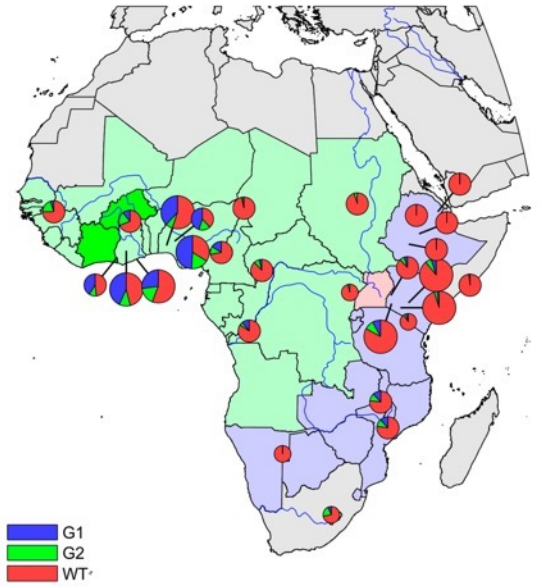
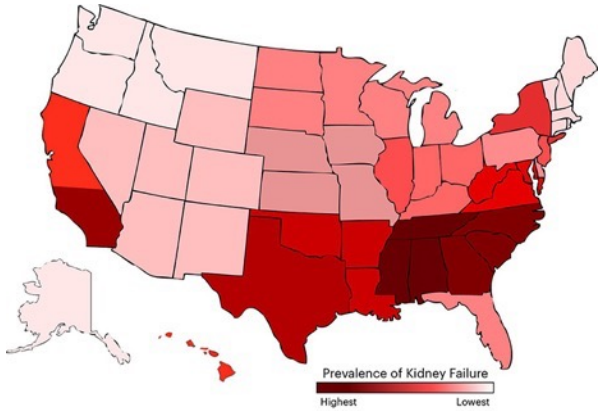
APOL1 Kidney Disease:
Seeking insight into Mechanisms

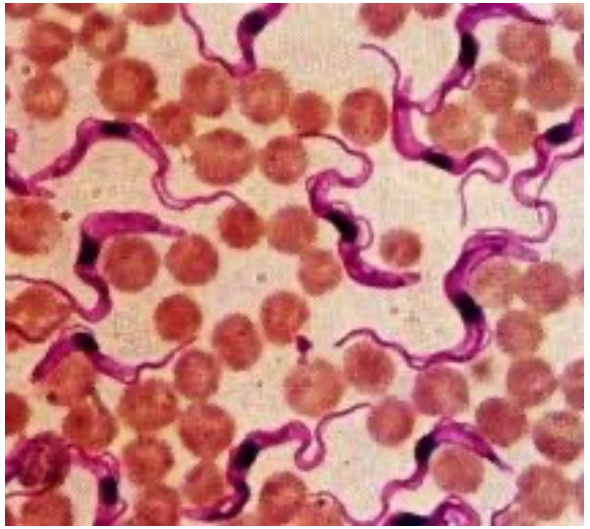
David Friedman

4/26/2024

KDIGO Controversies







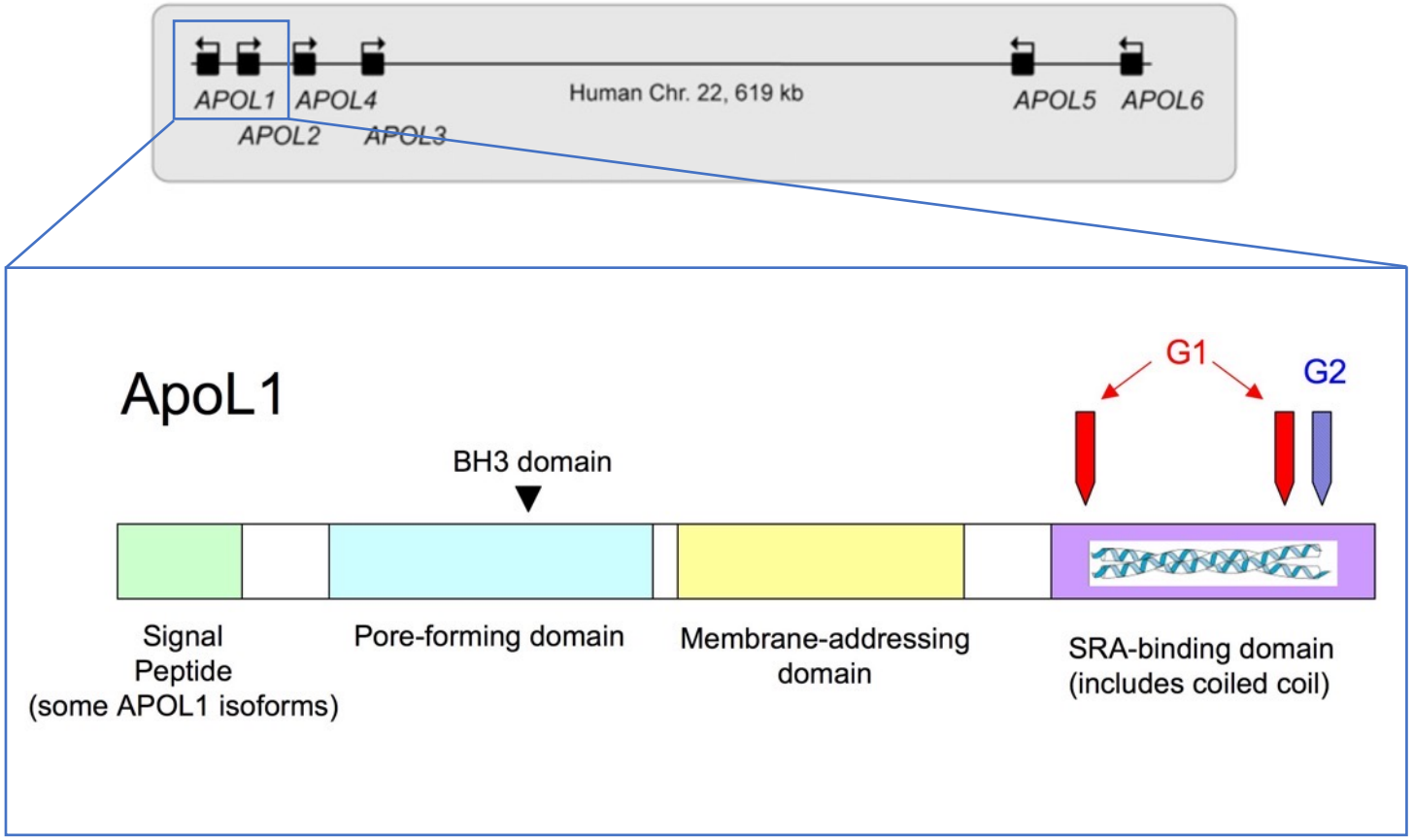
Disclosures

- Patents related to APOL1
- Research funding from and consulting for Vertex

Major themes:

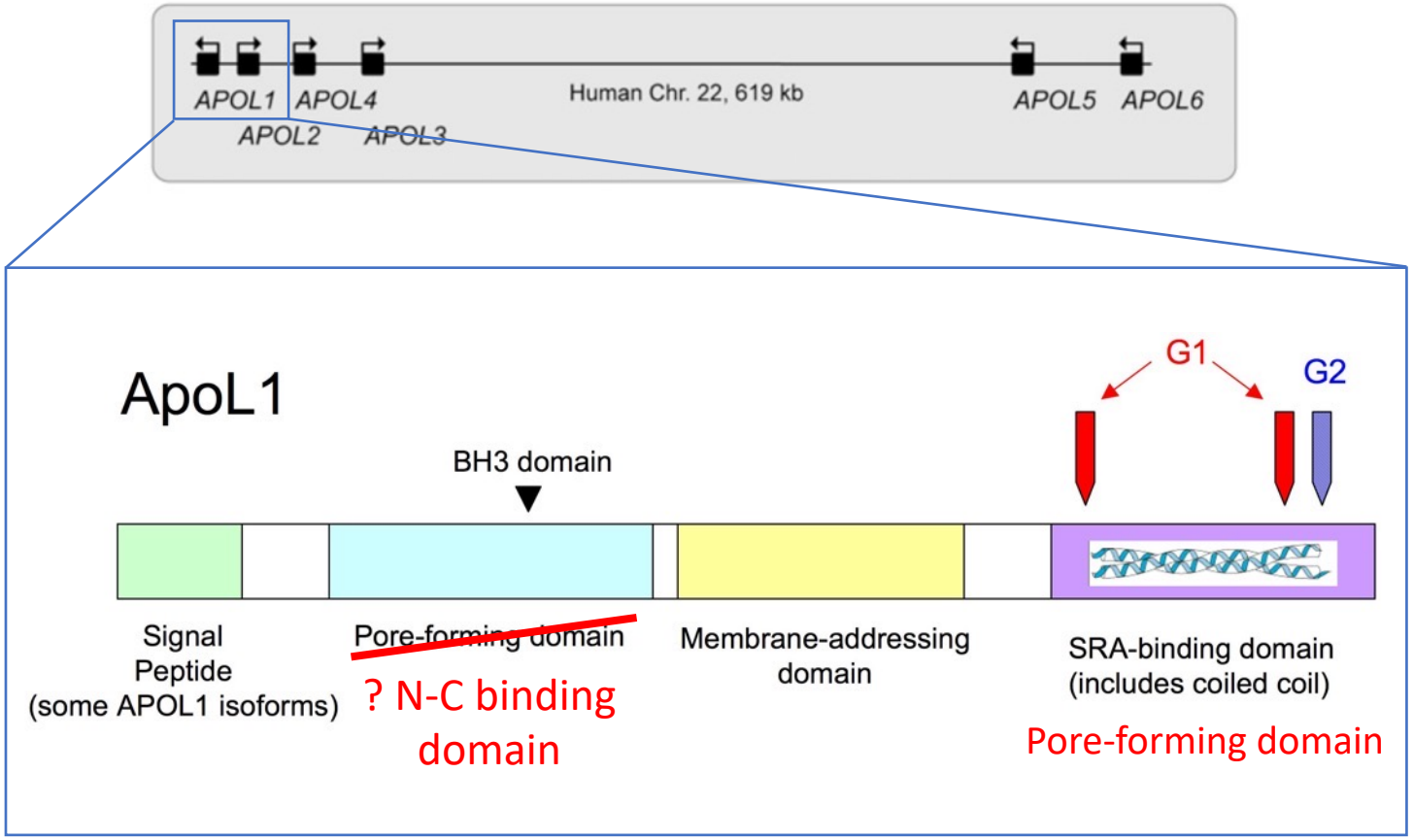
- APOL1 is an innate immunity gene
- Recessive, gain-of-function toxicity
- Why so many phenotypes?

APOL1 Basics



- Circulates on HDL3
- Expressed in many tissues, especially blood vessels
- In the kidney, protein found primarily in podocytes and the microvasculature, +/- tubules

APOL1 Basics



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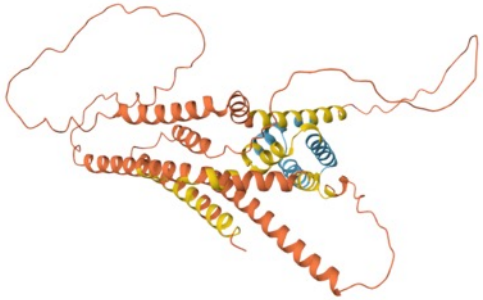
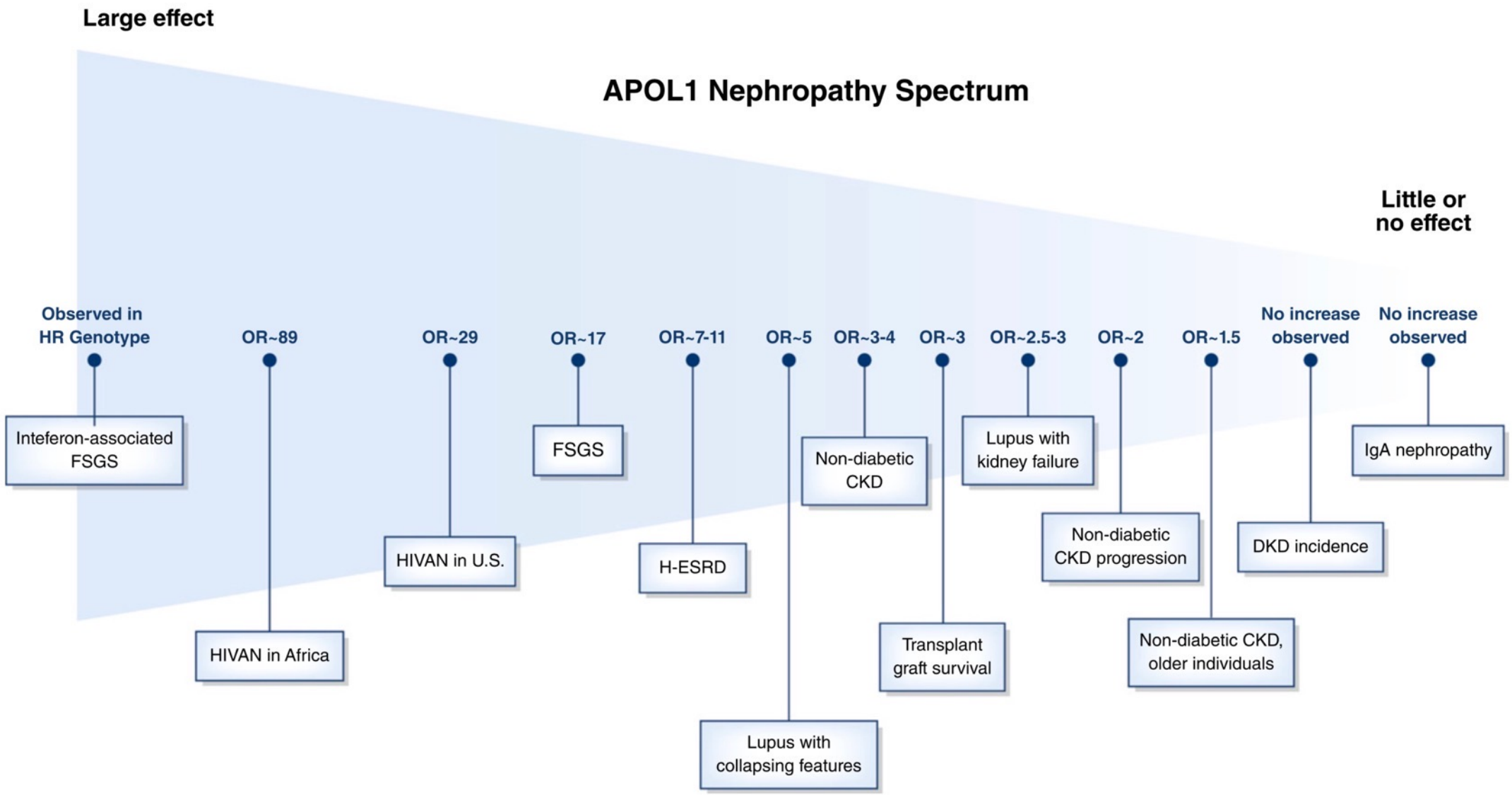
APOL1



