

Biological Basis of Chronic Kidney Disease Disparity: Discovery of a Culprit, *APOL1*

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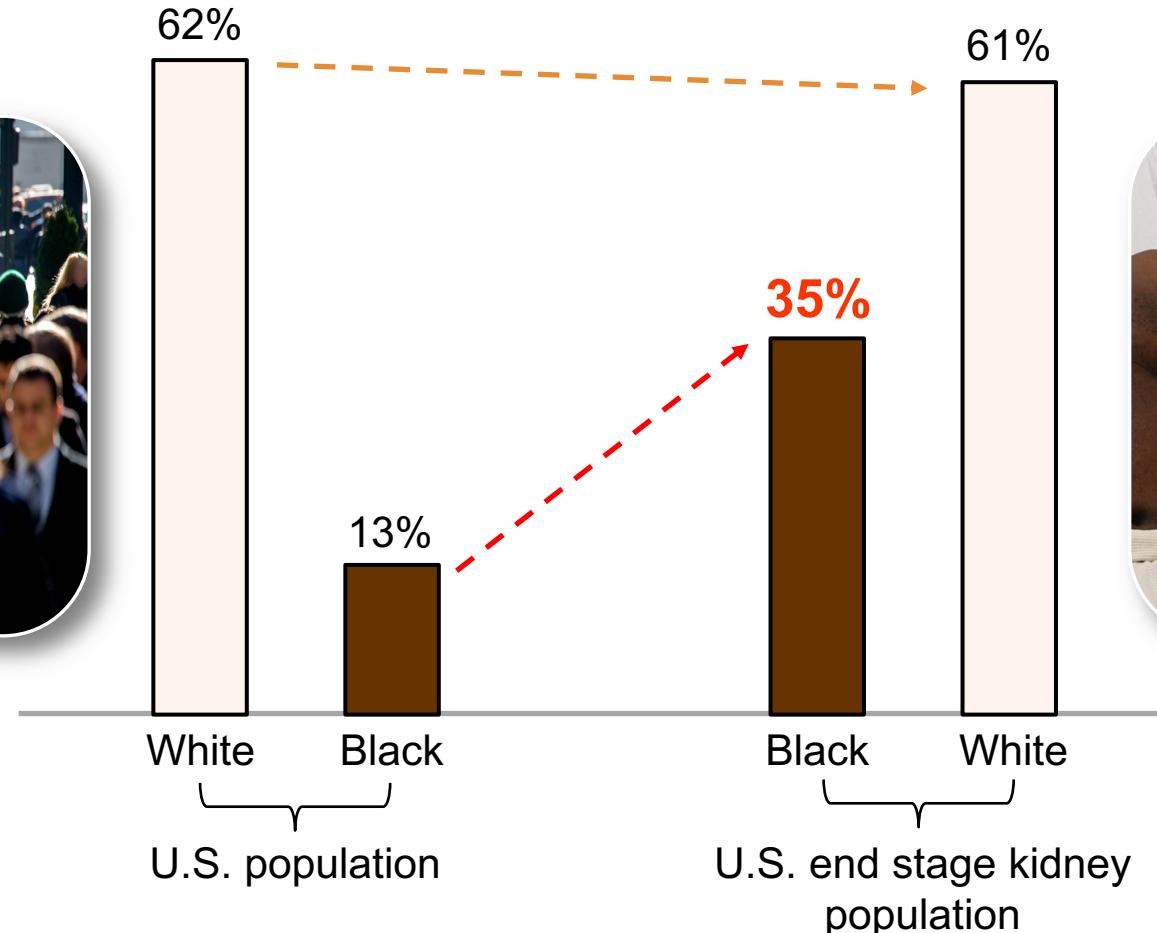
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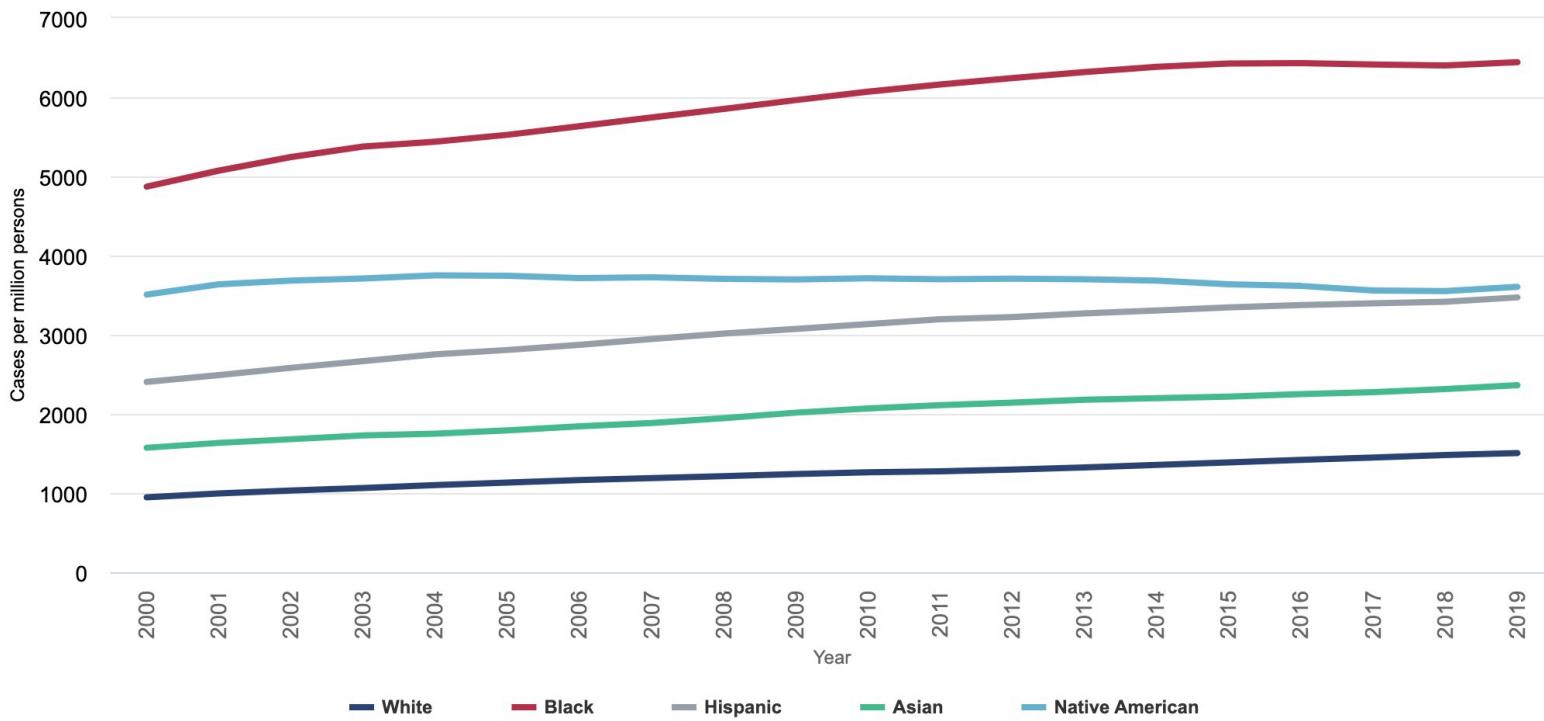
Duke Molecular Physiology Institute

