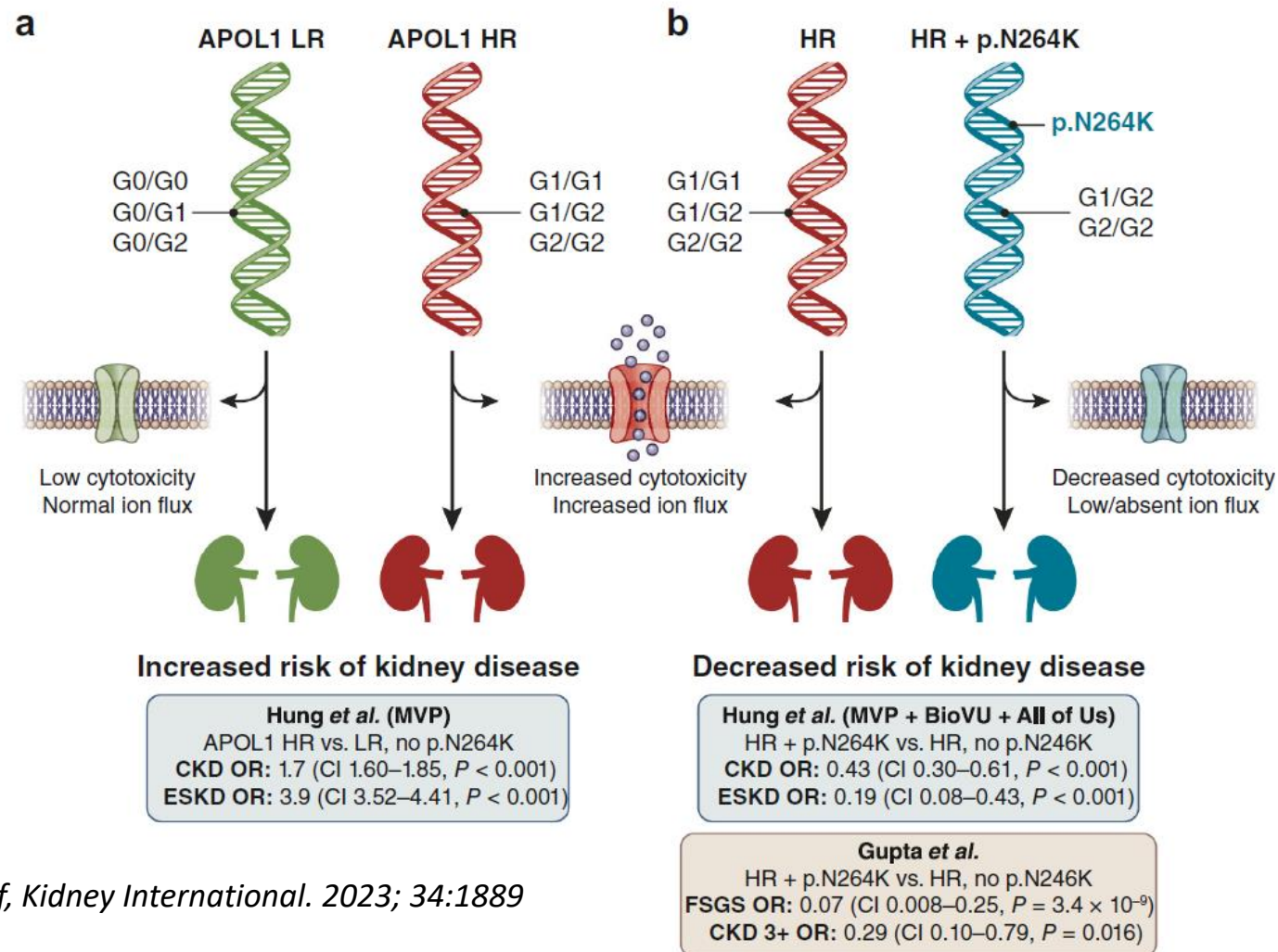


G1 or G2 APOL1 Cause Loss of Intracellular Potassium in HEK cells

- Gain-of-function cytotoxicity in podocytes
- Variant APOL1 forms pores → potassium depletion, cellular injury
- Key take-home: Toxic effect, not loss of function



N264K mutation in G2 decrease potassium loss → decreased risk of kidney disease



Madhavan and Schlondorff, *Kidney International*. 2023; 34:1889



Diagnostic Implications

When to Consider APOL1 testing?