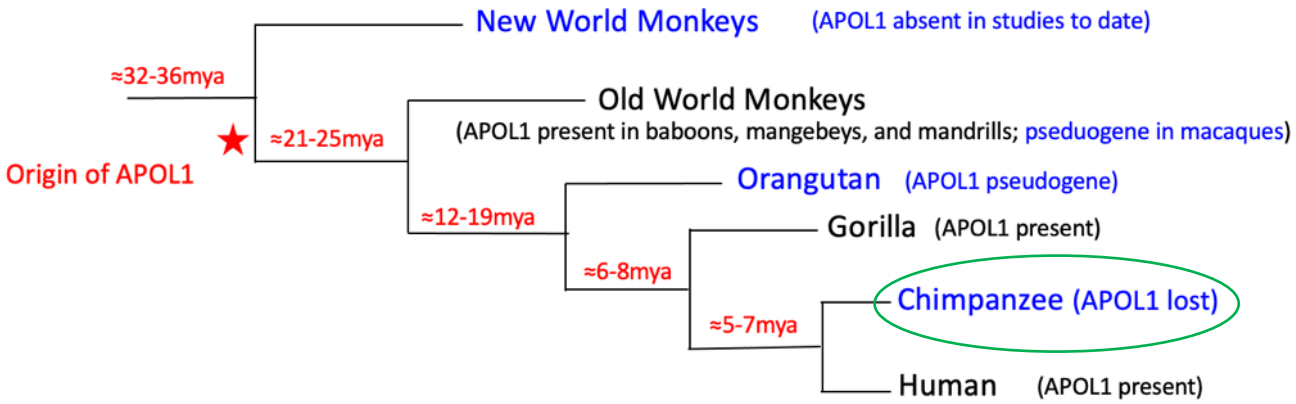
- 50-60% of African Americans have at least one copy of G1 and/or G2; much more variable among Africans
- Recessive mode of inheritance
- 12-15% of African Americans (~5 million individuals) are high-risk homozygotes
- Variants nearly absent in populations without African ancestry
- Unusually large effect size for common variants

APOL1 Nephropathy: one gene, many phenotypes



Friedman and Pollak CJASN 2020

APOL1 is not a “kidney” gene



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Human *Trypanosoma evansi* Infection Linked to a Lack of Apolipoprotein L-I

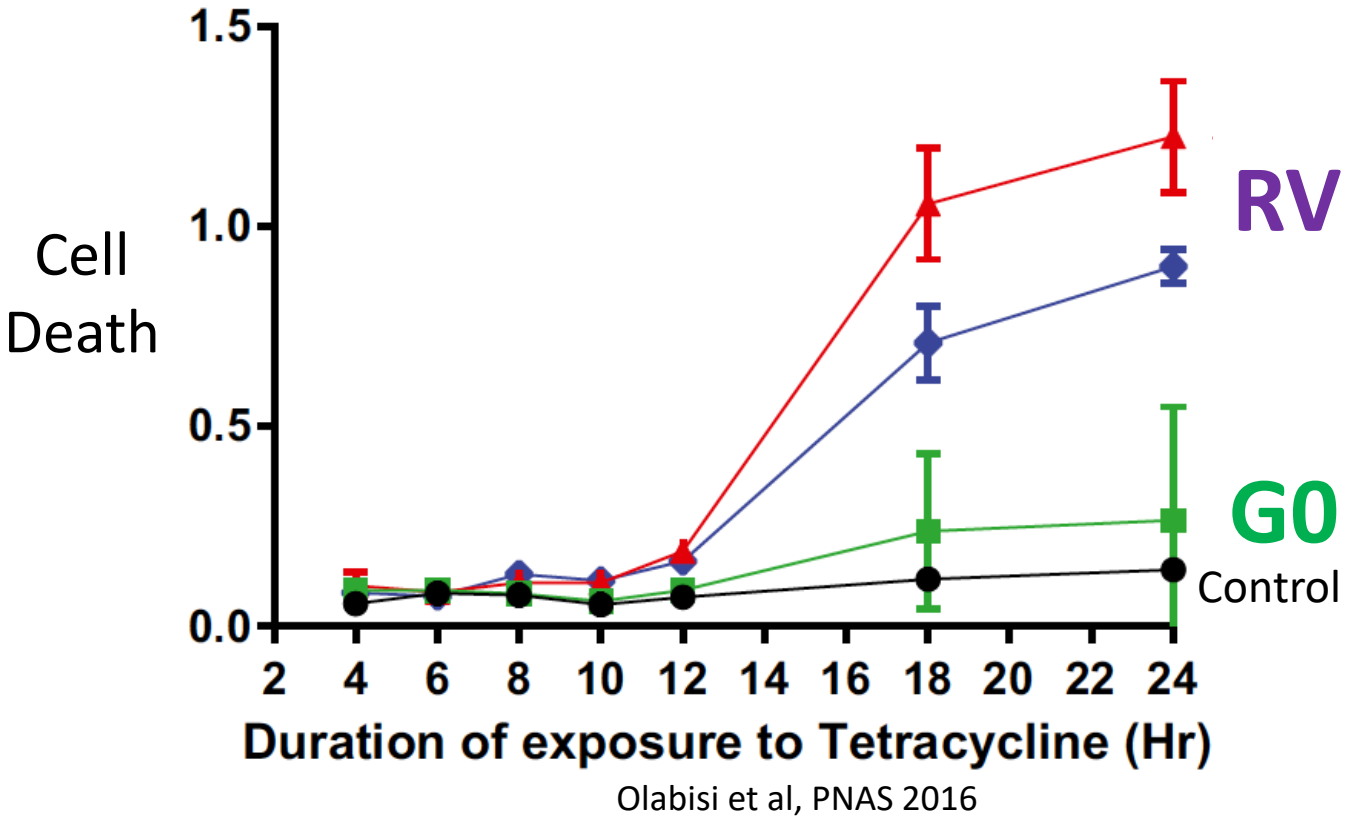
Benoit Vanhollebeke, Eng., Philippe Truc, Ph.D., Philippe Poelvoorde, M.Sc., Annette Pays, M.Sc., Prashant P. Joshi, M.D., Ravindra Katti, M.D., Jean G. Jannin, M.D., and Etienne Pays, Ph.D.