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



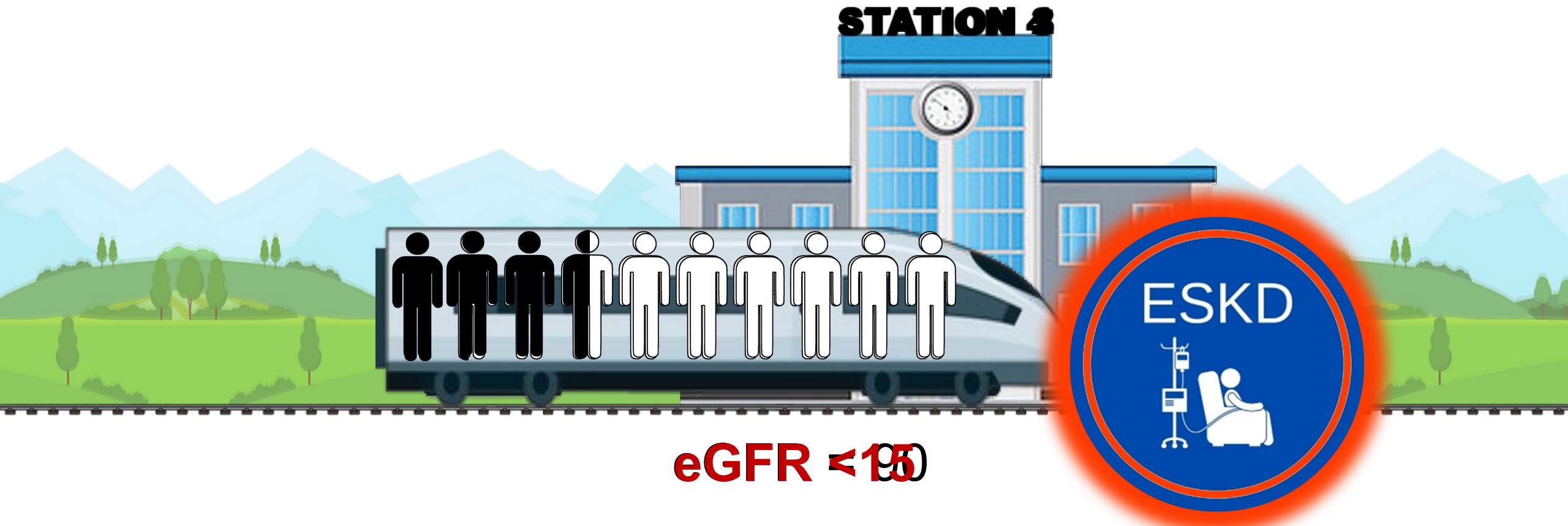
Data sources: United States Renal Data System Annual Data Report

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

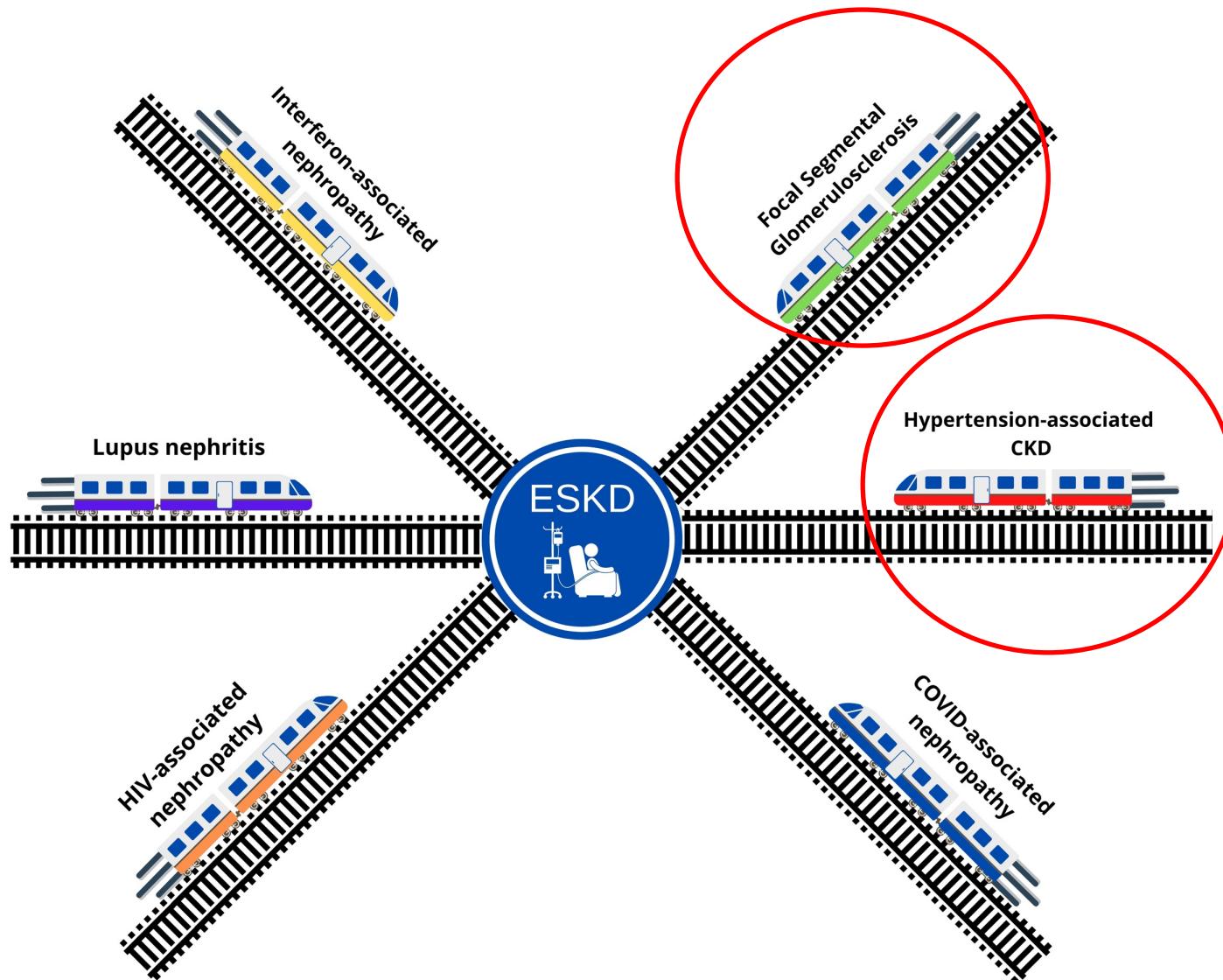
The Five Stations of Kidney Disease Progression to Dialysis



