APOL1
The End of the Beginning

ACOI 2022

John Prior

Disclosures

Nothing to disclose

Josh 1988

Josh was a 24 yo African American man who presented to the hospital for swelling of his extremities for 1 month

No PMH

Social hx – heroin addiction and IVDA. Little ETOH. No tobacco. Heterosexual with multiple partners

Family hx of HTN in mother (Sharon), father (Ron) and sister (Karen)

According to his mother he was preterm 5 lb baby with pre-eclampsia

Josh

On exam – BP 170/110. chronically ill. He appeared to have edema to his thighs and pleural effusions (confirmed on Xray). Fundi Grade 1

Labs : creatinine 1.5, mild pancytopenia

Urine showed +4 protein and rare granular casts

Studies : US showed 14 cm echo dense kidneys

Josh

We sent various serologies and treated his HTN with loop diuretics and enalapril with some success

What did we think Josh had and what did we do to diagnose?

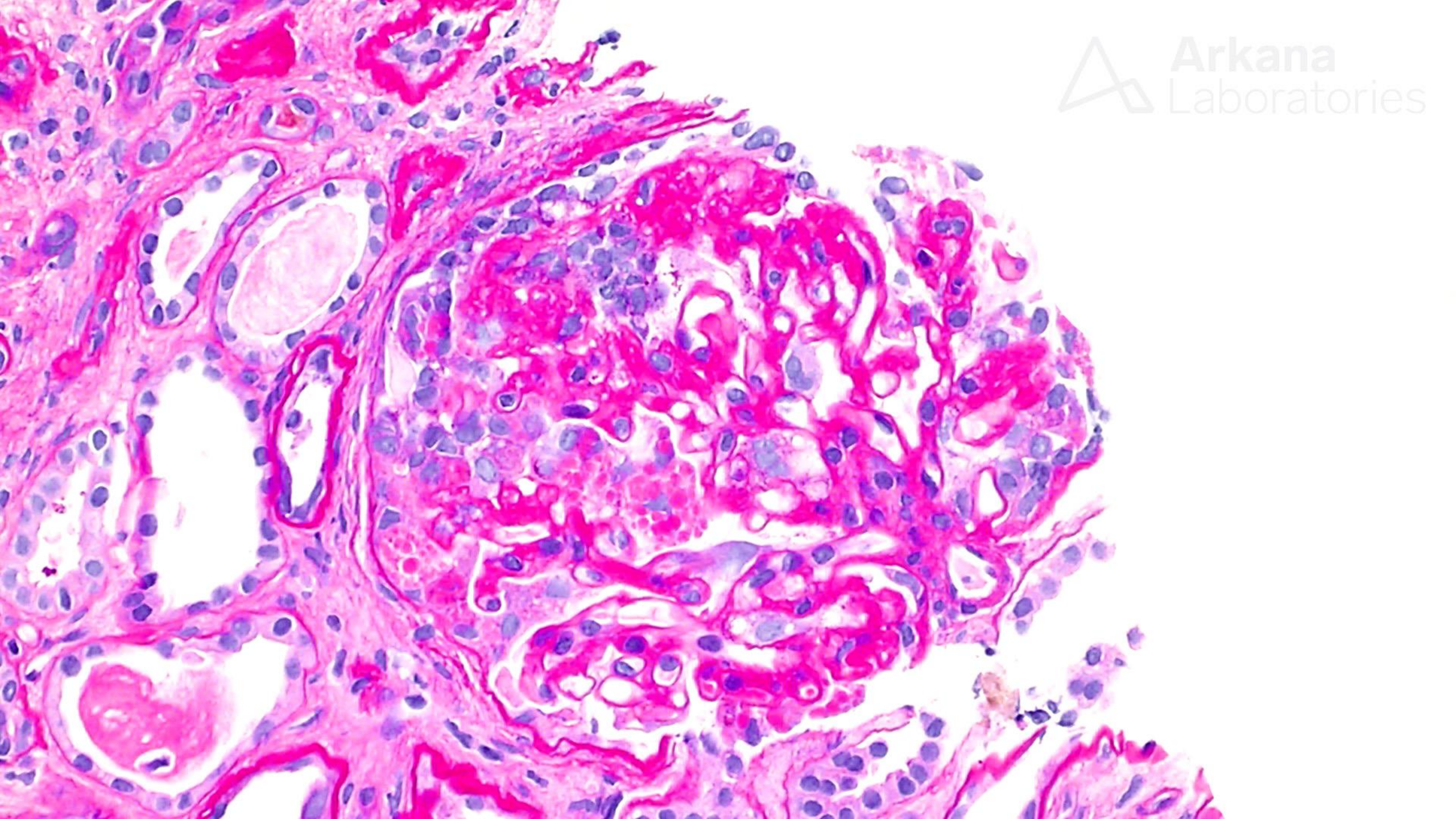
What glomerular disease does this patient have?

1. Focal segmental glomerulosclerosis
2. Amyloidosis
3. Diabetic glomerulosclerosis
4. Minimal change
5. Membranous

Josh

Serologies – Hep B surface Ag +, RPR -, ANA -, HIV + confirmed by Western blot

A biopsy was performed with angiographic guidance


Arkana
Laboratories

What glomerular disease does this patient have?

1. **Focal segmental glomerulosclerosis**
2. Amyloidosis
3. Diabetic glomerulosclerosis
4. Minimal change
5. Membranous

Josh

Clinical course – Josh was treated with enalapril and furosemide with better control of HTN

ID placed him on adjusted AZT

No hospitalizations but when he returned to clinic in 8 weeks his creatinine was now 14

Rebiopsy – global sclerosis and fibrosis no inflammation

Placed on hemodialysis via TVC and fistula placed

Kidney Disease on African Americans

Rates of CKD much higher in African Americans

Progression of CKD tends to be more severe

Risk of ESKD is 2X risk of general population (adjusted for known risks)

Many types of CKD have an accelerated course

Why?

Socioeconomics and access to care are only part of the story

History of APOL 1

MYH9 (myosin heavy chain 9) mutations were discovered and seemed to be associated with AA kidney disease – chromosome 22

1997 APOL 1 was discovered on chromosome 22.

Both MYH9 variants and APOL1 are closely associated genetically and further work (2010) variants of APOL1 (G1 and G2) were discovered and an association with CKD shown

Since that time much work has been done to define and solidify the association in CKD in African Americans

APOL1 Biology

Apolipoproteins play a role in lipid transport. Six types

APOL1 is expressed on many cells and serum

APOL1 made by the liver and associated with HDL in the serum

APOL1 is seen only in humans and a few non-human primates (gorillas)

APOL1 – Why is it important?

It exists as wild type (G0) and 2 variants (G1 and G2)

APOL1 is directly toxic to Trypanosomal disease (sleeping sickness) causing cell lysis

Trypanosomes have developed resistance to G0 but not to G1 or G2 so evolutionary pressure favoring G1 and G2 is high

Trypanosomal disease predominates in Central and West Africa and thus the G1/G2 variants originate from here

ABSENT IN POPULATIONS WITHOUT RECENT AFRICAN ORIGIN (last 1000 years)