SUMMARY

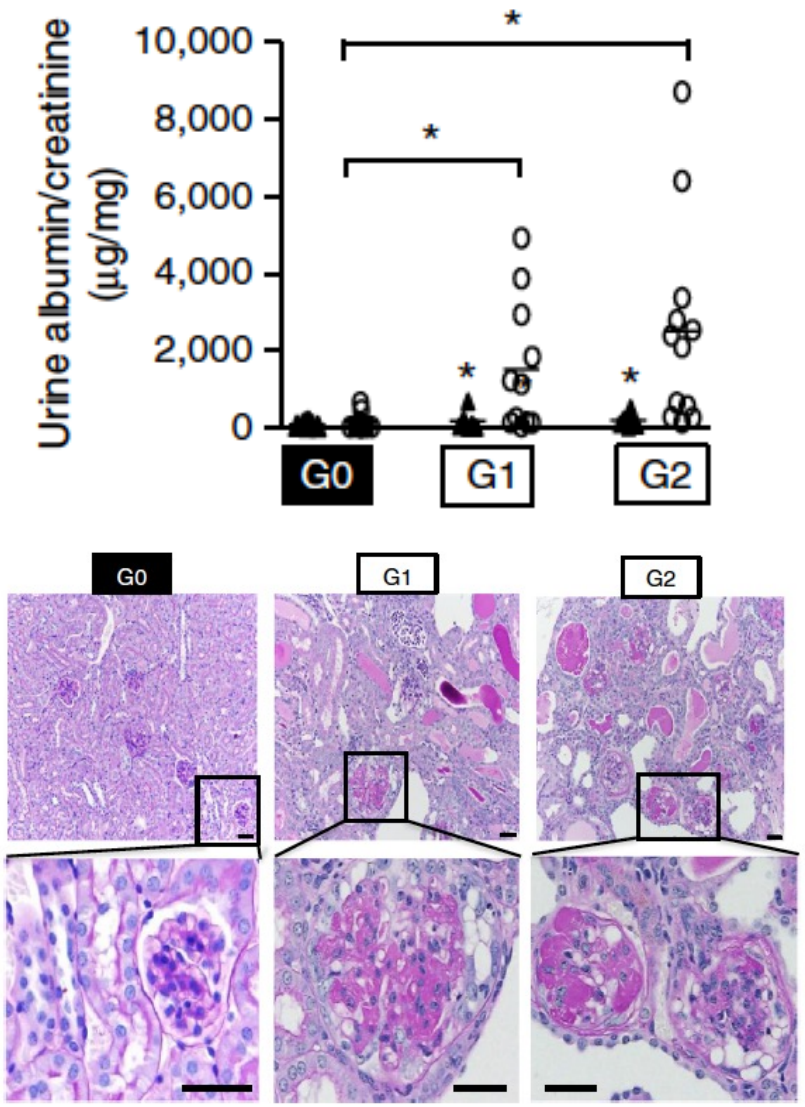
Humans have innate immunity against *Trypanosoma brucei brucei* that is known to involve apolipoprotein L-I (APOL1). Recently, a case of *T. evansi* infection in a human was identified in India. We investigated whether the APOL1 pathway was involved in this occurrence. The serum of the infected patient was found to have no trypanolytic activity, and the finding was linked to the lack of APOL1, which was due to frameshift mutations in both *APOL1* alleles. Trypanolytic activity was restored by the addition of recombinant APOL1. The lack of APOL1 explained the patient's infection with *T. evansi*.