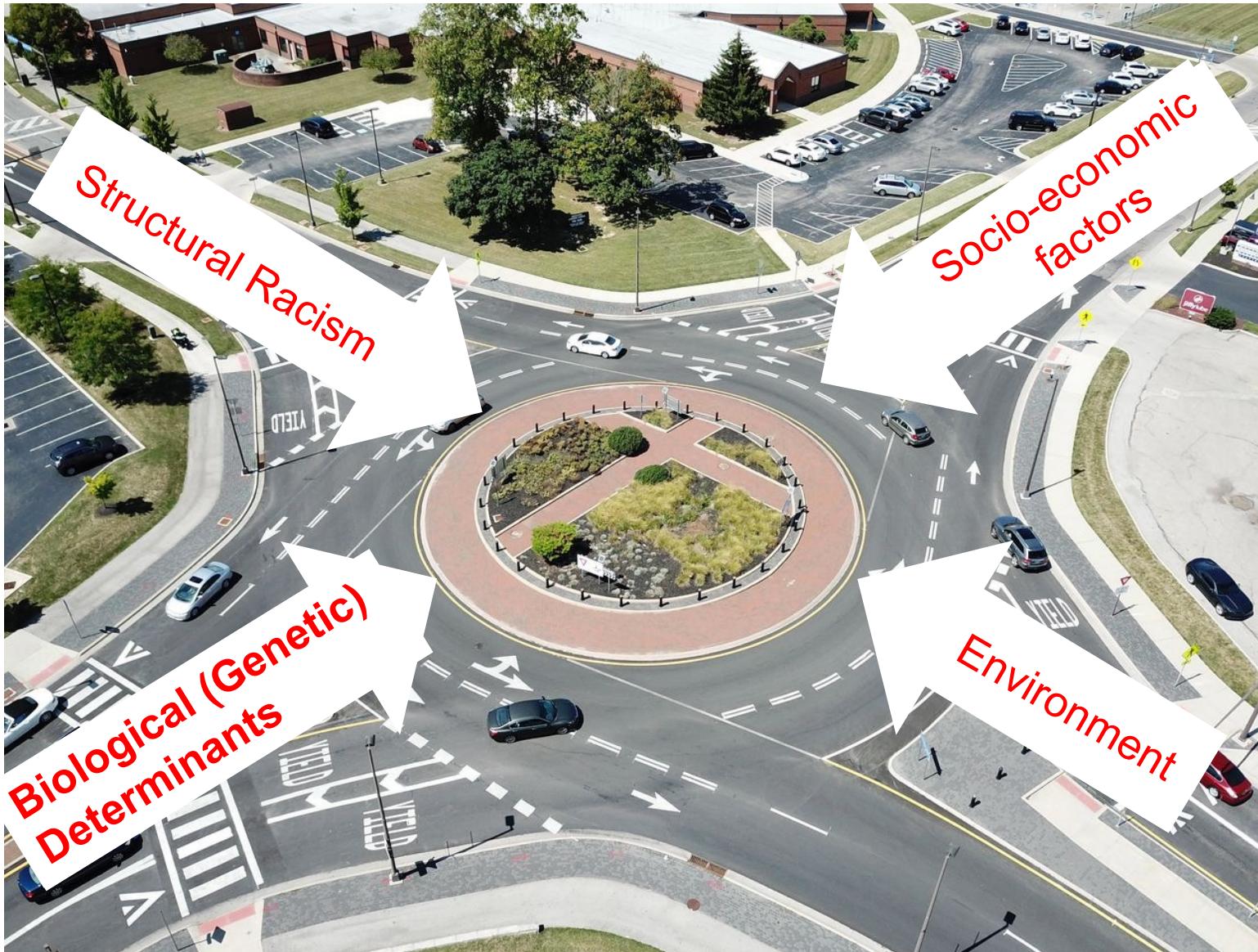
eGFR <15

35% Black Americans
~~(disproportionate to US population)~~

Various Forms of Kidney Diseases Terminates in ESKD



End-stage kidney disease is a roundabout; many roads lead to it



Early Hints of Plausible Biological Driver of ESKD: Familial Aggregation of ESKD for African Americans



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The Familial Risk of End-Stage Renal Disease in African Americans

Barry I. Freedman MD , Beverly J. Spray PhD, Audrey B. Tuttle PA-C,
Vardaman M. Buckalew Jr MD

African Americans have higher overall incidence rates of end-stage renal disease (ESRD) compared with American whites. Hypertensive nephrosclerosis (HN), nephropathy secondary to diabetes mellitus types I and II, and chronic glomerulonephritis (CGN) all occur more frequently in African Americans. To explore the possibility that hereditary factors may play a role in the increased risk of ESRD in African Americans, the family history of 131 African American hemodialysis patients (cases) was compared with 115 age-, sex-, and race-matched non-ESRD controls. Odds ratios (ORs) were calculated to define the prevalence of a relative with ESRD among cases versus controls. Chi-square values were estimated from a log-linear model, while controlling for gender, to test for significance of ORs. Forty percent (12/30) of HN cases, 35% (18/51) of type II diabetes mellitus-induced renal failure cases, and 13% (5/38) of CGN cases had a first-, second-, or third-degree relative with ESRD. The presence of a first-degree relative with ESRD increased an African American's risk for developing ESRD ninefold (OR, 9.13; 95% confidence interval [CI], 2.6 to 31.8; $P < 0.001$). The presence of a first- or second-degree relative increased the risk fivefold (OR, 5.23; 95% CI, 2.2 to 12.3; $P < 0.0002$). First-, second-, or third-degree relatives with ESRD were more prevalent among cases with ESRD due to hypertension and type II diabetes mellitus compared with CGN ($P \leq 0.05$). Gender differences among the ORs were nonsignificant ($P > 0.2$) and socioeconomic class (level of education and income) did not differ markedly between cases and controls. A strong familial association of ESRD exists in African Americans, particularly in those with hypertension and type II diabetes mellitus-induced renal disease. An inherited predisposition to renal injury is likely to be present in some African American families, although shared environmental exposure may contribute to the observed risk.