- Young onset non-diabetic CKD in patients of African ancestry
- FSGS (including collapsing variant)
- Evaluation of potential living donors with Sub-Saharan African ancestry
- Limitations: Currently no approved therapy. However, helps guide prognosis and clinical trial access



Box 1. Principles to guide decision-making for *APOL1* testing of populations, families, or individuals

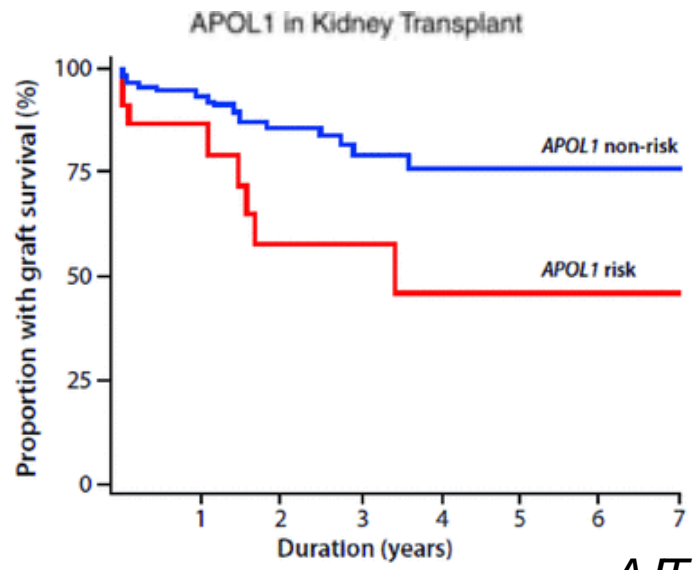
| |
|---|
| The individual (or their substitute decision-maker) provides informed consent. |
| AND |
| The individual is a member of a population with known or suspected high prevalence of <i>APOL1</i> risk variants (<i>e.g.</i> , self-identified recent African ancestry OR member of population with a high level of genetic admixture). |
| AND |
| The individual has kidney disease OR is a prospective living kidney donor OR has a relative with an <i>APOL1</i> high-risk genotype. |
| AND |
| CKD care and screening are available AND <i>APOL1</i> test results could change management (<i>e.g.</i> , an effective treatment for <i>APOL1</i> is available OR results could lead to increased surveillance for CKD OR results would inform risk/benefit evaluation in decision-making about living kidney donation). |
| AND |
| If <i>APOL1</i> genetic testing does not present an unacceptable risk of harm as determined by the individual. |
| AND |
| Appropriately qualified counseling is available to support voluntary and informed decision-making about testing. |
| AND/OR |
| <i>APOL1</i> test results could assist in relieving significant anxiety or inform reproductive decision-making. |

Ojo et al, *Kidney International*. 2025
doi.org/10.1016/j.kint.2025.05.017.