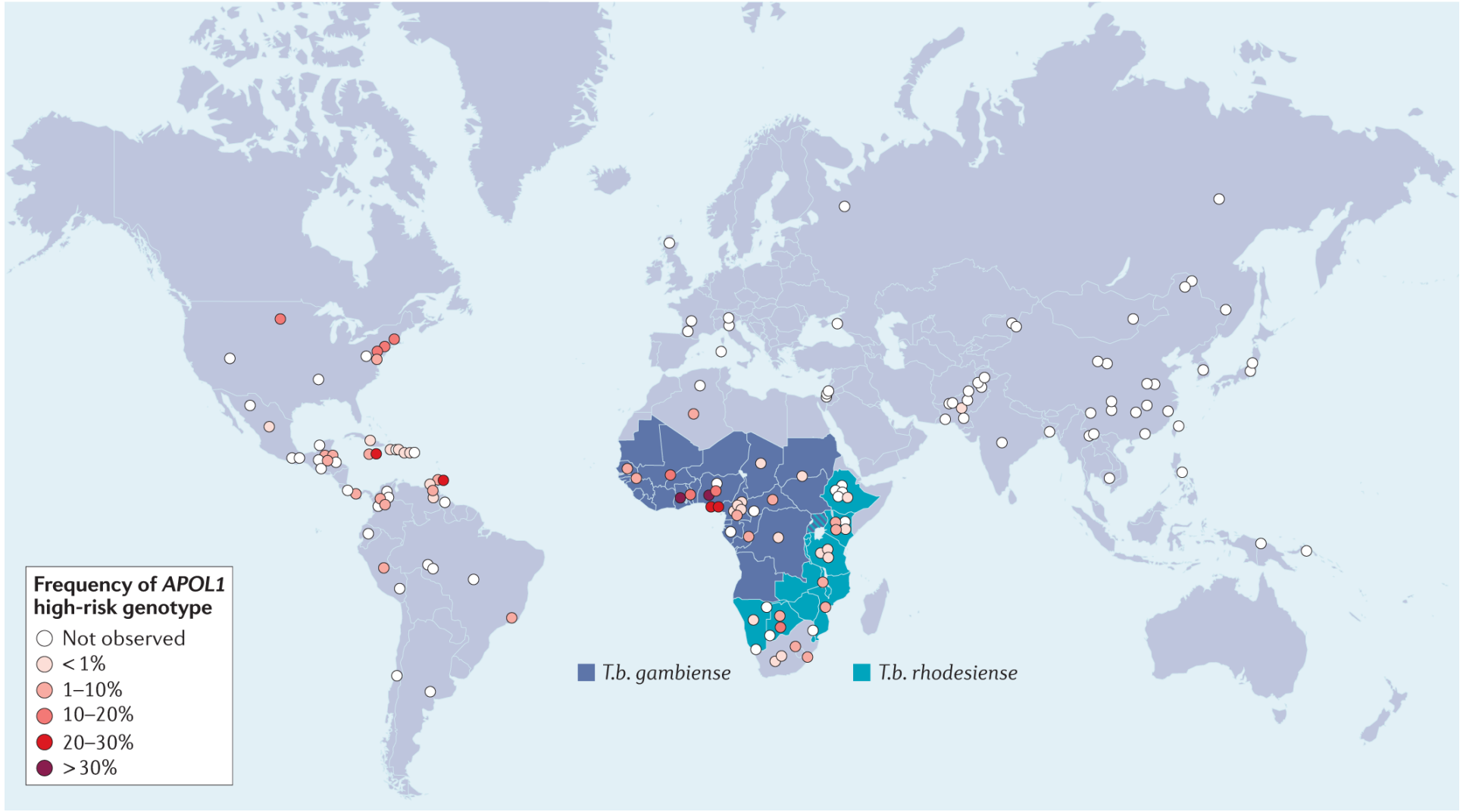
APOL1 Population Studies

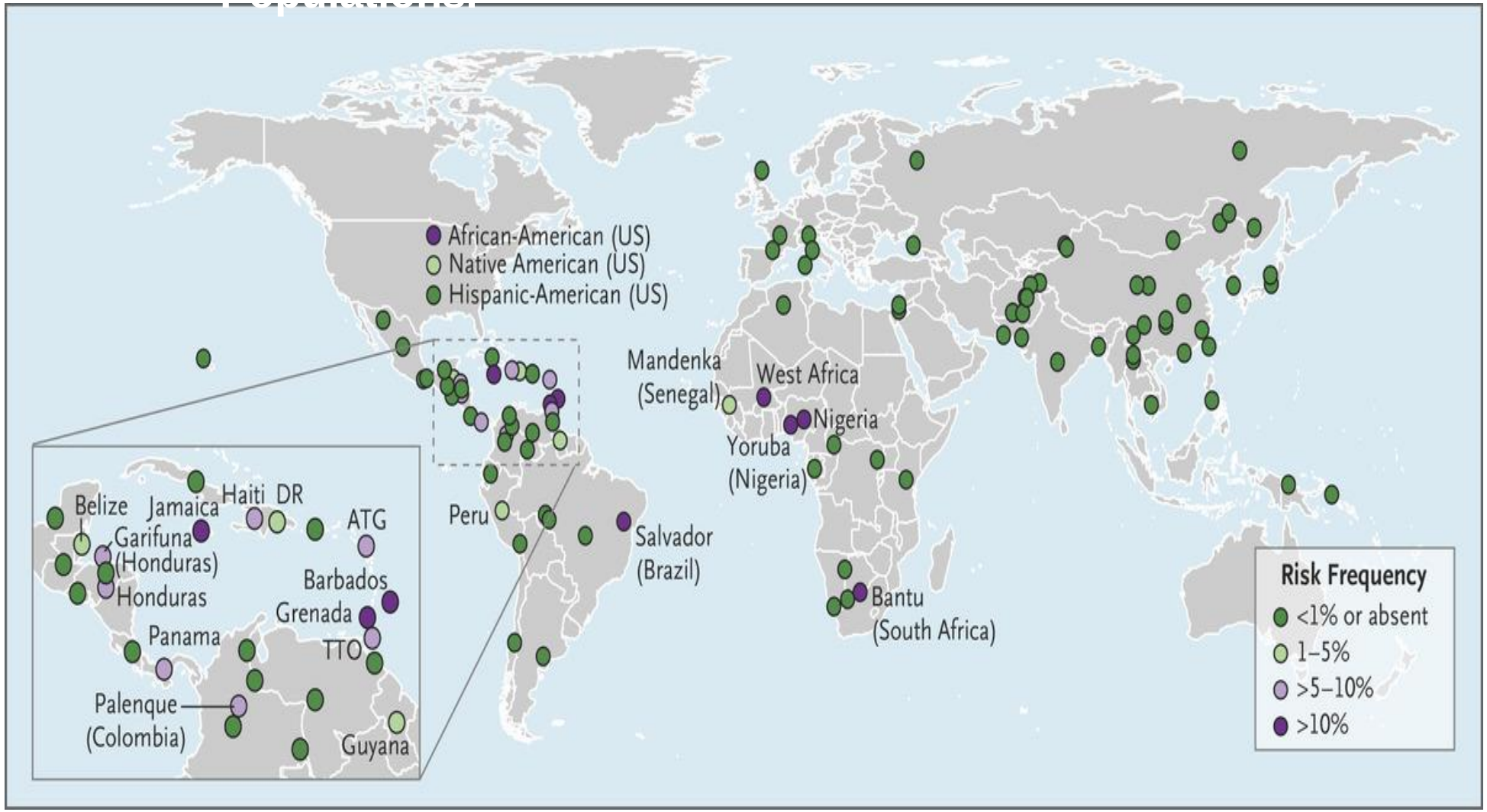
G1 and G2 alleles are most prevalent in West Africa with prevalence of 40% in Nigeria and Ghana

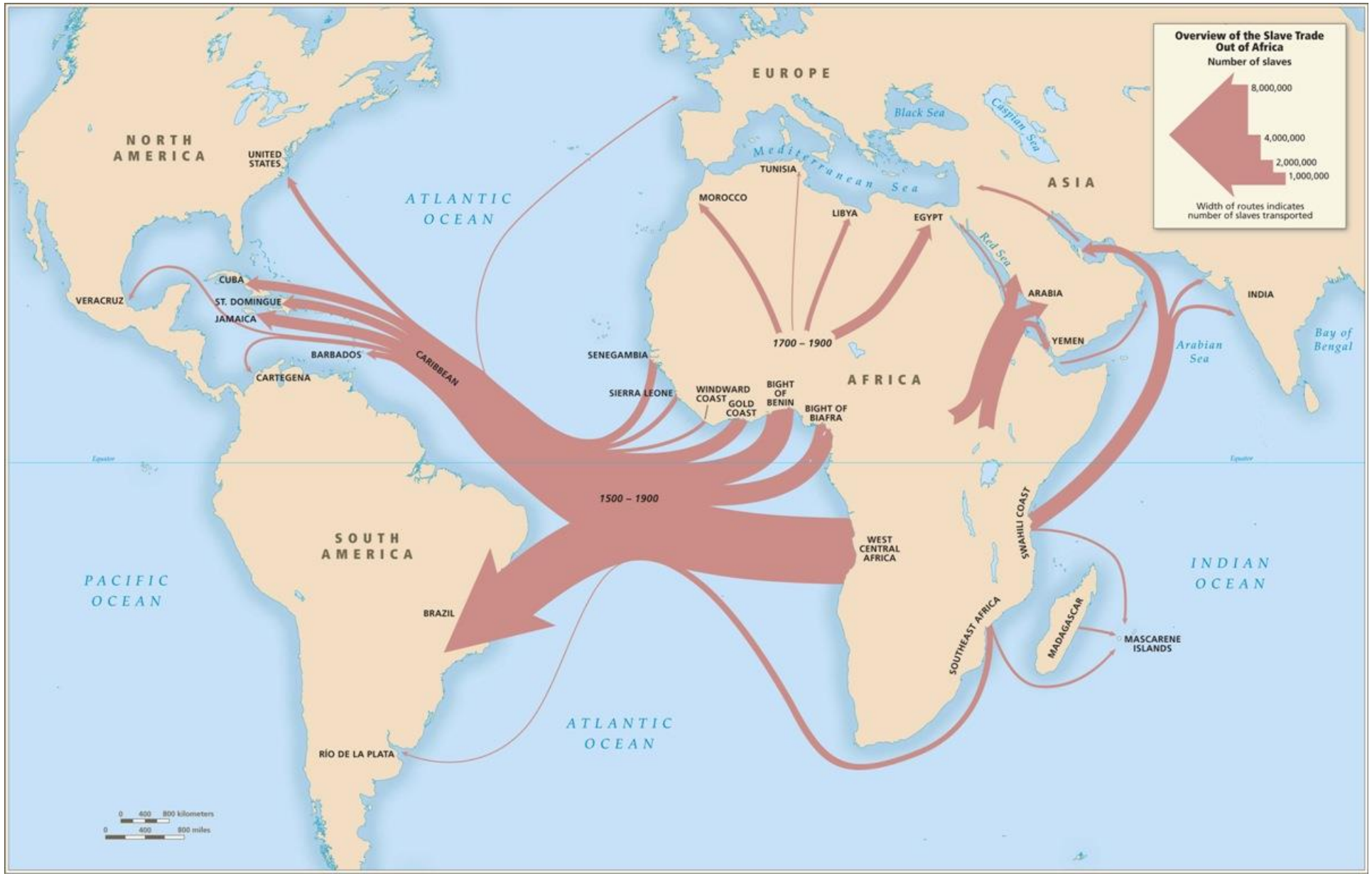
US AA prevalence – 39% low risk (0 or1), 13% high risk (2)

