APOL1 Kidney Disease: Seeking insight into Mechanisms

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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
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- Circulates on HDL3
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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

Large effect

APOL1 Nephropathy Spectrum

Observed in HR Genotype

Interferon-associated FSGS

HIVAN in Africa

OR-89

HIVAN in U.S.

OR-29

OR-17

OR-7:11

OR-5

OR-3:4

OR-3

OR-2.5:3

OR-2

OR-1.5

No increase observed

No increase observed

FSGS

Non-diabetic CKD

Lupus with kidney failure

Non-diabetic CKD progression

Non-diabetic CKD, older individuals

Transplant graft survival

DKD incidence

Lupus with collapsing features

Friedman and Pollak CJASN 2020
APOL1 is not a “kidney” gene.

Not required in mammals or humans for kidney development or function.
G1 and G2 are toxic, gain-of-function variants

Beckerman et al, Nat Med 2017

Cell Death

Duration of exposure to Tetracycline (Hr)

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 Membrane
APOL1 forms a pore and causes cell lysis

Cytoskeleton
APOL1 alters the structure of the podocyte or causes podocyte de-differentiation

Endoplasmic Reticulum
APOL1 misfolds in E.R. and causes E.R. stress

Mitochondria
APOL1 enters mitochondria and opens a pore in the inner mitochondrial membrane

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**

**Threshold model**

2 RV alleles required to exceed toxicity threshold
BAC-transgenic APOL1 Mouse

Mouse with full human APOL1 seq.

Plasmid for interferon-γ

Albuminuria after pCpG-Muγ treatment

CTRL
G0/G0
G1/G1
G2/G2

G2/G2 mouse

G0/G0 mouse

Gizelle McCarthy/Angelo Blasio, DMM 2021
Dosage effects vs. G0 rescue models

RV/RV: severe disease
RV/- (hemizygote, 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
A Tale of Two Mice
A Tale of Two Mice

2 APOL1 G2 copies
No disease
Severe disease
Interferon treatment
Lethal in 2-3 days

~28 APOL1 G2 copies
No disease
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
One gene, many phenotypes

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- Sudden onset/insidious
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Explanations
- Genetic Modifiers?
- Different Triggers?
- Cell types?
- Organelles?
- Pathways?

Multiple mechanisms?