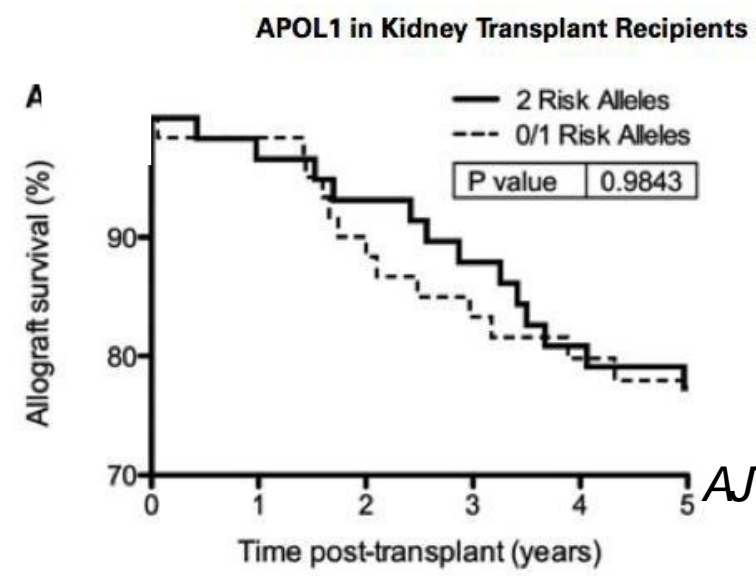
Transplant Considerations

- Deceased donor HR APOL1 genotype → increase risk of *de novo* collapsing glomerulopathy → worse allograft survival
- Impact of recipient's APOL1 genotype on allograft survival is under ongoing study
- Living donor HR genotype may also reduce graft survival (mixed result; area of controversy). Area of ongoing research.
- APOL1 testing increasingly considered for living donors of African ancestry

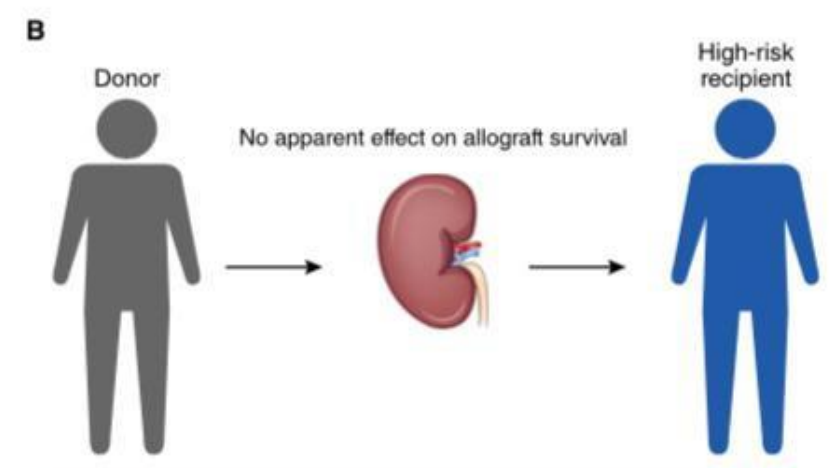
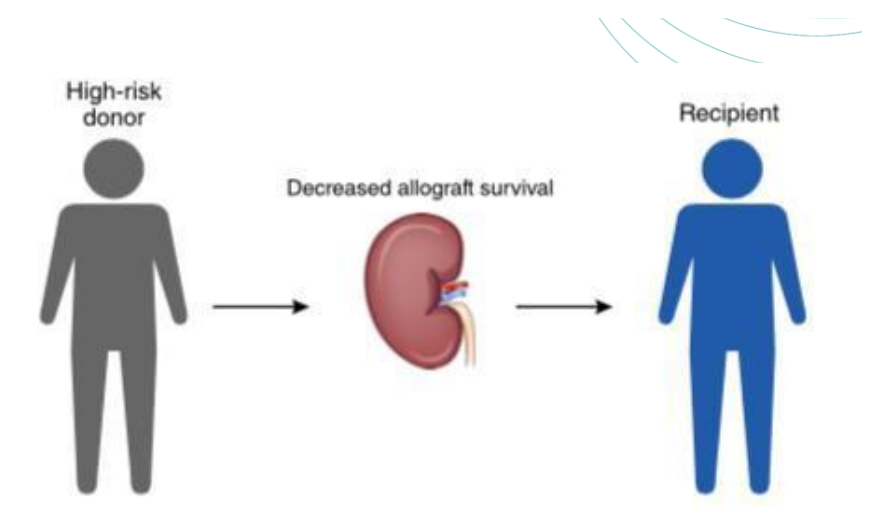




AJT 2011



AJT 2012



Conclusion:

- Risk of allograft dysfunction travels with donor APOL1 genotype
- Suggests kidney-expressed rather than circulating RV APOL1 promotes kidney injury

Association of Collapsing Glomerulopathy with Donor APOL1 Risk Variants in Kidney Allografts from Black Donors