Early Hints of Plausible Biological Driver of ESKD: Familial Aggregation of ESKD for African Americans

Kidney Disease in the First-Degree Relatives of African-Americans With Hypertensive End-Stage Renal Disease

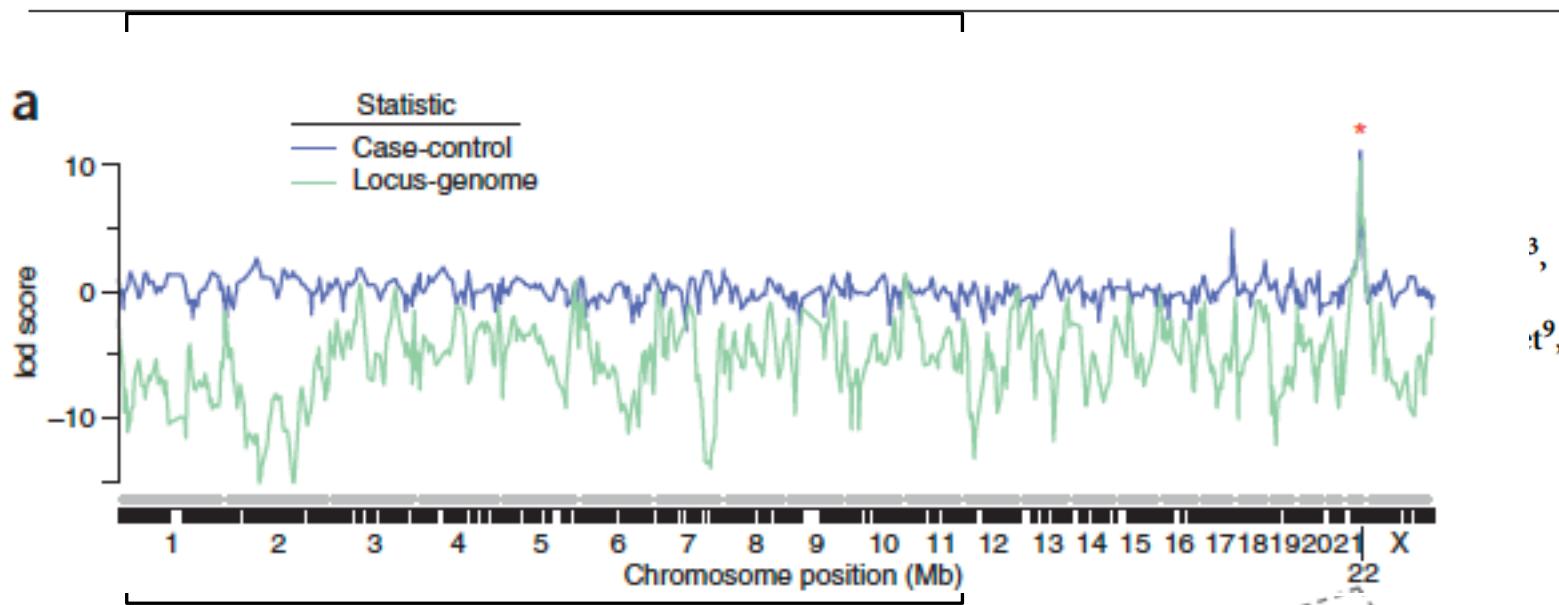
Suzanne Bergman, MD, Beverly O. Key, BSN, Katharine A. Kirk, PhD, David G. Warnock, MD,
and Stephen G. Rostand, MD

- The incidence of treated end-stage renal disease (ESRD) in the United States is four times more frequent in African-Americans (AAs) than in whites. This is explained neither by a greater prevalence of hypertension and diabetes mellitus nor by socioeconomic issues. To investigate familial risk of renal disease in AAs, we examined the records of 472 AA dialysis patients in Jefferson County, Alabama. Applying strict criteria, we identified 85 index cases of ESRD associated only with hypertension (H-ESRD). We examined the records of 75 index cases and studied the first-degree relatives of 40 patients. The numbers of men and women with H-ESRD were similar (38 and 37, respectively). There was no statistical difference in age at the onset of dialysis (women 53.7 ± 13.5 years [$\pm SD$] and men 49.2 ± 12.2 years; $P = 0.0863$). We found evidence for renal disease in 26 of 40 (65%) index cases with participating families. Hypertension was present in all 40 families (100%) and diabetes mellitus was present in 24 families (60%). Eighteen of the 75 H-ESRD index patients had a first-degree relative with ESRD. In total, we found evidence for renal disease in 35 of 75 (47%) families. We conclude that there is a strong concordance of renal disease in the families of AAs with H-ESRD.

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The hunt for the gene mutation that explains the high incidence of ESKD in African Americans.

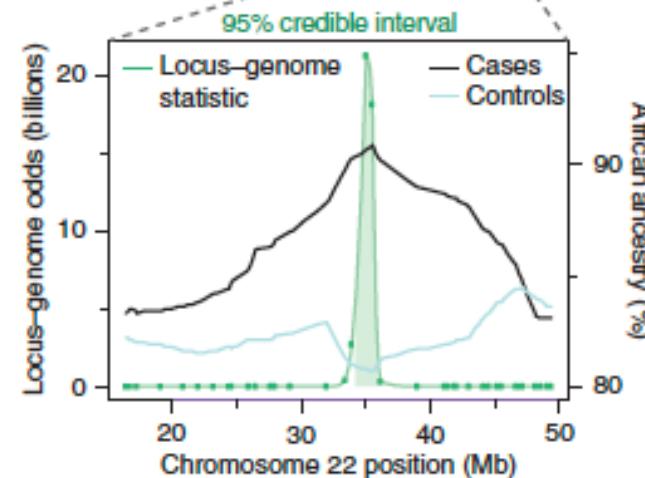


#Approach: Admixture-mapping linkage-disequilibrium (MALD) genome scan

#Discovery cohorts: **190** AAs with **FSGS**
222 Controls

#Result:

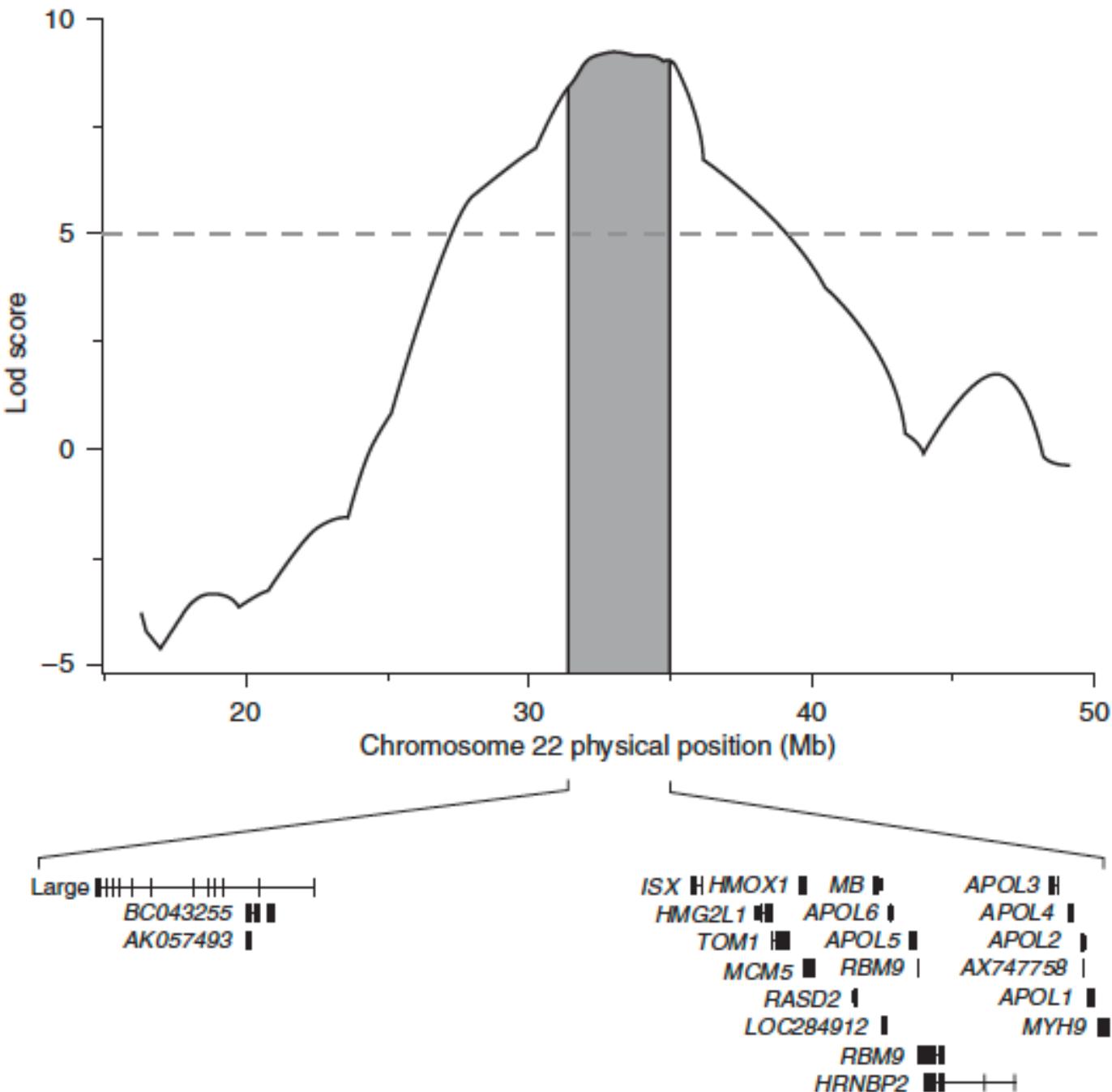
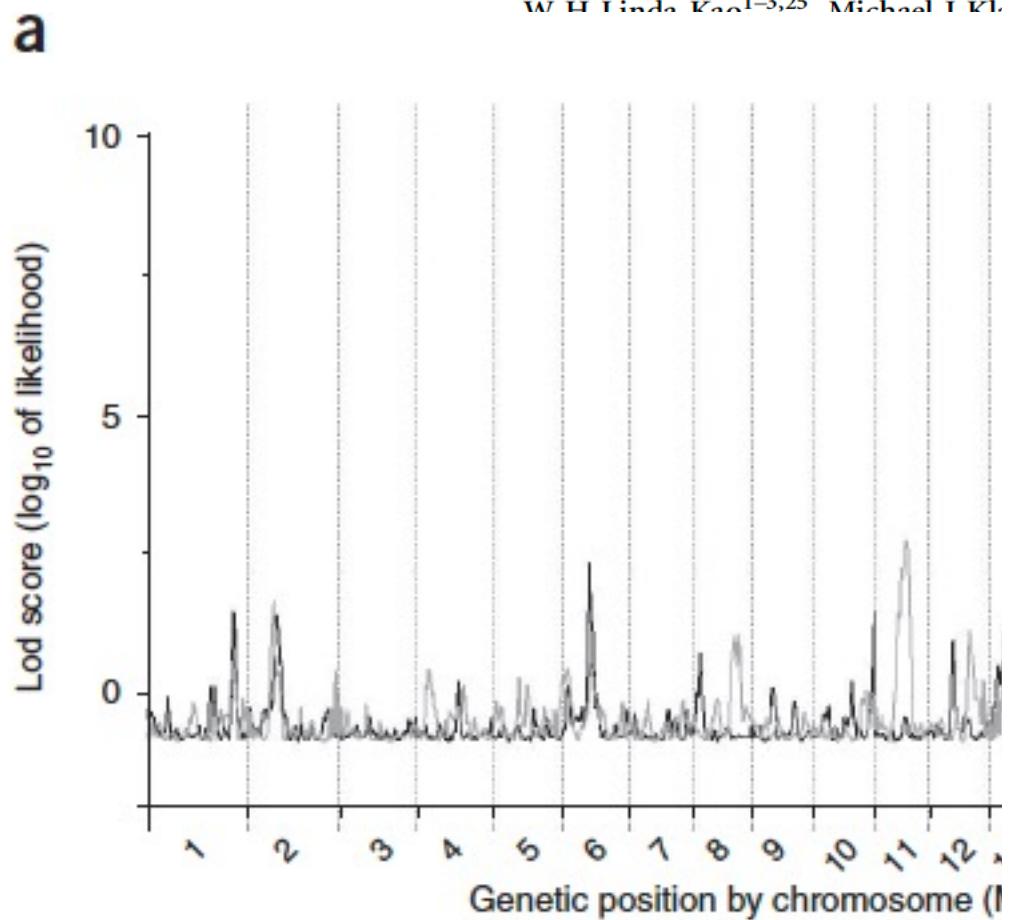
Region on Xsome 22 → regional fine mapping → **MYH9**



The hunt for the gene mutation ESKD in African Americans.