Other populations

- 10% - Jamaican, Barbadian, Grenadian, Brazilian
- 5-10% Trinidadian, Panamanian, Haitian, Honduran
- 1-5% Dominican, Peruvian
- Hispanic – higher risk Mexican, Central American, Puerto Rican


Frequency of APOL1 high-risk genotype
Not observed
< 1%
1–10%
10–20%
20–30%
> 30%
T.b. gambiense
T.b. rhodesiense


African-American (US)
Native American (US)
Hispanic-American (US)
Mandenka (Senegal)
West Africa
Nigeria
Yoruba (Nigeria)
Peru
Salvador (Brazil)
Bantu (South Africa)
Belize
Jamaica
Haiti
DR
ATG
Garifuna (Honduras)
Honduras
Barbados
Grenada
TTO
Panama
Palenque (Colombia)
Guyana
Risk Frequency
<1% or absent
1–5%
>5–10%
>10%


Overview of the Slave Trade Out of Africa
Number of slaves
8,000,000
4,000,000
2,000,000
1,000,000
Width of routes indicates number of slaves transported
NORTH AMERICA
UNITED STATES
EUROPE
ATLANTIC OCEAN
Black Sea
Caspian Sea
Mediterranean Sea
TUNISIA
MOROCCO
LIBYA
EGYPT
ASIA
Red Sea
ARABIA
INDIA
YEMEN
Arabian Sea
Bay of Bengal
CUBA
ST. DOMINGUE
JAMAICA
VERACRUZ
BARBADOS
CARTEGENA
CARIBBEAN
1700 – 1900
SENEGAMBIA
SIERRA LEONE
WINDWARD COAST
GOLD COAST
BIGHT OF BENIN
BIGHT OF BIAFRA
AFRICA
1500 – 1900
SOUTH AMERICA
WEST CENTRAL AFRICA
SWAHILI COAST
PACIFIC OCEAN
INDIAN OCEAN
BRAZIL
SOUTHEAST AFRICA
MADAGASCAR
MASCARENE ISLANDS
ATLANTIC OCEAN
RÍO DE LA PLATA
0 400 800 kilometers
0 400 800 miles

APOL1 population

The slave trade has driven the dissemination of APOL1 variants as families were captured and moved to various nation

APOL1 prevalence in US and other nations is reminder of our dark historical past

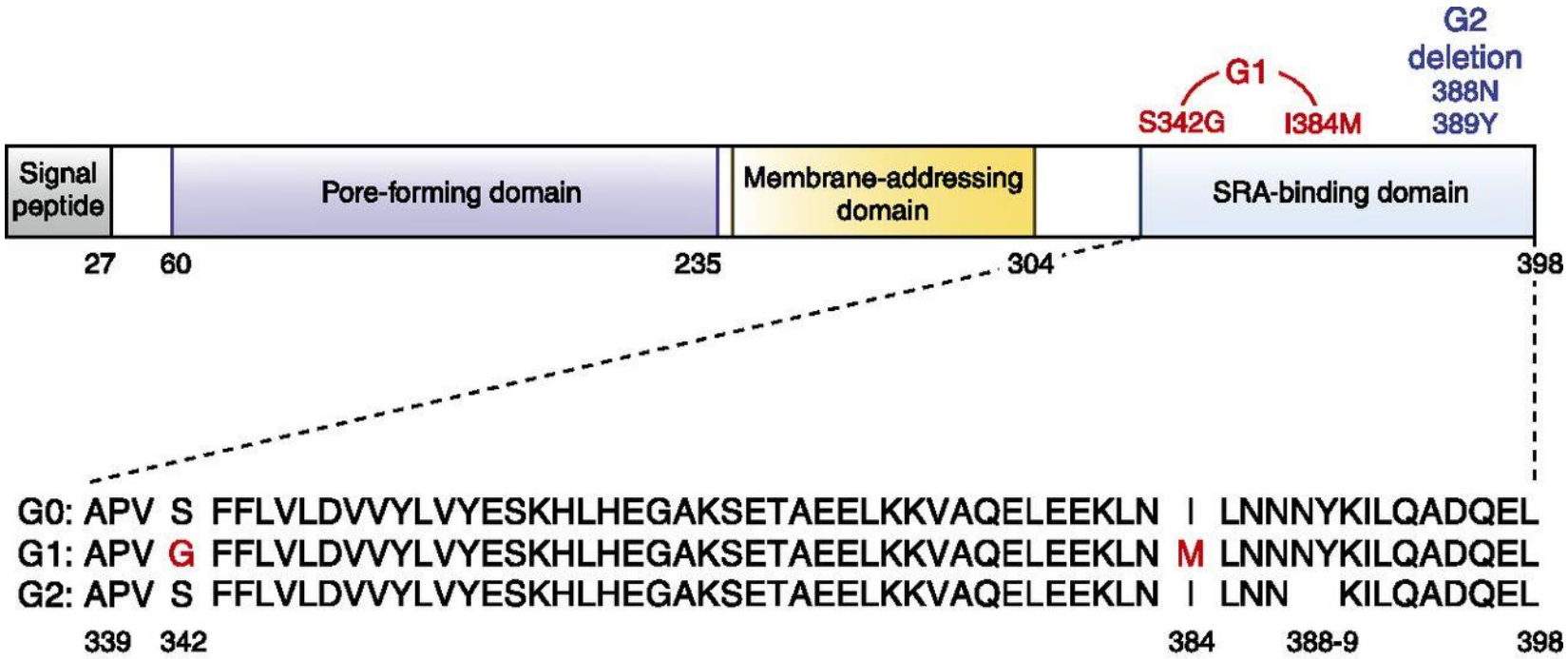
Not Critical Race Theory – just historical truths

APOL1 Genetics

APOL 1 is found on chromosome 22 in association with MYH9
It exists in 3 states G0 (wild), G1 and G2
G1 – SNP gain of function (Trypanosome resistance)
G2 – base pair deletion gain of function (Trypanosome resistance)
G0/GO, G0/G1, G0/G2 are considered low risk alleles
G1/G1, G1/G2, G2/G2 are considered high risk alleles
Not essential for kidney development

Seems to be inherited in an autosomal recessive pattern

APOL1 protein and its variants.



Non-risk APOL1 (~87%): G0/G0, G0/G1, G0/G2
High-risk APOL1 (~13%): G1/G1, G2/G2, G1/G2

David J. Friedman, and Martin R. Pollak CJASN
2021;16:294-303

African American CKD Questions

Why is CKD more common in African Americans?

Why is CKD more severe in African Americans?

Why are African Americans more likely to reach ESKD?

Why are certain kidney diseases worse in African Americans?

Why do African American donated kidneys tend to fail earlier?

Why is AKI worse in African Americans with sepsis?

Why is mortality lower in African Americans on dialysis?