Methods



Retrospective
study from two North
American centers



47 recipients of
kidneys from
Black donors that
developed CG



APOL1
genotypes of donors
available
in 44 patients



Controls: 560 recipients
of kidneys from Black
donors

Results

Kidney recipients with CG



55%
Black



40%
female



Onset of CG

9.5
months post-
transplantation

APOL1 risk variants in Donors

CG Cases



Controls



16%

0
KRVs

45%

41%

1
KRV

43%

43%

2
KRVs

12%

Donor 2 KRVs

**higher risk of CG compared to donors with
no KRVs**

aHR: 12.51 [95% CI: 4.83 – 32.39, p<0.001]

and

inferior graft survival

aHR: 1.49 [95% CI: 1.03 – 2.16, p=0.04]

Donor 1 KRV

**higher risk of CG compared to donors with
no KRVs**

aHR: 3.39 [95% CI: 1.36 – 8.46, p=0.009]

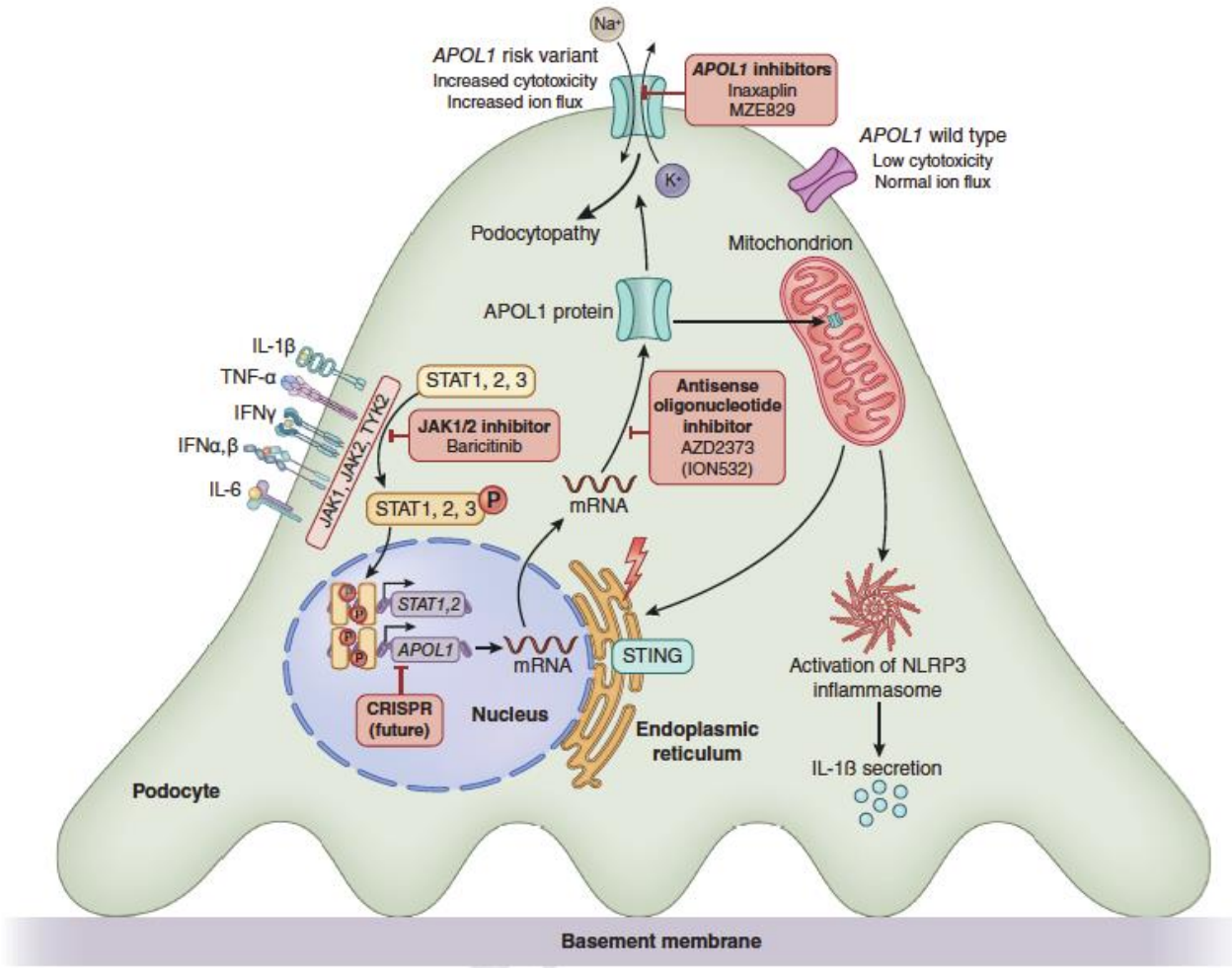
aHR: adjusted Hazard Ratio, **CG:** collapsing glomerulopathy, **CI:** confidence interval, **KRV:** kidney-risk variants

Conclusions:

Donor APOL1 KRVs confer a dose-dependent risk for CG, but only 2 KRVs impact graft survival. Identifying other risk factors may improve kidney use from Black donors.