MYH9 is associated
disease in African

WU Linda Van1-3,25 Michael T K1,

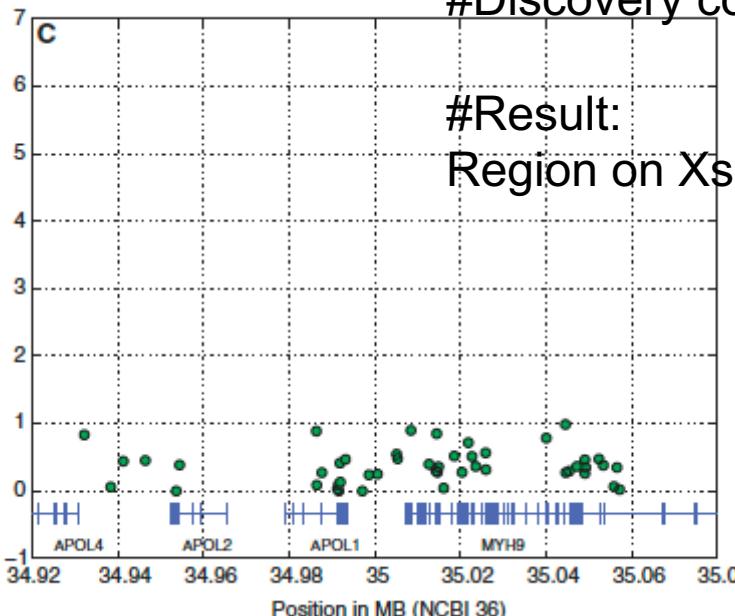
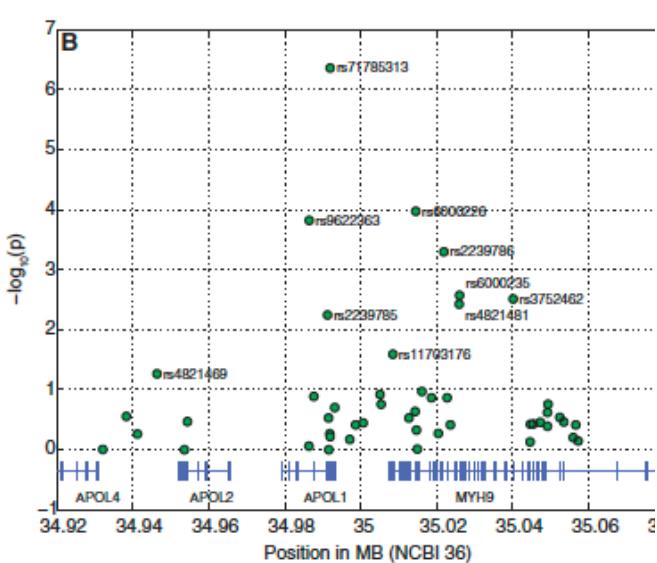
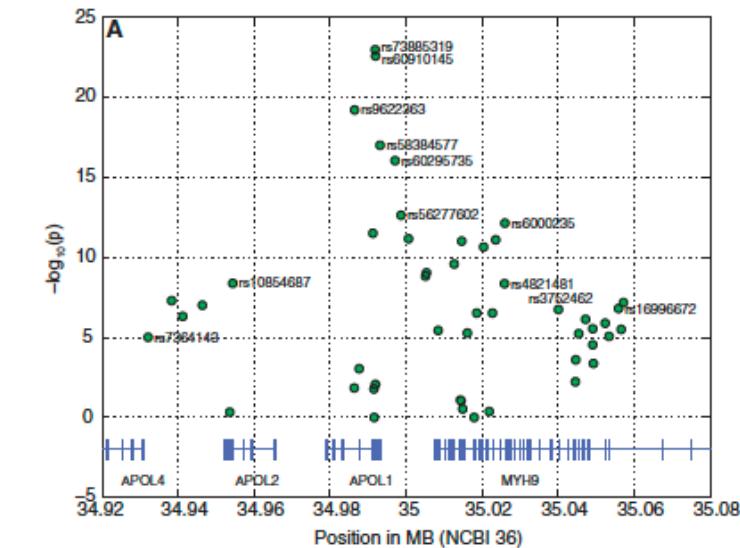


The chromosomal region is correct, the identified gene is wrong.

Fine-mapping association with *MYH9*

The apex of the MALD peak occurred at the MALD mapping SNP rs735853, located in an intron close to the 3' end of *MYH9* (Fig. 2), which encodes nonmuscle myosin heavy chain IIA. A total of 35 genes were present in the 95% credible interval of the MALD peak (Supplementary Fig. 1b). As *MYH9* is expressed in podocytes²², cells essential for glomerular filtration, and as extremely rare codon-changing mutations in *MYH9* have been previously associated with familial clusters of glomerulonephritis²², we considered *MYH9* the most plausible positional and functional candidate gene. We hypothesized that one or more genetic variations in *MYH9*, with substantial allele frequency differences between Africans and Europeans, accounted for the chromosome 22 MALD association with FSGS, and we therefore tested additional SNPs in *MYH9* for association with FSGS on the 412 subjects genotyped in the MALD scan, for whom chromosomal ancestry data were available.

Indicting the real culprit gene.



Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans

Giulio Genovese,^{1,2,*} David J. Friedman,^{1,3*} Michael D. Ross,⁴ Laurence Lecordier,⁵ Pierrick Uzureau,⁵ Barry I. Freedman,⁶ Donald W. Bowden,^{7,8} Carl D. Langefeld,^{8,9} Taras K. Oleksyk,¹⁰ Andrea L. Uscinski Knob,⁴ Andrea J. Bernhardy,¹ Pamela J. Hicks,^{7,8} George W. Nelson,¹¹ Benoit Vanhollebeke,⁵ Cheryl A. Winkler,¹² Jeffrey B. Kopp,¹¹ Etienne Pays,^{5,†} Martin R. Pollak^{1,13†}