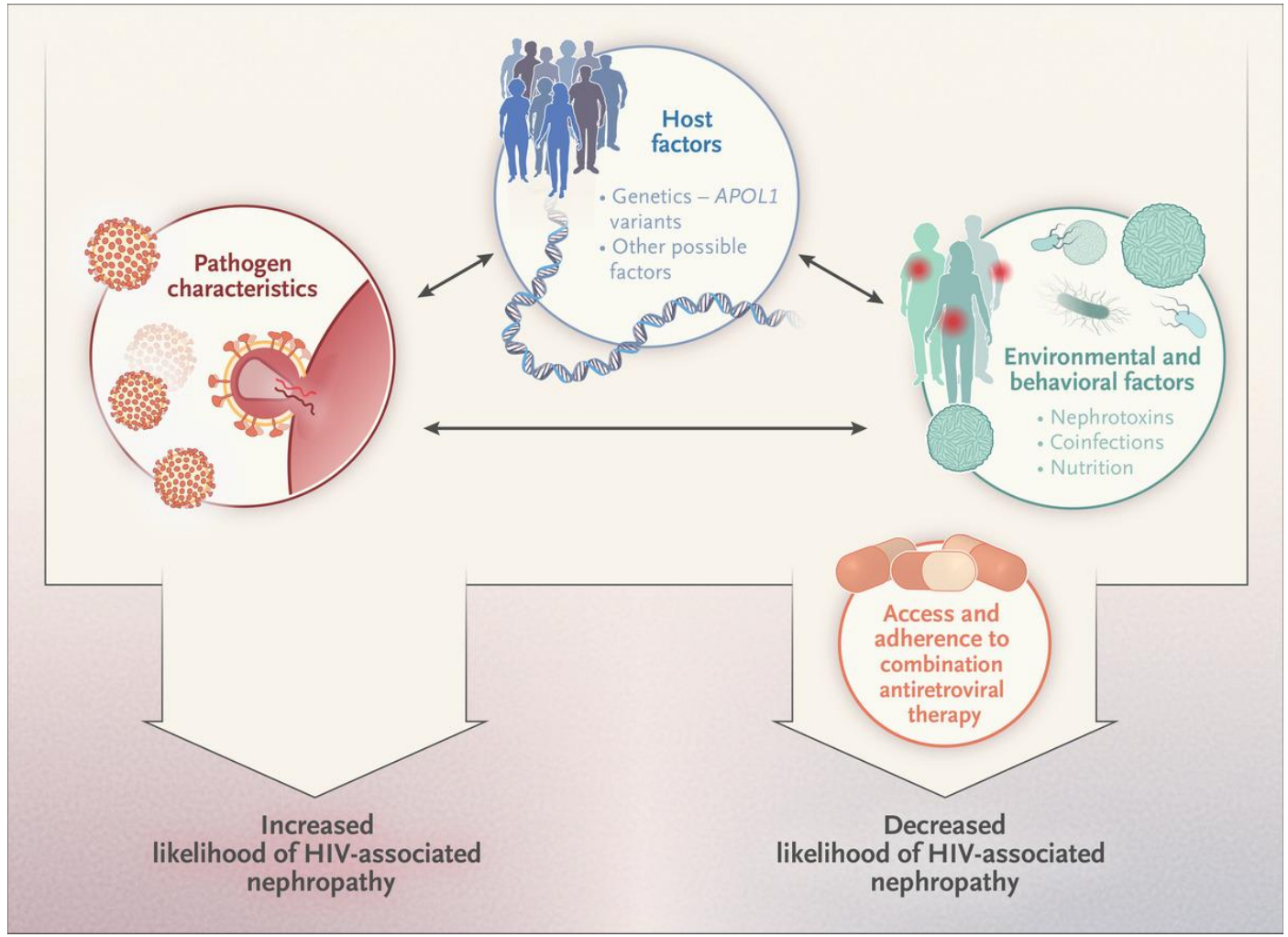
Do APOL1 variants have anything to do above?

What is the Importance of APOL1 in Kidney Disease?

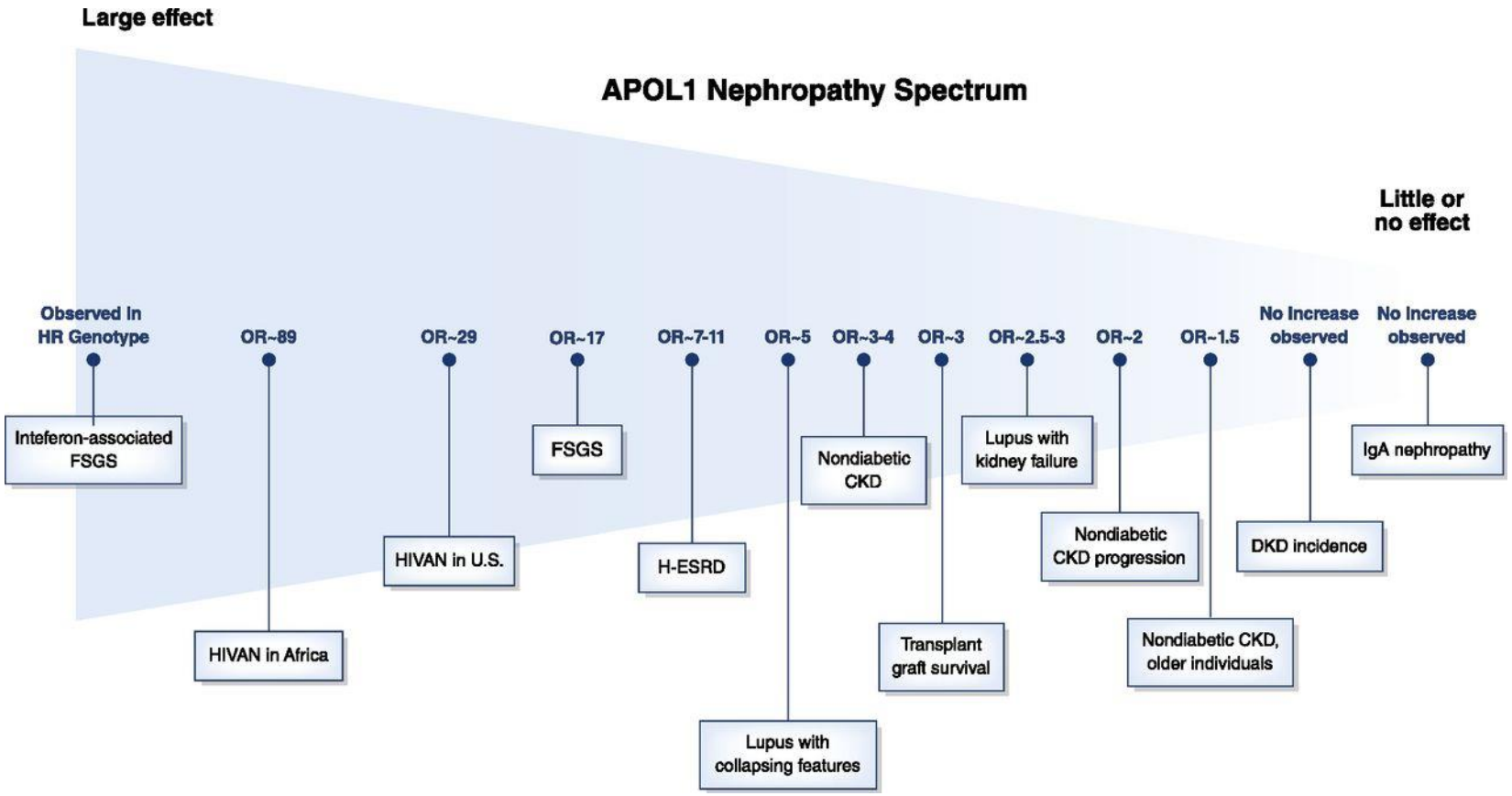
Josh had HIVAN with clinical onset of disease to ESKD < 6 months. Why?

HIVAN was one of the first diseases studied which showed important association of APOL1 variant with disease

Untreated HIVAN leads to collapsing glomerulopathy which is a rapidly progressive form of FSGS. In 1988 we had only AZT as an option for treatment. (No APOL1 testing)


Host factors
• Genetics – APOL1 variants
• Other possible factors
Pathogen characteristics
Environmental and behavioral factors
• Nephrotoxins
• Coinfections
• Nutrition
Access and adherence to combination antiretroviral therapy
Increased likelihood of HIV-associated nephropathy
Decreased likelihood of HIV-associated nephropathy

APOL1 risk variants increase the risk of many different types of kidney disease in Black individuals.



David J. Friedman, and Martin R. Pollak CJASN 2021;16:294-303

APOL1 and the Kidney

Since 2010 APOL1 has been studied in various disease populations with surprising results.

High risk variants are associated with increased severity and progression in many diseases

- HIVAN
- FSGS
- HTN Nephrosclerosis
- COVID AKI
- IFN FSGS
- Sickle Cell
- Collapsing Glomerulopathy
- SLE