Ibrahim Batal, Alexei V. Mikhailov, Syed A. Husain, et al. Association of Collapsing Glomerulopathy with Donor APOL1 Risk Variants in Kidney Allografts from Black Donors. 2025, CJASN DOI: 10.2215/CJN.0000000778
Visual Abstract by: Alejandro García-Rivera, MD

Investigational Therapies for APOL1-Mediated Kidney Disease



- **Inaxaplin and MZE829:** Blocks APOL1 cation transport function → reduced proteinuria
- **JAK inhibitors:** Suppress interferon-induced APOL1 expression
- **AZD2373:** antisense oligonucleotides → block APOL1 protein expression
- Other

The NEW ENGLAND JOURNAL of MEDICINE

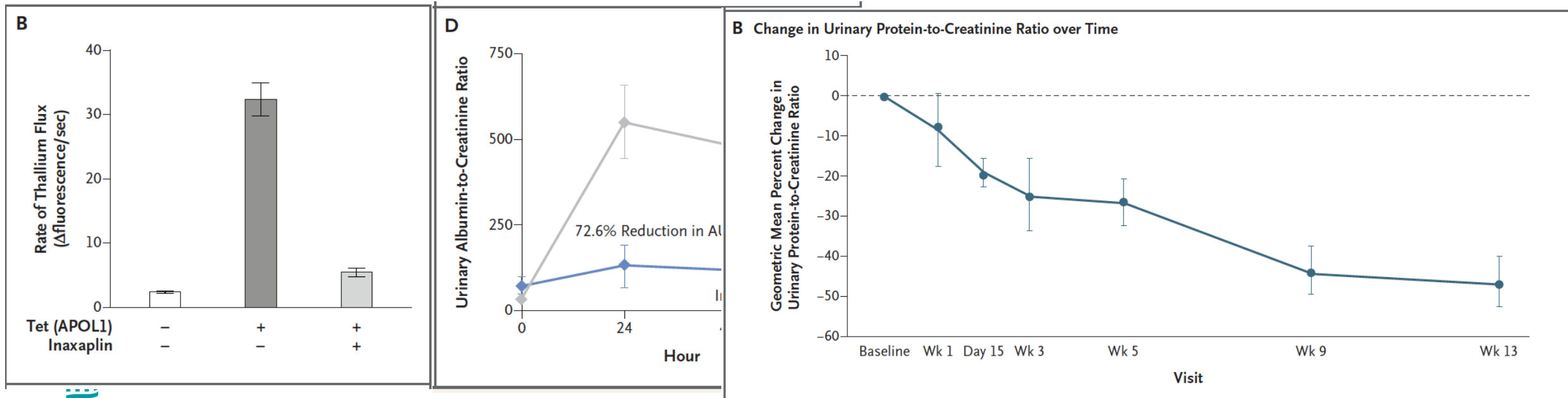
ESTABLISHED IN 1812

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Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

O. Egbuna, B. Zimmerman, G. Manos, A. Fortier, M.C. Chirieac, L.A. Dakin, D.J. Friedman, K. Bramham, K. Campbell, B. Knebelmann, L. Barisoni, R.J. Falk, D.S. Gipson, M.S. Lipkowitz, A. Ojo, M.E. Bunnage, M.R. Pollak, D. Altshuler, and G.M. Chertow, for the VX19-147-101 Study Group*



Question #2

True or False:

APOL1 genotype explains all of the racial disparity in rates of kidney disease?



Health Disparities & Ethical Considerations

- Important to avoid mislabeling APOL1 as a "Black kidney gene"
- APOL1 variants relate to ancestry, not race per se
- Need for careful counseling on genetic results to avoid stigma



Question #2

True or False:

APOL1 genotype explains all of the racial disparity in rates of kidney disease?