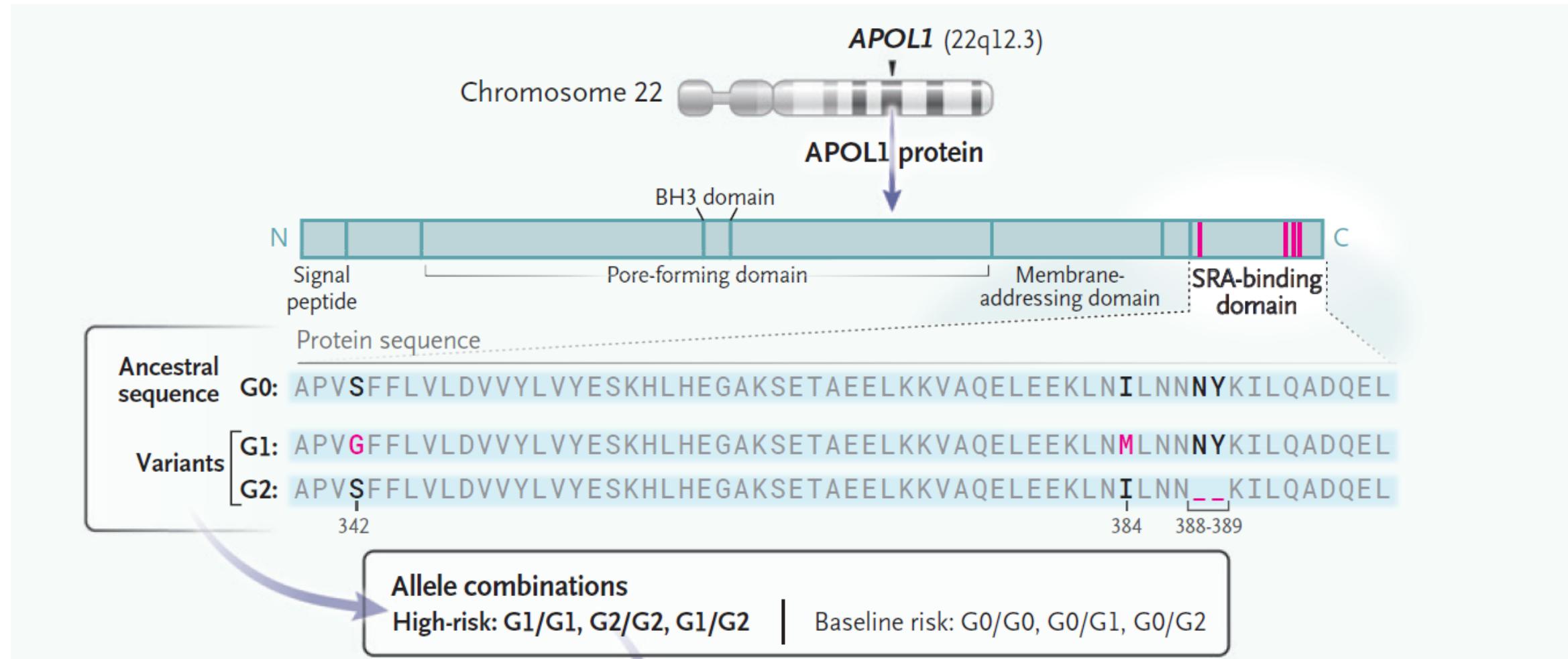
SCIENCE VOL 329 13 AUGUST 2010

#Approach: Admixture-mapping linkage-disequilibrium (MALD) genome scan

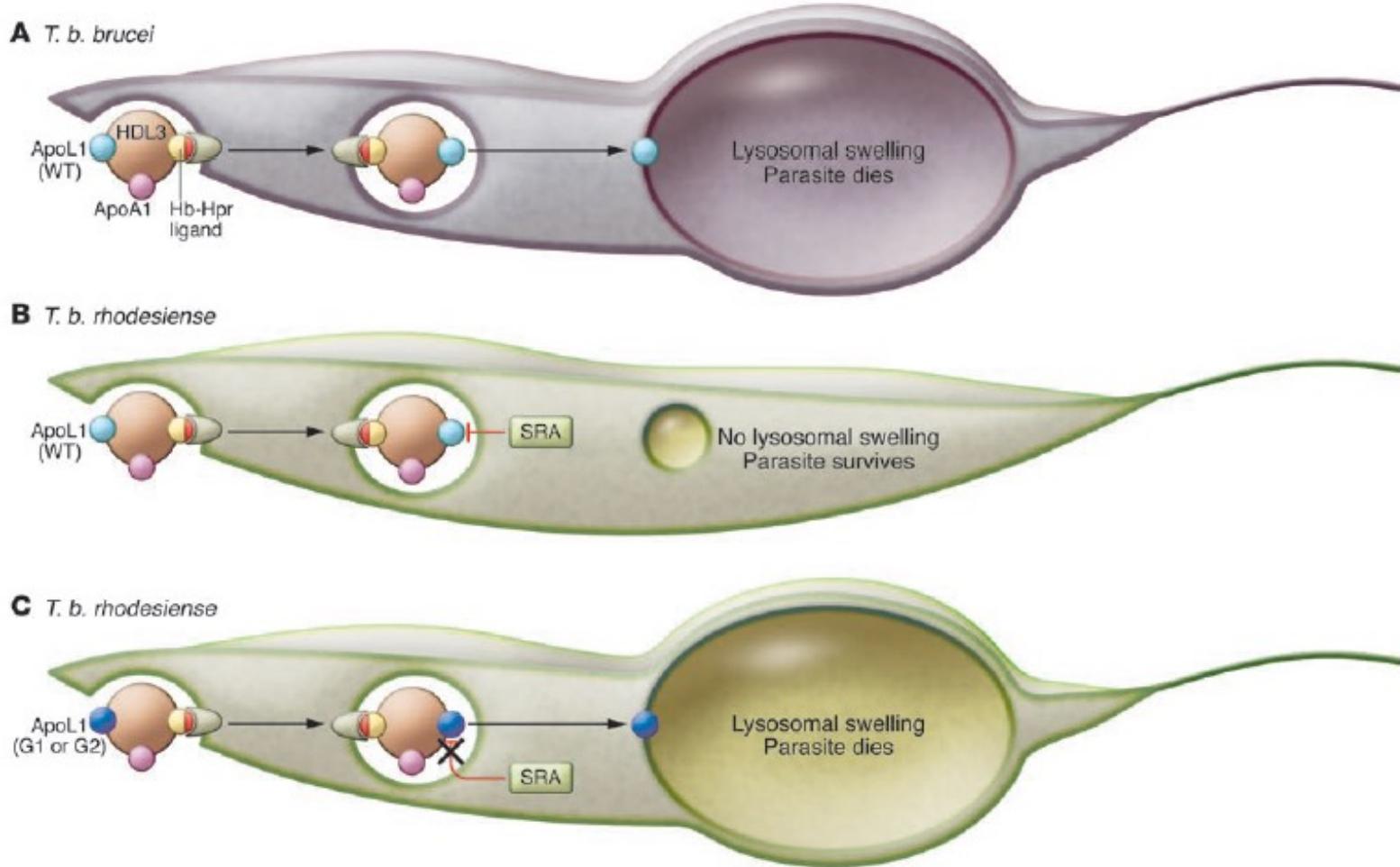
#Discovery cohorts: 205 AAs with FSGS;
180 Controls

#Result:
Region on Xsome 22 → regional fine mapping → APOL1

APOL1 gene variants (G1 and G2) explain much of the excess risk of kidney failure in African Americans