Not required in mammals or humans for kidney development or function

G1 and G2 are toxic, gain-of-function variants

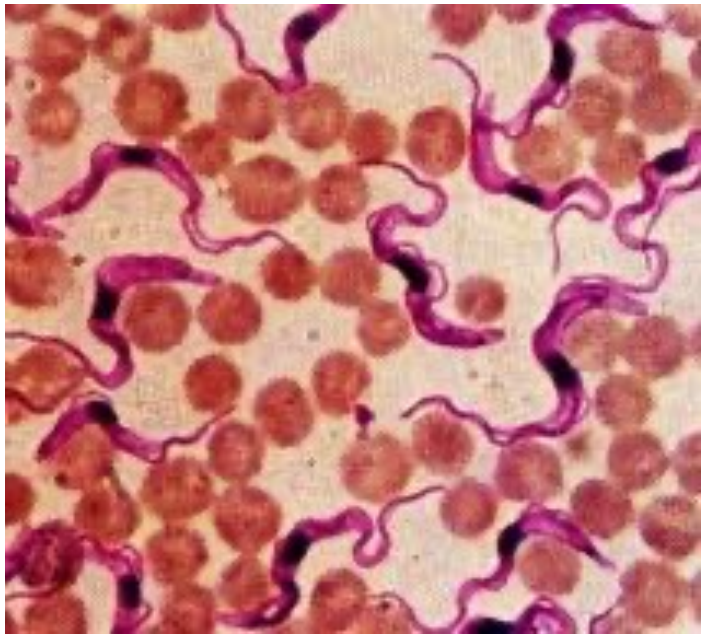


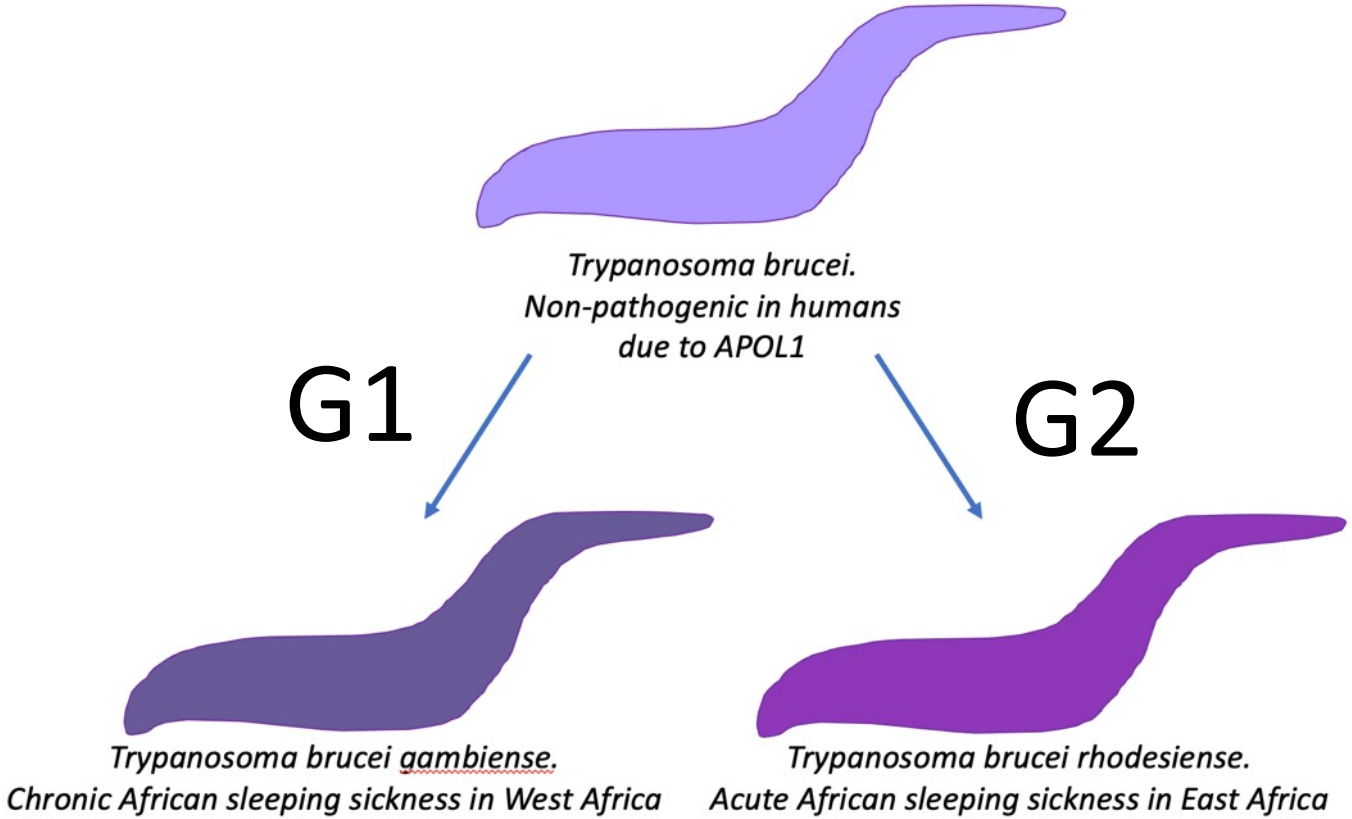
Olabisi et al, PNAS 2016



Beckerman et al, Nat Med 2017

1. What does APOL1 do?
2. Why are these highly deleterious risk variants so common?

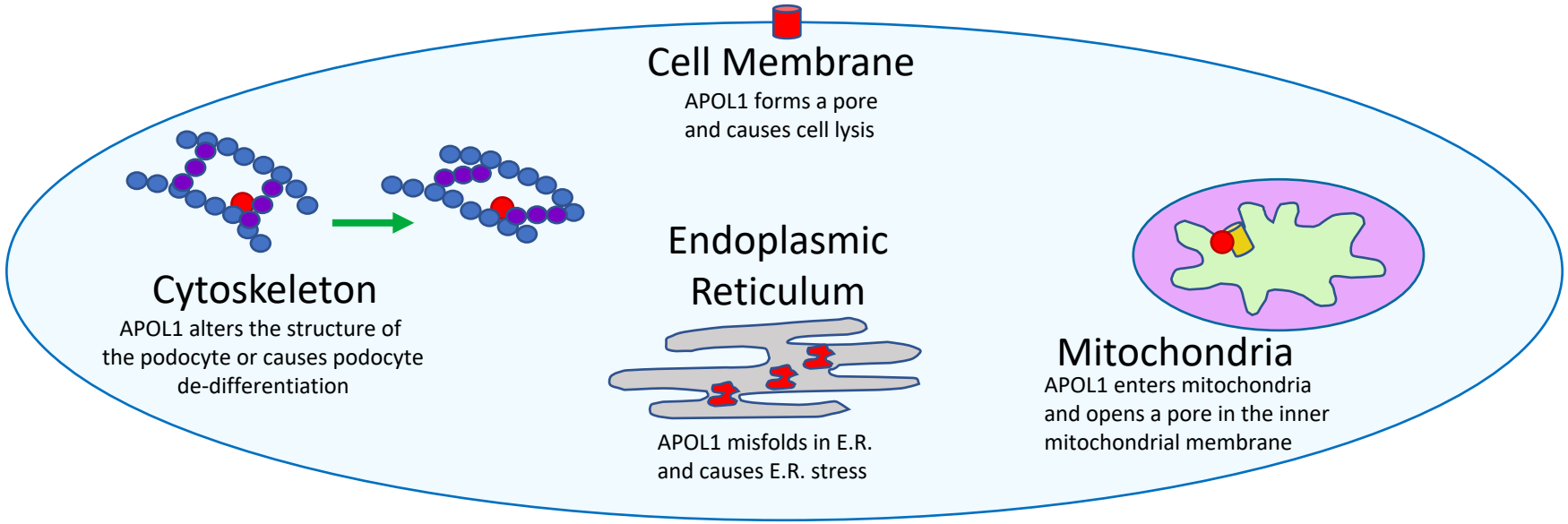




APOL1 risk variants protect against African trypanosomiasis

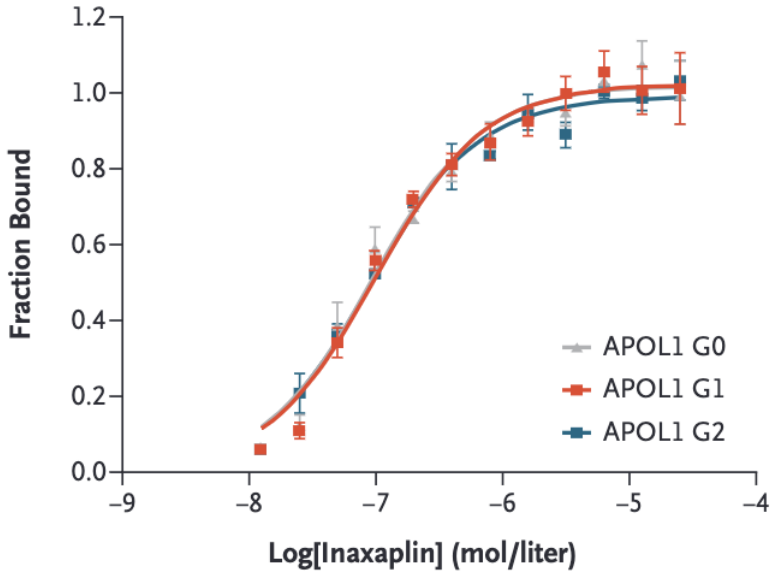
Understanding Mechanism of Disease:

How does the behavior of risk variant APOL1 differs from G0?

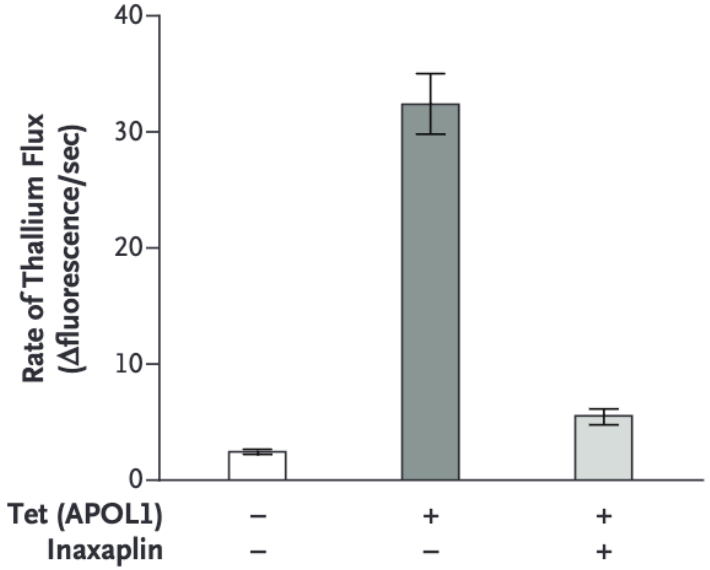


Cell consequences

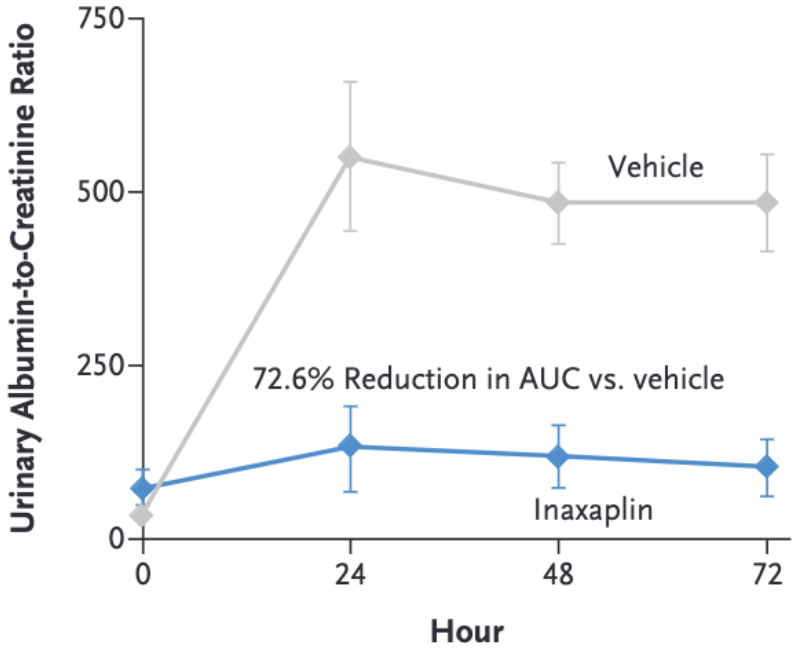
Inaxaplin:



Binds APOL1



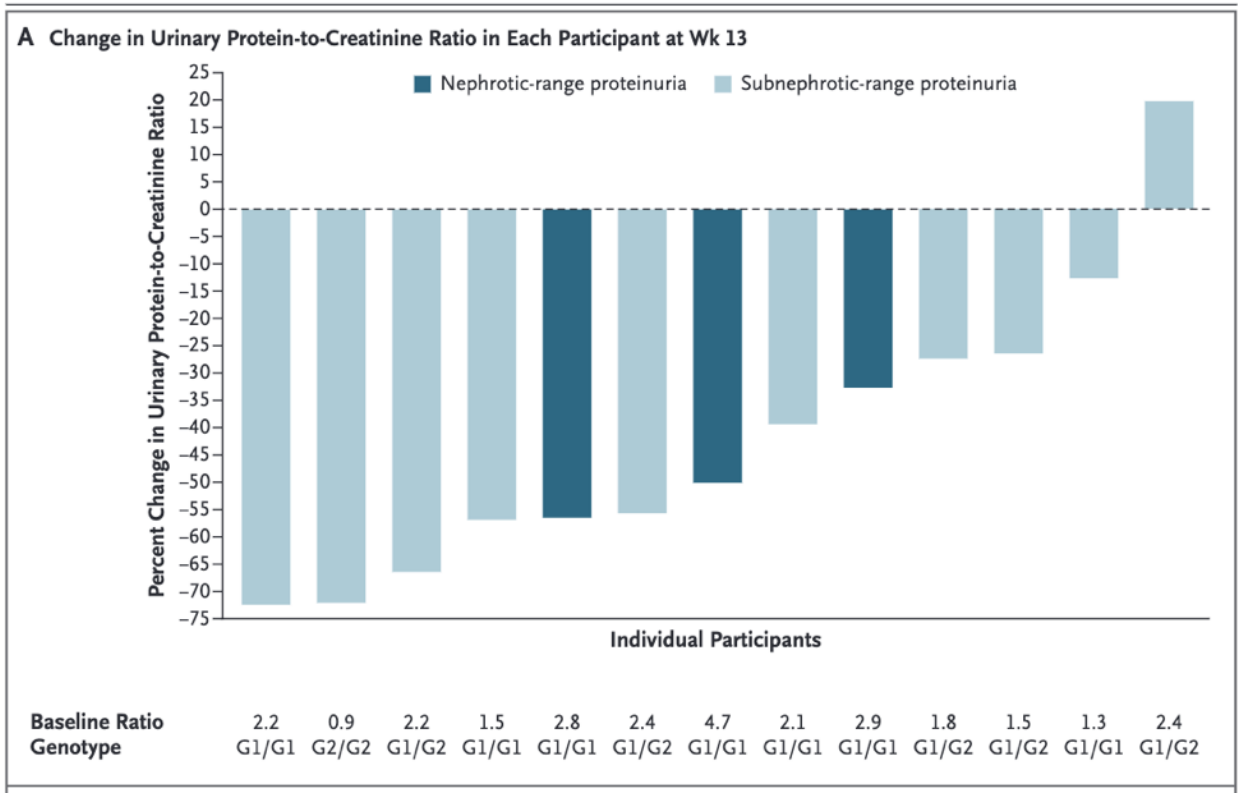
Blocks Cation Flux

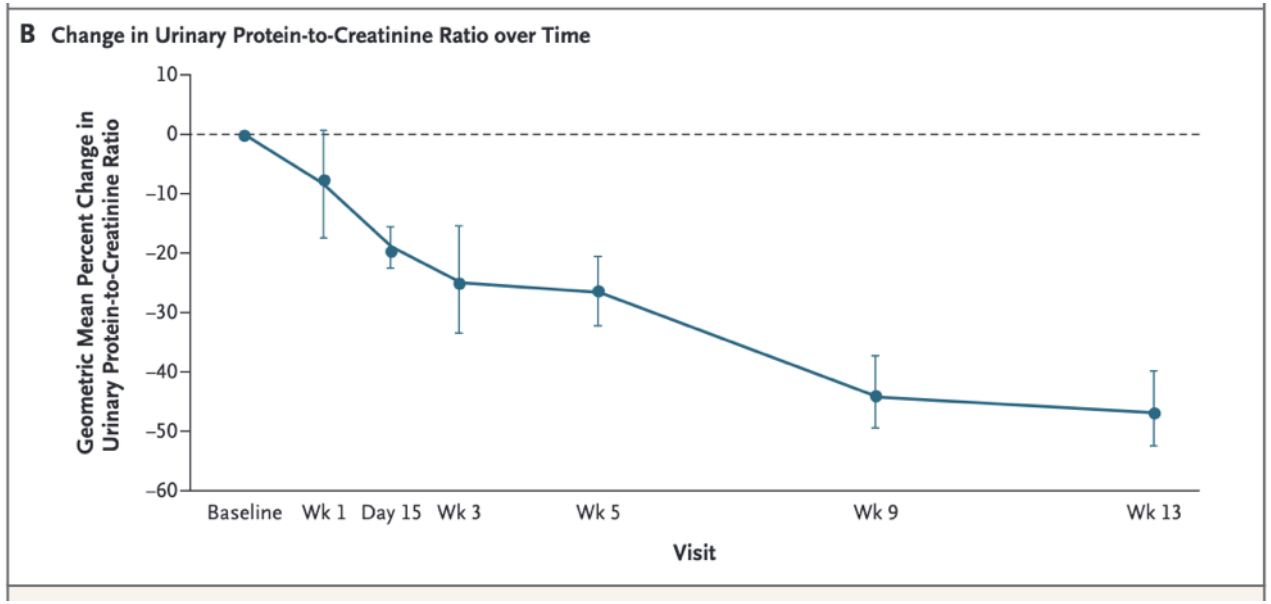


Reduces Proteinuria

Egbuna et al., NEJM 2023

Inaxaplin:

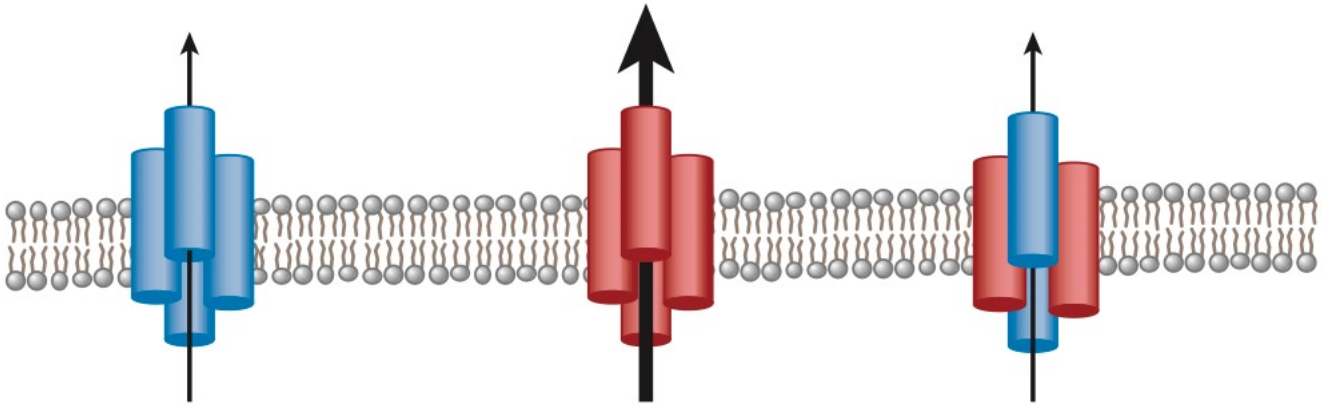




Reduces proteinuria in FSGS

Egbuna et al., NEJM 2023

Understanding recessive, gain-of-function toxicity

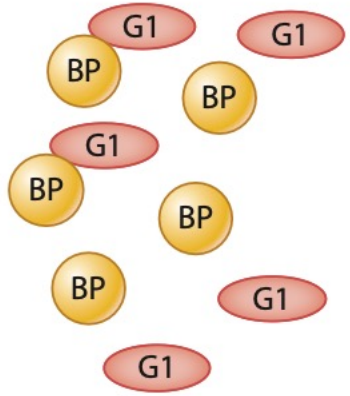


G0 channels:
low flux

RV channels:
high flux

Mixed channels:
low flux

G0 rescue model



2 RV alleles required
to exceed toxicity threshold

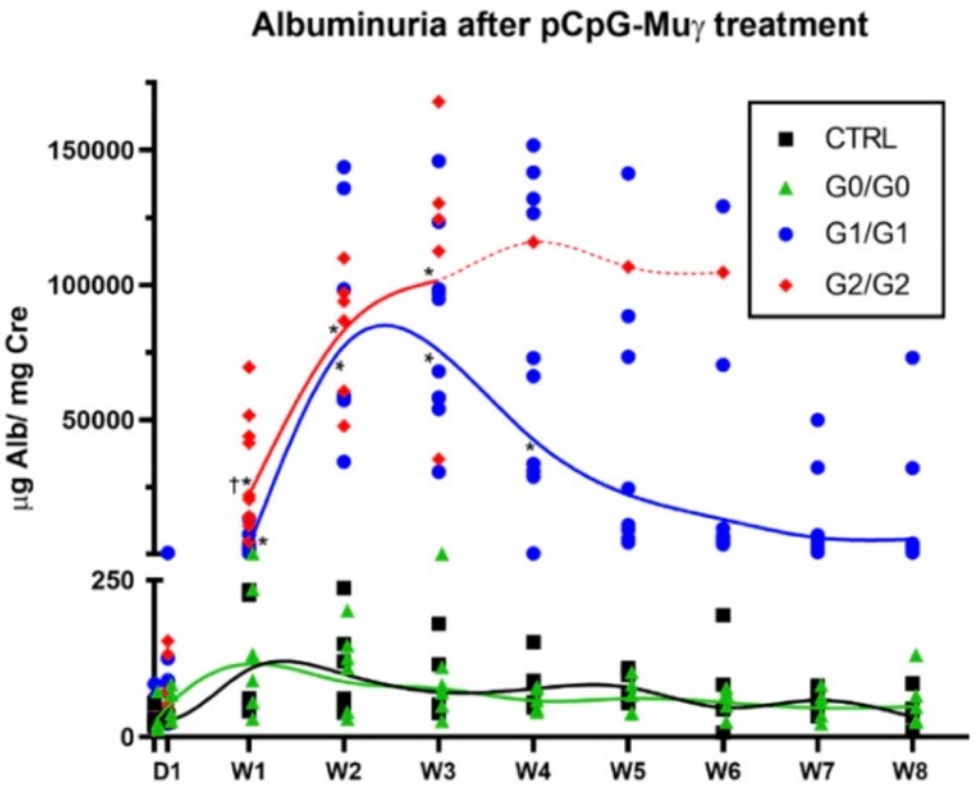
Threshold model

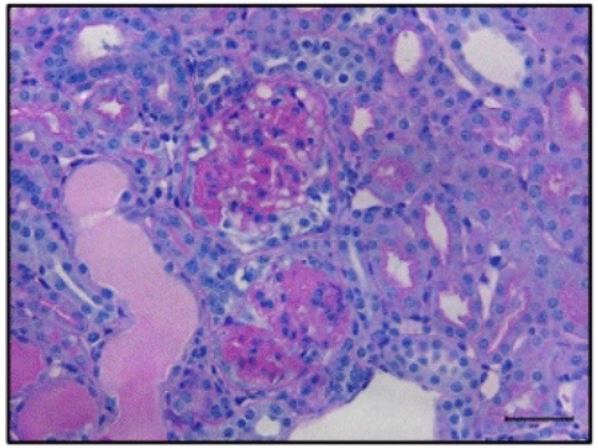
BAC-transgenic APOL1 Mouse

Mouse with full human APOL1 seq.