False



Case Vignette

39 year old non-diabetic African American male with history of hypertension and FSGS presents for routine follow up visit. His proteinuria is stable at 0.8g/day. However, his eGFR has been declining over the past 3 years from 45 to 35 despite optimal BP management with lisinopril and chlorthalidone.

1.He asked the following questions:

Case Questions:

- 1.Likelihood of HR APOL1? (~13% in African Americans)
- 2.Should you test? Reasonable, especially with FSGS pattern of injury
- 3.Does HR APOL1 impact CKD progression? Yes, higher risk of progression
- 4.New interventions? Clinical trials with Inaxaplin, AZD2373, JAK inhibitors; supportive measures (BP, RAAS block)



Board Peals

- APOL1 G1 and G2 variants → major risk factor for FSGS, COVAN, HIVAN and certain non-diabetic CKD
- Disease inheritance is recessive (two hits needed)
- High-risk genotype accelerates CKD progression
- Deceased donor HR APOL1 → poorer transplant outcomes
- No strong evidence for incident diabetic nephropathy association



Take Home Messages

1. *APOL1* variants explain much of the excess risk of kidney disease in Black Americans
2. Clinical utility of genotyping evolving—important in certain CKD, transplant contexts
3. New therapies on the horizon targeting *APOL1* expression/function



CLINICAL TRIALS

| Clinical Trials | Study Overview | Contact information |
|---|--|--|
| Jak-STAT Inhibition to Reduce AMKD (JUSTICE Trial) (Sponsor: NIH) | A phase 2, double-blind, randomized, placebo-controlled study of baricitinib in patients with FSGS or HTN-CKD. | www.kidneycareandjustice.com ; (Clinicaltrials.gov; NCT05237388) |
| Adaptive Study of Vx-147 in Adults and Adolescents With AMKD (Sponsor: Vertex) | A phase 2/3, Double-blind, randomized, placebo-controlled study of Vx-147 in patients with AMKD. | (Clinicaltrials.gov; NCT05312879) |
| APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO) (Sponsor: NIH) | Prospectively assess the effects of RRVs APOL1 on outcomes for kidney transplantation. | (Clinicaltrials.gov; NCT03615235) |
| AZD2373 (APPRECIATE) (Sponsor: AstraZeneca) | A phase 2, Double-blind, randomized, placebo-controlled study of AZD2373 in patients with AMKD. | (Clinicaltrials.gov; NCT06824987) |



Key References

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- APOL1 risk variants, race, and progression of chronic kidney disease, NEJM 2013; PMID: 24206458
- Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice, Nat. Med 2017; PMID: 28218918
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- APOL1 kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases, PNAS 2016; PMID 26699492
- Innate immunity pathways regulate the nephropathy gene APOL1, Kidney international 2015; PMID 25100047
- JAK inhibition blocks COVID-19-induced JAK/STAT/APOL1 signaling in glomerular cells and podocytopathy in human kidney organoids, JCI Insight; PMID: 35472001
- Inaxaplin for proteinuric kidney disease in persons with two APOL1 variants, NEJM, 2023; PMID: 36920755
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- The APOL1 genotype of African American kidney transplant recipients does not impact 5-year allograft survival, Am J Transplant, 2012; PMID: 22487534
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- Genetic Inhibition of APOL1 Pore-Forming Function Prevents APOL1-Mediated Kidney Disease, JASN 2023; PMID: 37798822
- Strong protective effect of the APOL1 p.N264K variant against G2-associated FSGS and kidney disease, Nat Commun 2023; PMID: 38036523
- APOL1-mediated monovalent cation transport contributes to APOL1-mediated podocytopathy in kidney disease, JCI, 2024; PMID:38227370
- Collapsing Glomerulopathy in the Allografts is Associated with Donor APOL1 Risk Variants and Upregulation of Autophagy Pathway, CJASN, PMID:40622771
- APOL1 kidney disease: conclusions from a Kidney Disease:Improving Global Outcomes (KDIGO) Controversies Conference, Kidney Int., 2025; PMID: 40582702