Surprisingly, data with DM is inconclusive

APOL1 Kidney Disease

Not all patient with high risk alleles have kidney disease

Current theory is that it takes 2 hits to cause disease

2^{nd} hit is usually inflammatory or hemodynamic

Sometimes obvious and sometime surreptitious

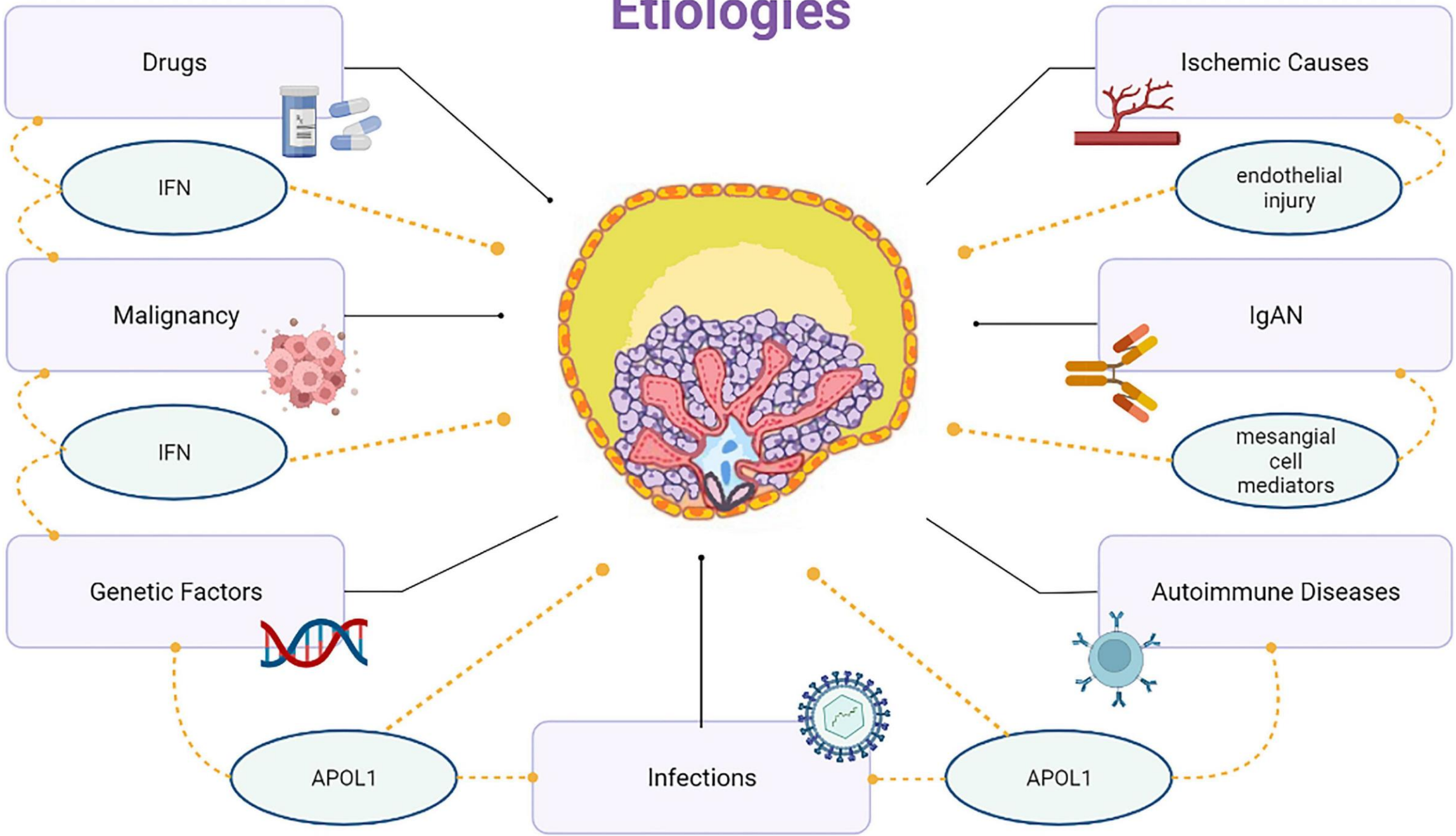
APOL1 Nephropathy

Current spectrum of APOL1 kidney disease

1. Normal
2. HTN Nephrosclerosis/Proteinuria
3. FSGS Collapsing glomerulopathy (75% AA APOL1)
4. ESKD histology unknown

Also associated with worse CKD in most non-diabetic kidney disease

Collapsing Glomerulopathy Etiologies



APOL1 and SARS CoV2

SARS CoV2 was associated with a high incidence of AKI (12% Asia and 35% North America)

African American patients had higher incidence of AKI

Shetty et al described 6 African American patients with SARS CoV2 and AKI who had biopsy proven collapsing glomerulopathy

3 patients were genotyped and all had high risk APOL1 variants

One discordant transplant

Arkana study showed 2X risk of AKI in SARS CoV2 with high risk APOL1

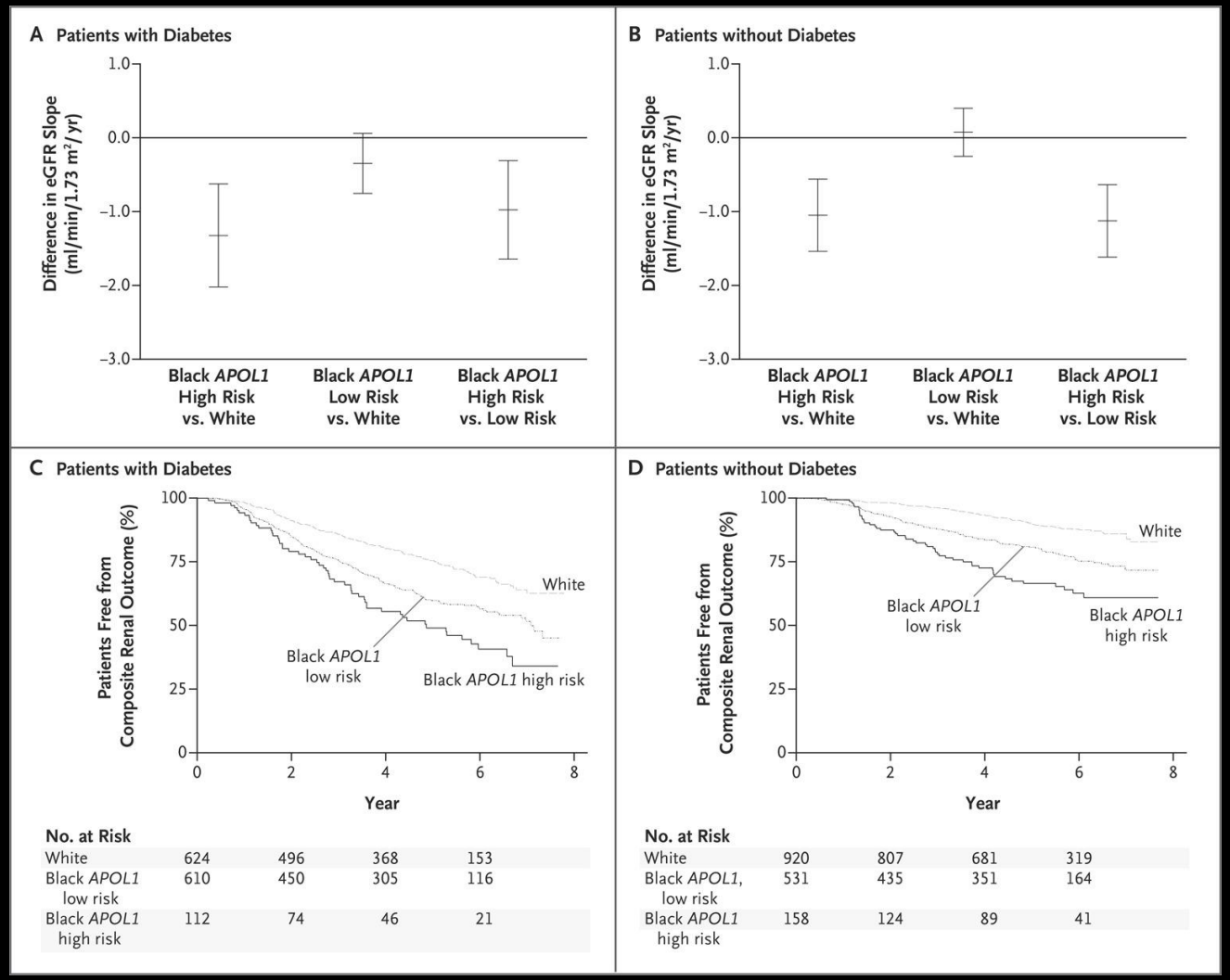
APOL1 and Diabetic Kidney Disease

APOL1 risk variants don’t predict DM nephropathy

APOL1 risk variants seem to speed progression

Could this AA patient clinically diagnosed with DM nephropathy have FSGS? Biopsy

Between-Group Comparisons of the Estimated Glomerular Filtration Rate (eGFR) Slope and Proportion of Patients Free from a Primary Outcome Event in the CRIC Study.