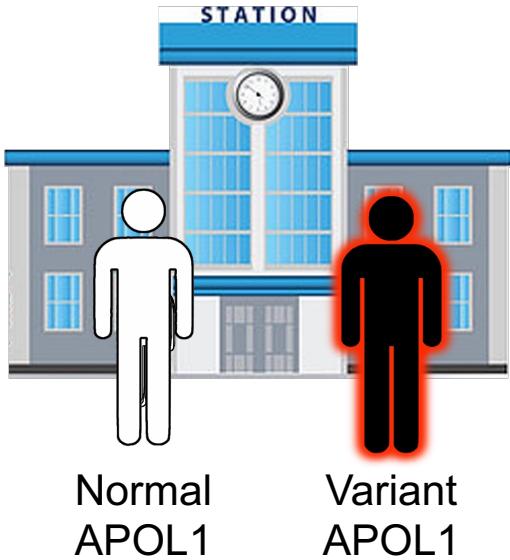


APOL1 G1 and G2 were selected for innate immune benefits



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%**

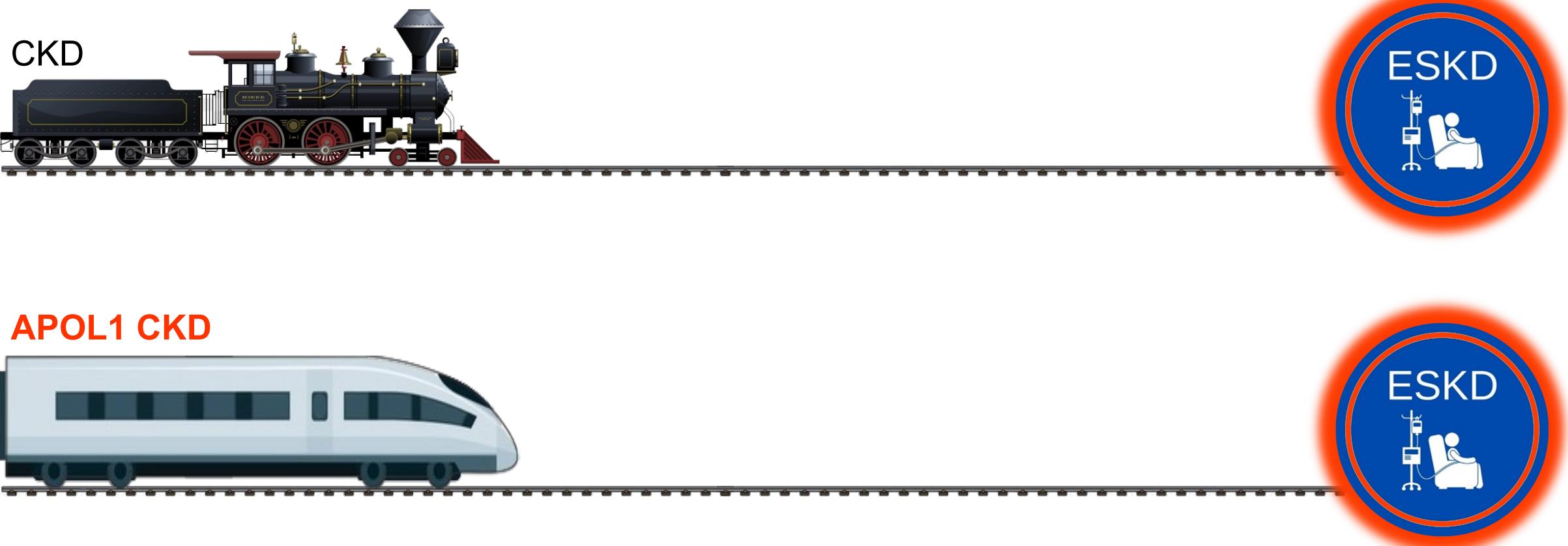
Lupus nephritis



Frequency of HR APOL1: **25%**

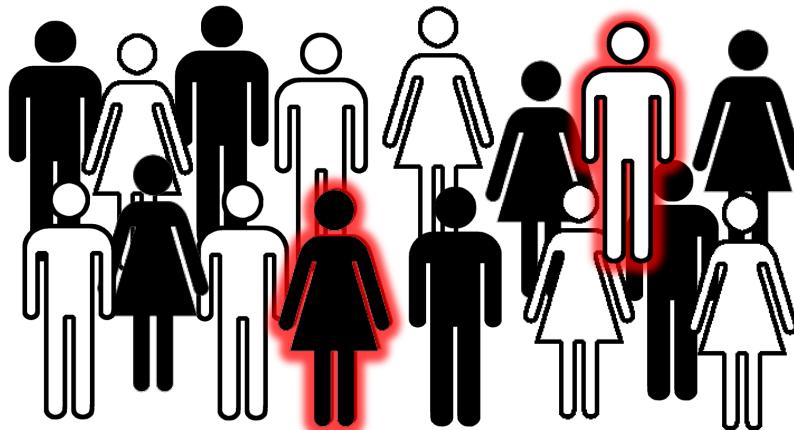


High Risk APOL1 Accelerates Progression of Kidney Disease to Dialysis (It speeds up the train)

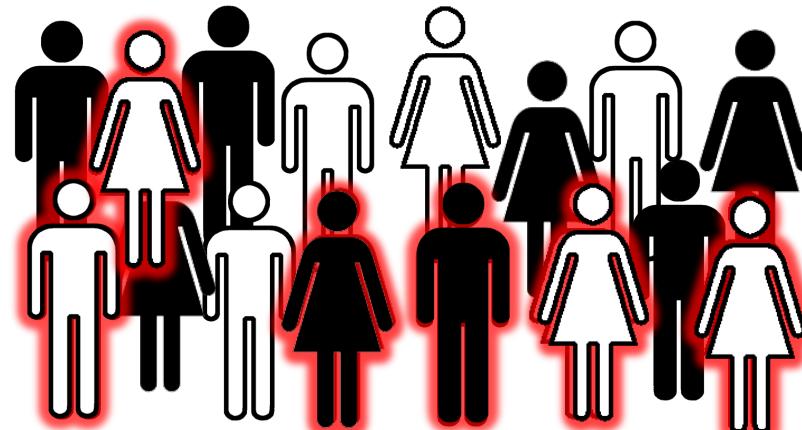


No Known Intervention That Slows This CKD Progression

Never Smoked



Ever Smoked



Lung Cancer

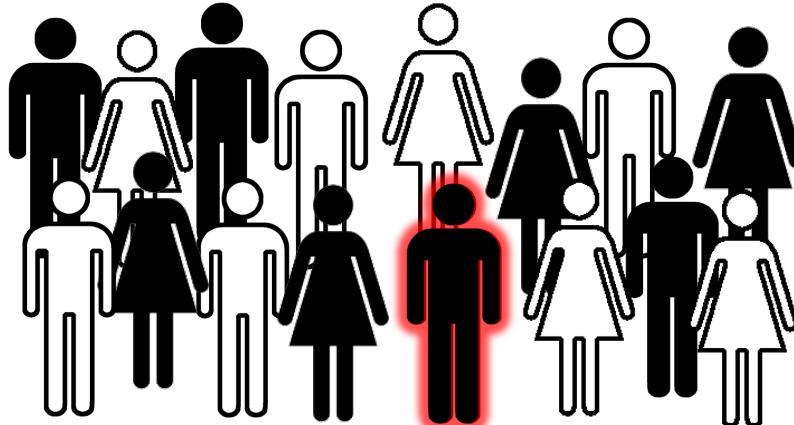
↑ Risk Males

7.8x

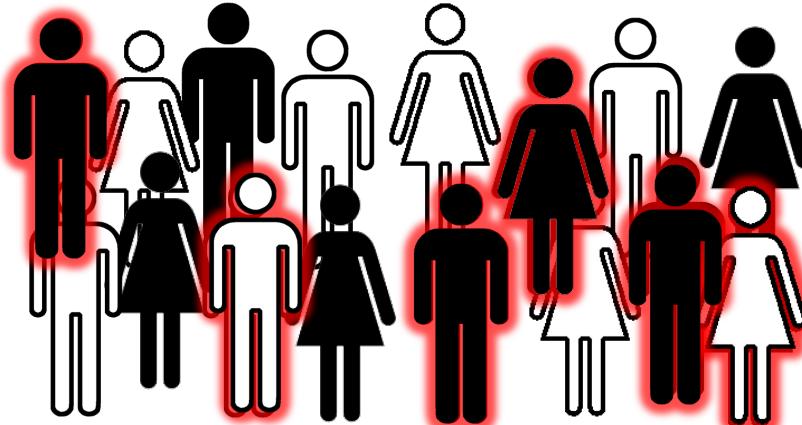
↑ Risk Females

11.8x

Low-Risk APOL1 Genotype



High-Risk APOL1 Genotype



↑ FSGS Risk

17%

↑ Hypertension
Attributed Kidney
Disease Risk

7-10x

A Key Take Home Point

“It is the theory which decides what we can observe”

-Albert Einstein

i.e, our understanding and interpretation of observations are deeply influenced by the theoretical frameworks we use. In essence, what we believe shapes what we see or, at the very least, how we interpret what we see.

Questions

APOL1-Mediated Kidney Disease: Olabisi Lab Research Strategy