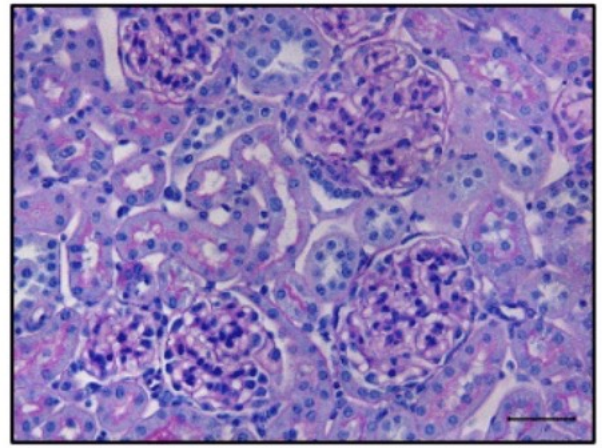
+

Plasmid for interferon-γ





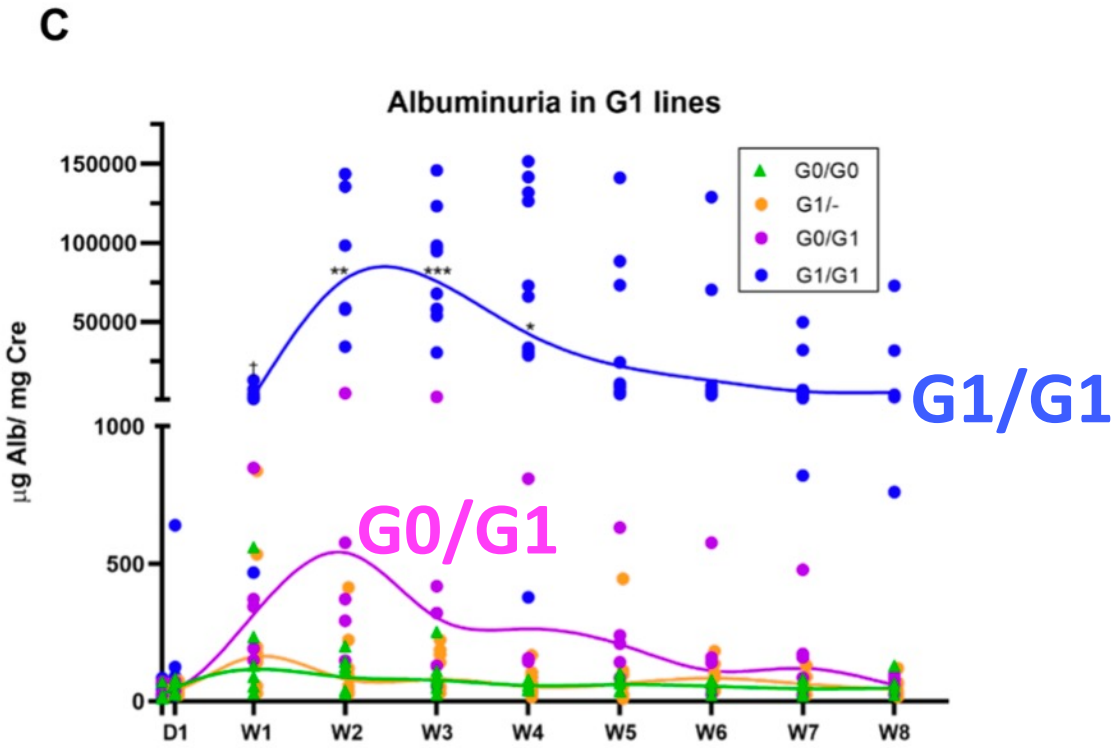
G2/G2 mouse

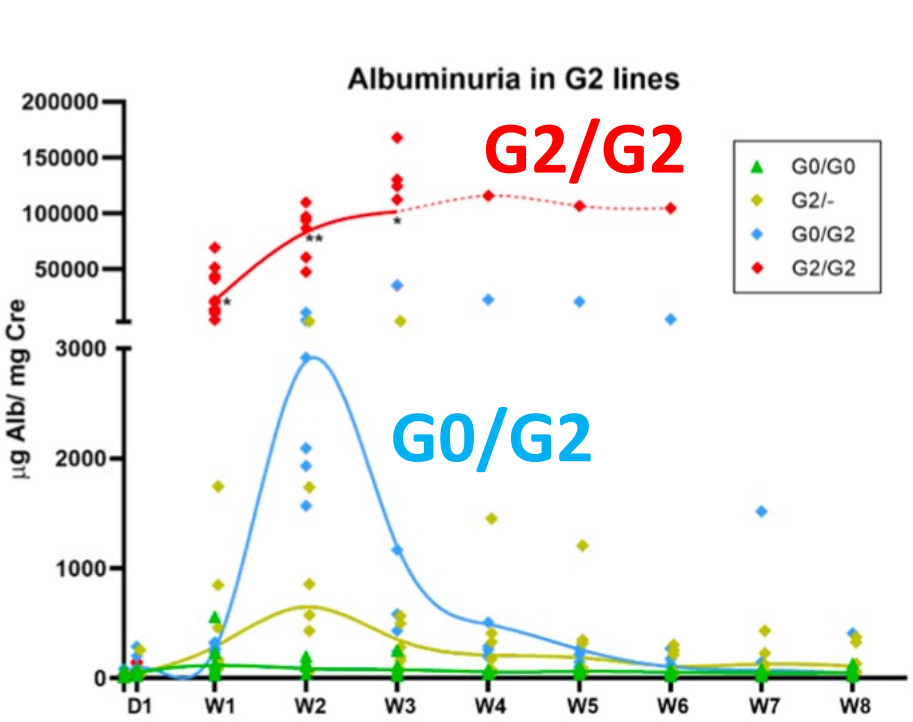


G0/G0 mouse

Gizelle McCarthy/Angelo Blasio, DMM 2021

Dosage effects vs. G0 rescue models

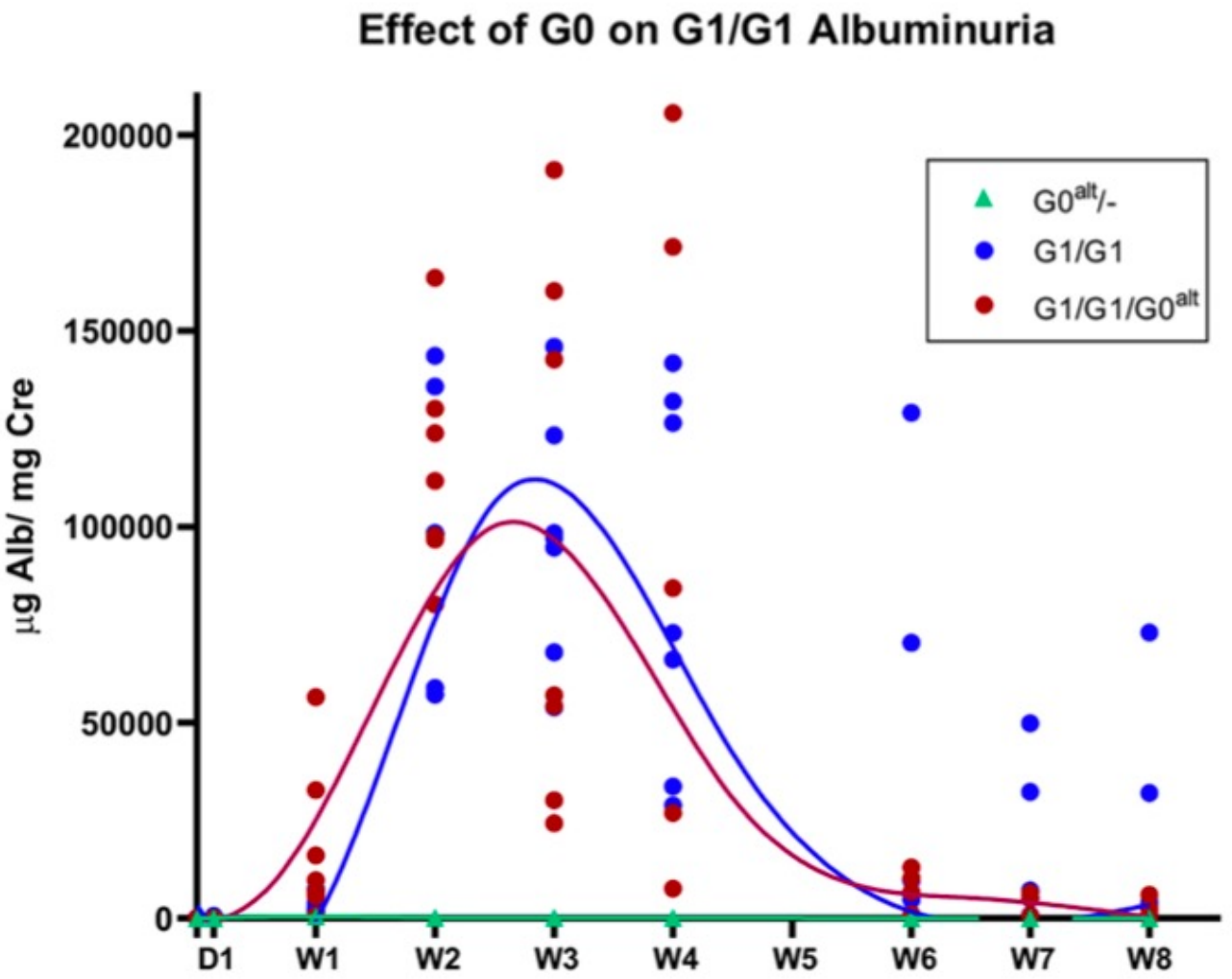




RV/RV: severe disease
RV/- (hemizyogte, 1 RV): trace disease
RV/G0: mild disease compared to RV/RV
G0/G0: no disease

Gizelle McCarthy/
Angelo Blasio, DMM 2021

Experiments have not supported rescue model



Gizelle McCarthy/Angelo Blasio, DMM 2021

A Tale of Two Mice

A Tale of Two Mice

2 APOL1 G2 copies

~28 APOL1 G2 copies

No disease ← baseline → No disease

Severe disease ← Interferon treatment → Lethal in 2-3 days

A Tale of Two Mice

No disease ← baseline → No disease

Severe disease ← Interferon treatment → Lethal in 2-3 days

HR Genotype + elevated expression + 3rd factor?

One gene, many phenotypes

High-risk APOL1 genotype

Sudden onset/insidious

Nephrotic/non-proteinuric

Rapid/slow GFR loss

Glomerular/vascular

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<u>Explanations</u>

Genetic Modifiers?

Different Triggers?

Cell types?

Organelles?

Pathways?

Multiple mechanisms?