Parsa A et al. N Engl J Med 2013;369:2183-2196

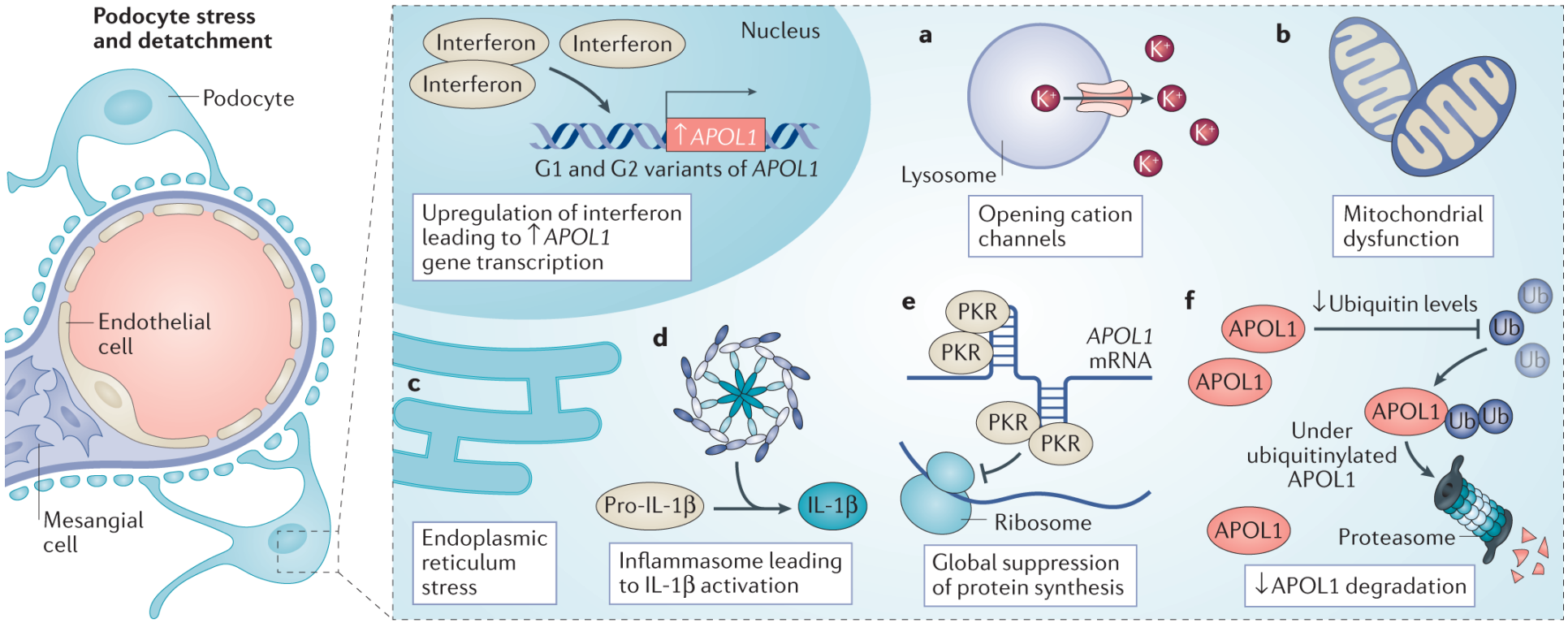
How Does APOL1 Cause Disease?

We honestly don’t know

Expression of the antigen in tissue and not circulating APOL1 is important (more on that later)

Transgenic mouse models exist

Pathology focused on podocytes and endothelium – alterations of cell permeability, mitochondrial permeability leading to cell injury and apoptosis


Podocyte stress and detatchment
Podocyte
Endothelial cell
Mesangial cell
Nucleus
Interferon
Interferon
Interferon
↑APOL1
G1 and G2 variants of APOL1
Upregulation of interferon leading to ↑APOL1 gene transcription
a
K+
Lysosome
Opening cation channels
b
Mitochondrial dysfunction
c
Endoplasmic reticulum stress
d
Pro-IL-1β
IL-1β
Inflammasome leading to IL-1β activation
e
PKR
PKR
PKR
PKR
APOL1 mRNA
Ribosome
Global suppression of protein synthesis
f
↓Ubiquitin levels
APOL1
APOL1
Ub
Ub
Ub
APOL1
Ub
Ub
Under ubiquitinylated APOL1
APOL1
Proteasome
↓APOL1 degradation

APOL1 Nephropathy Treatment

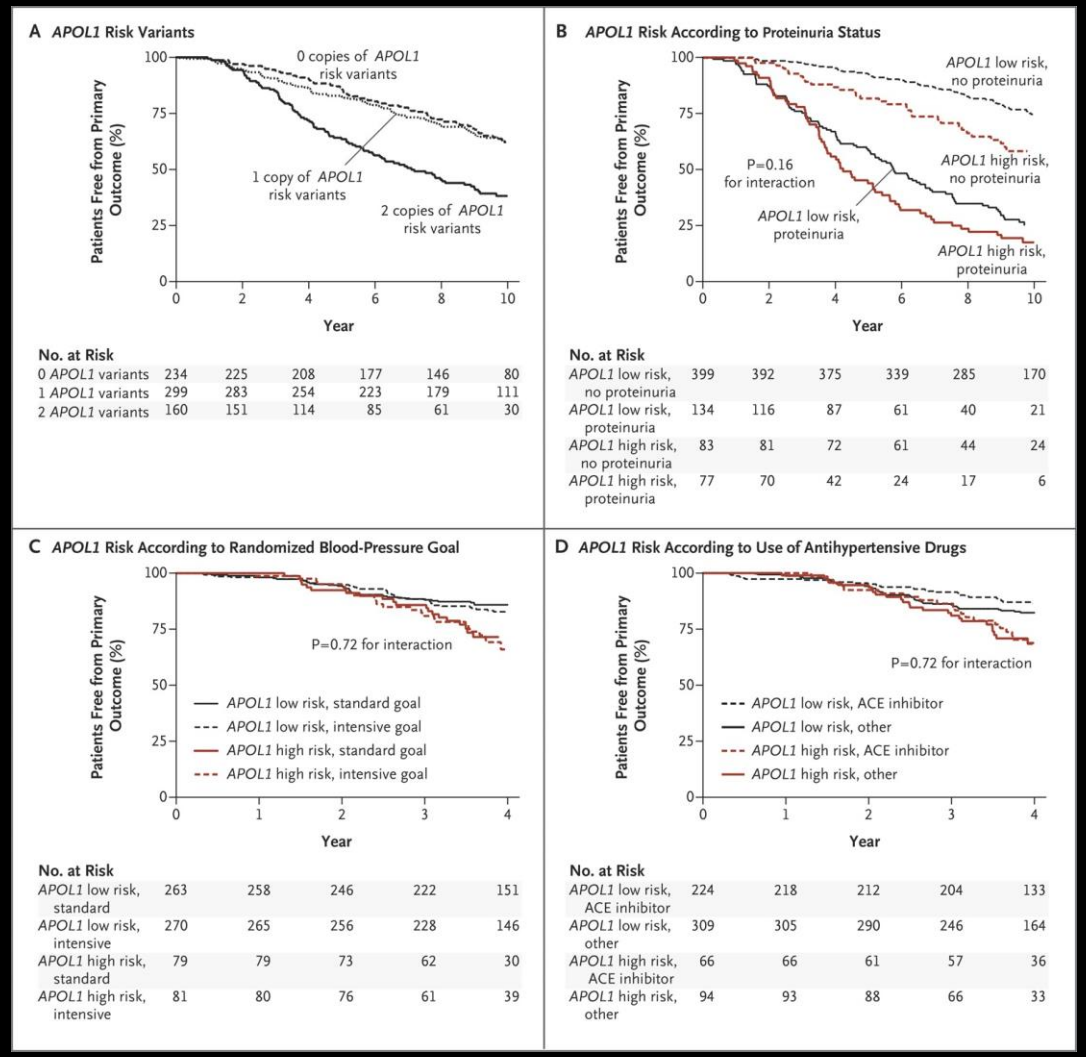
No specific treatment noted. They are treated like non- APOL1 patients with limited effect

Immunosuppression for FSGS results in decrease in proteinuria but no improvement in kidney survival

ACE HTN control results in decreased proteinuria without improved kidney survival. (Does improve patient survival)

? SGLT2, ? fineronone

Proportion of Patients Free from Progression of Chronic Kidney Disease in AASK.



Parsa A et al. N Engl J Med 2013;369:2183-2196

Josh

Josh is on dialysis. His course is complicated by AIDS associated infections and unfortunately, he dies 2 years into therapy due to refractory PJP pneumonia

TOO Damn Young

Days of AZT monotherapy

APOL 1 and Dialysis

Are patient with high risk APOL1 allele more likely to die than their fellow patients?

1. Yes
2. No
3. Same as everyone else

APOL1 and Dialysis

Paradoxically the survival of African American patients is higher than non- African American patients on dialysis (Not so in real life)

APOL1 high risk alleles are highly prevalent in ESKD (selection bias)

Survival of patients with high risk alleles is higher than low risk African American patients and non-African American patient

Interestingly, it did not appear to be due to lower CV mortality

APOL 1 and Dialysis

Are patient with high risk APOL1 allele more likely to die than their fellow patients?

1. Yes
2. **No**
3. Same as everyone else

Sharon

Because you took care of Josh, Sharon (Josh's mom) asks if you will see her for kidney disease. It is now 25 years from Josh's death

Sharon is 60 and has had HTN most of her life

Recent labs show an eGFR CKD EPI of 15

Her UAC is 600.

She asks several questions.

1. How should her kidney disease be treated?
2. Did her eclampsia/preeclampsia cause her kidneys to fail?
3. She wants to know whether she can be tested for APOL1?

Sharon – Pre-eclampsia/Eclampsia

Woman who have pre-eclampsia/eclampsia seem to be at increased risk for CKD and HTN in future

APOL1 status has some effect but in a surprising way

It is the risk status of the fetus that determines susceptibility

A fetus with high risk alleles predicts risk to a greater extent than her own APOL1 status

Circumstantial evidence that Josh was high risk

Sharon

What about long term therapy?

Dialysis – lower mortality with high risk alleles

Transplant - ?

Sharon

Transplant is the best option

Sharon has two potential donors – husband Ron and daughter Karen

Ron has no medical issues except for HTN. GFR and UAC normal

Karen has no medical issues except for HTN. GFR and UAC normal

Is APOL1 testing useful here to help determine long term allograft function?

APOL1 Testing Pre-Transplant

APOL1 high risk variants in donor predict long term allograft function.

High risk variants in donor predict worse GFR and shorter longevity

High risk variants also predict donor prognosis – high risk APOL1 means lower GFR, more HTN and albuminuria

High risk variants in recipients were not predictive

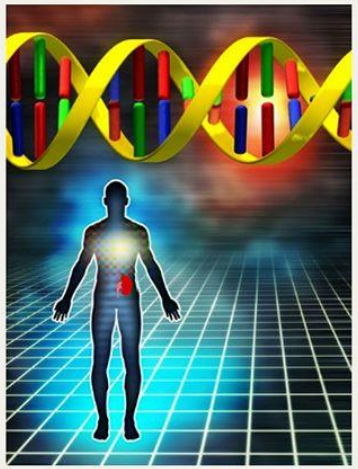
Testing donors pre-transplant worthwhile to both

Sharon was G0/G1. Husband G2/G2. Daughter G0/G2

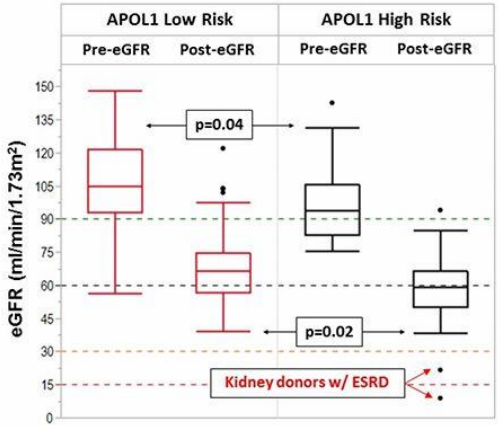
APOL1 Genotype and Renal Function of African American Live Donors

METHODS

Retrospective cohort
African American donors
Genotyped for *APOL1*



OUTCOME 12 years post-donation renal function



CONCLUSION *APOL1* high-risk genotype in African American live kidney donors is associated lower pre- and post-donation renal function.

doi: 10.1681/ASN.2017060658

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

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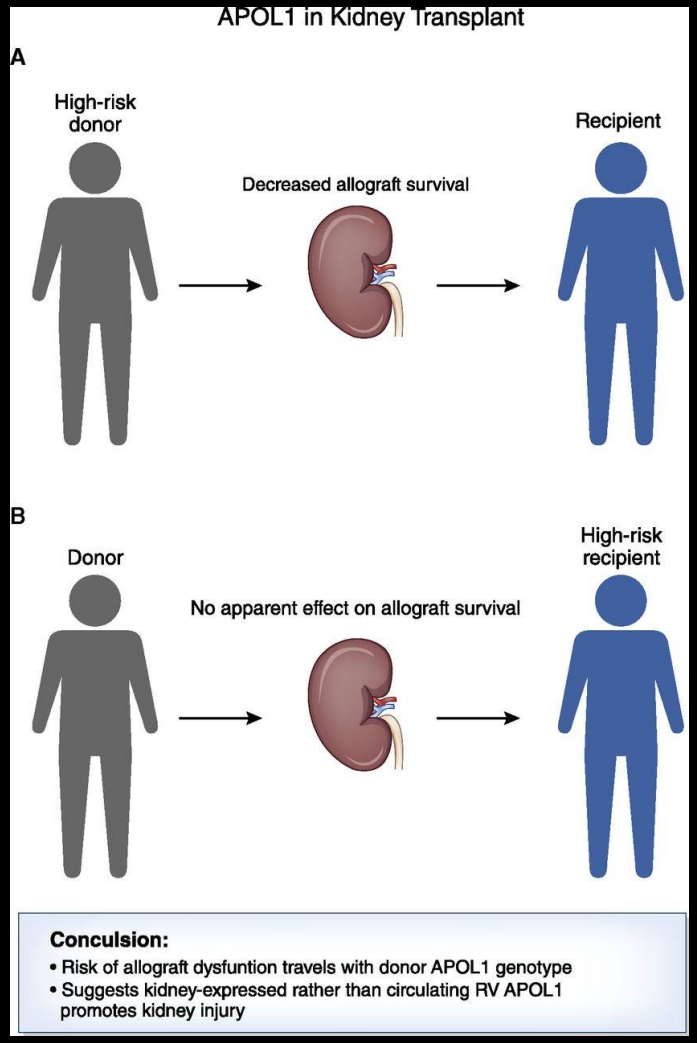
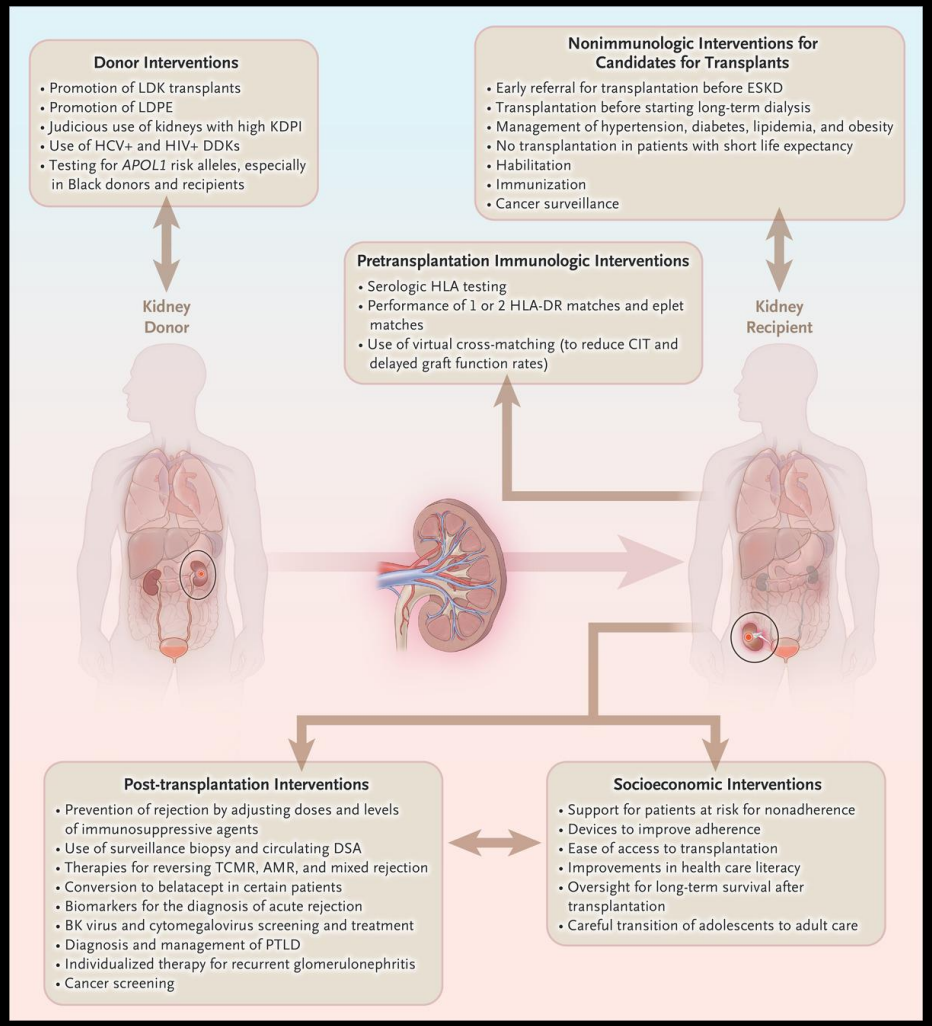


CJASN
Clinical Journal of the American Society of Nephrology

Interventions for Kidney Donors, Candidates, and Recipients That Affect Long-Term Survival.

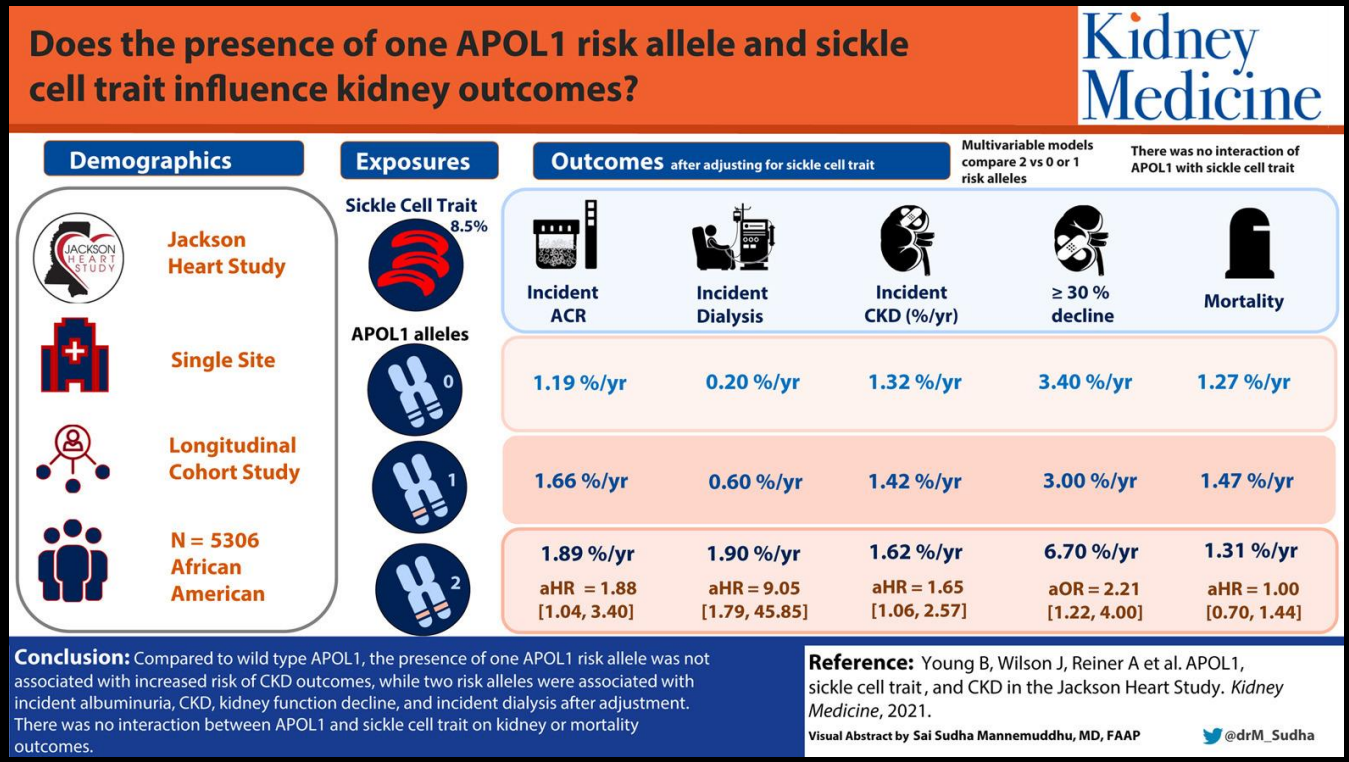


S Hariharan et al. N Engl J Med 2021;385:729-743.

The NEW ENGLAND JOURNAL of MEDICINE

APOL1 and Sickle Cell Disease

High risk APOL1 variants influence the course of Sickle Cell disease and trait



Kidney Medicine 2021 3962-973.e1DOI: (10.1016/j.xkme.2021.05.004)

APOL1 and Other Systems

CV dx – do APOL1 risk variants predict CV disease and mortality

HIV

Sepsis

APOL1 kidney-risk variants and cardiovascular disease: An individual participant data meta-analysis

METHODS

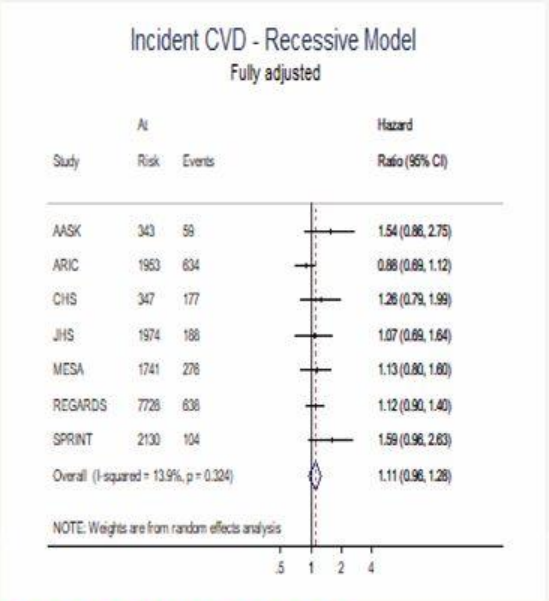
8 research cohorts of African Americans

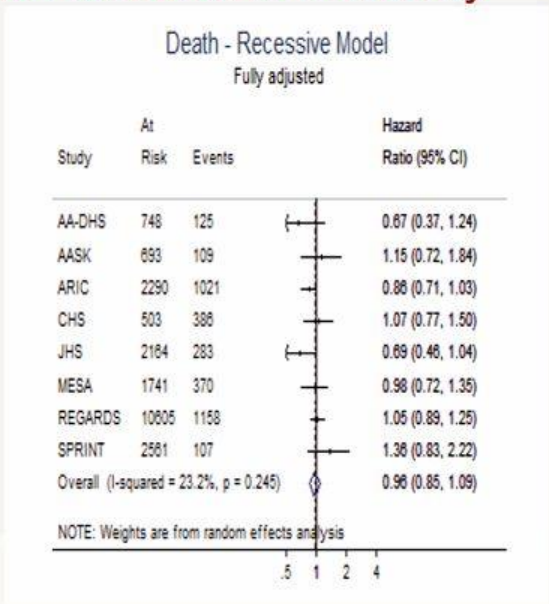
APOL1 kidney-risk genotype
Adjudicated cardiovascular disease and mortality

Two-stage meta-analysis
N=21,305

RESULTS

No independent association between *APOL1* kidney risk alleles and cardiovascular disease or mortality





CONCLUSION *APOL1* kidney-risk variants may not have a direct effect on cardiovascular disease or mortality after accounting for kidney measures.

doi: 10.1681/ASN.2019030240

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APOL1 and Testing

Difficulty here is what does the knowledge get you?

Identify high risk group who should be routinely screened for early intervention

FSGS VS DM nephropathy

Donor selection

Family planning

Prior to drug use associated with collapsing glomerulopathy

Biopsy if APOL1 low risk

Table 1.

Clinical scenarios in which *APOL1* genotyping may be useful

Clinic Location	Potential Indication	Comments
Transplant clinic	Evaluation of living-kidney donor candidates	Await NIH APOLLO Study results
Nephrology clinic	Improve compliance in HIV^+ patients at risk for HIV-associated nephropathy	Highly active antiretroviral therapy curative
Nephrology clinic	Improve compliance in patients with SLE at risk for severe lupus nephritis or ESKD	
Nephrology clinic	Detect possible nondiabetic nephropathy in individuals with T2D and CKD	In those who have not undergone a diagnostic kidney biopsy
Nephrology clinic	Patients with bland chronic injury or FSGS on kidney biopsy	Provides more definitive diagnosis of underlying etiology
Medicine clinic	Prior to IFN administration	
Family planning	Screen parents from families with multiple members having ESKD	
Clinical research	Test novel therapies for *APOL1* nephropathy	APOL1 small molecule inhibitors and antisense oligonucleotides may soon be tested
Clinical research	Rapid evaluation of deceased donors before allocation of kidneys for transplantation	Await NIH APOLLO Study results

APOL1 Summary

APOL1 risk variants are associated with many kidney diseases

Partially explain high incidence and poor prognosis in African American patients with CKD (70%)

Donor screening

Seems to be “2 hit” mechanism of injury

Does it protect dialysis patients?

APOL1 Beginning of the Middle

Further modeling in transgenic mice may further understanding of pathophysiology

Because it is non-essential to kidney development and it is gain of function it would be an easy target for pharmacologic or genetic intervention. Improving transplant outcomes with screening of donors. APOLLO

Diabetic kidney disease

Discovery of Autoantibodies Targeting Nephrin in Minimal Change Disease Supports a Novel Autoimmune Etiology

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Two independent patient cohorts
(Bx proven MCD + Active NS)

Nephrotic Syndrome Study Network

Patients at our institutions

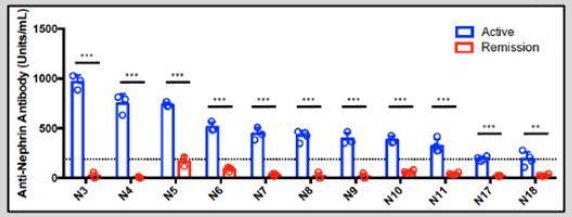
ELISA for anti-nephrin antibodies (both cohorts)

Immunofluorescence evaluation of renal biopsies for punctate IgG (our cohort)

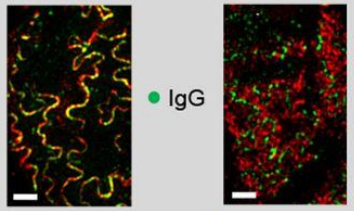
Comparison of circulating nephrin autoantibodies pre and post treatment response (both cohorts)

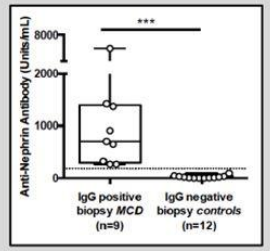
Circulating nephrin autoantibodies are present in almost 1/3 of patients with MCD in the NEPTUNE cohort and correlate with disease activity

29%
(18/62)



Nephrin autoantibodies are detectable both in serum and renal biopsies of patients with MCD





Nephrin is the target of circulating autoantibodies in a subset of patients with minimal change disease

doi: 10.1681/ASN.2021060794

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