



EPIDEMIOLOGY OF *APOL1* KIDNEY DISEASE

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Accra
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DISCLOSURES

- None

Outline

- Distribution of *APOL1*
- Spectrum of *APOL1* nephropathy
- Association of *APOL1* HR genotypes with kidney disease in US, SSA and UK
- *APOL1* and HIV kidney disease in children
- Association of *APOL1* HR genotypes and renal outcomes
- 2nd hits

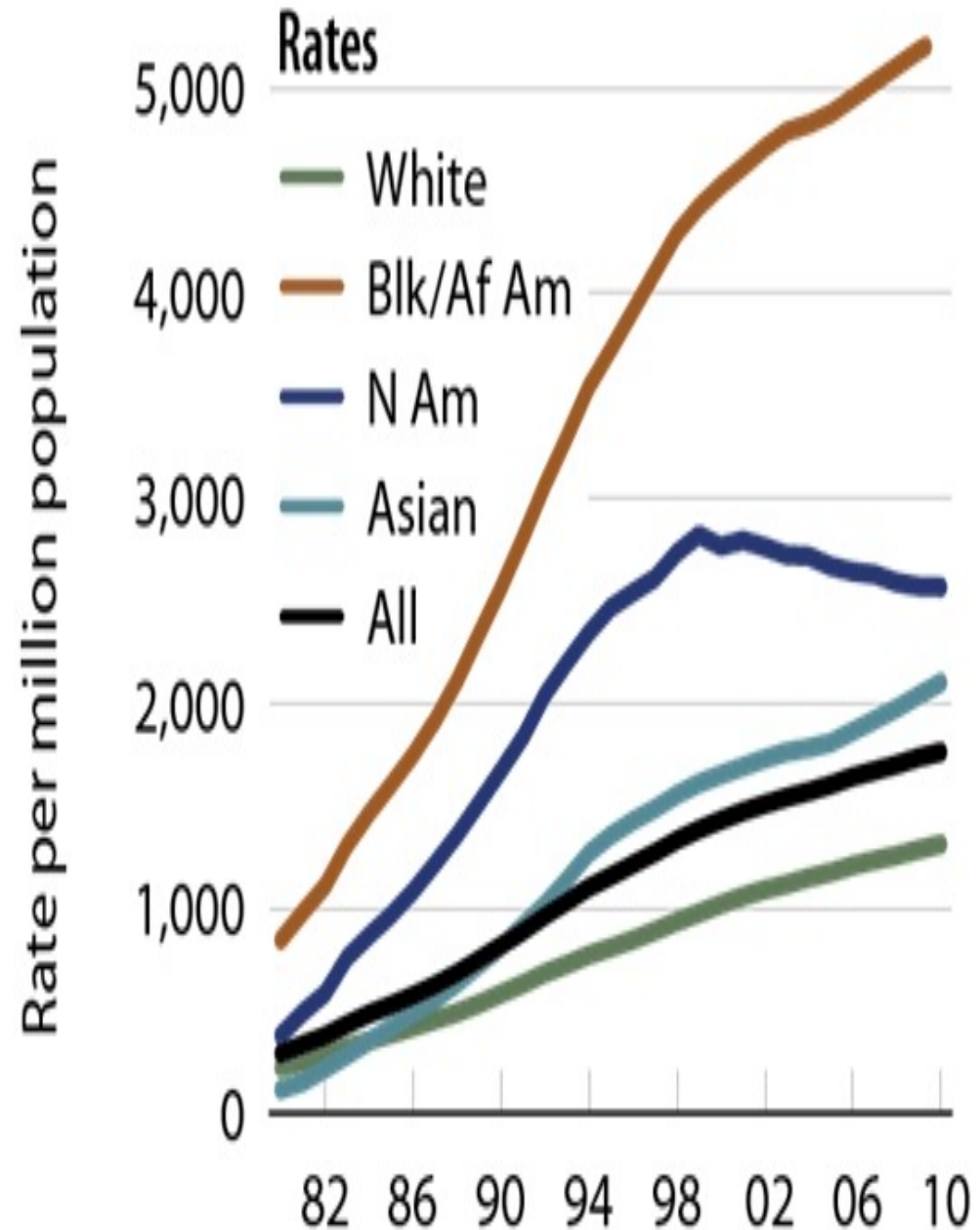
CKD and African Ancestry

Patterns of kidney disease associated with African ancestry

- FSGS
- Hypertensive nephrosclerosis
- Steroid resistant nephrotic syndrome
- HIVAN

CKD prevalence

- CKD is a major public health problem
- Estimated 3,2million people on RRT, with CKD incidence growing by 6% annually (WHO)
- Cumulative lifetime risk for CKD varies by ancestry
- African descent are the most affected (4X more likely than of European origin)
- HIV CKD **18-50X** increase in people of African descent



Rates adjusted for age and gender (USRDS 2012)

APOL1 Prevalence across Populations

Map Ref.	Population	Country	%G1 ^G	%G1 ^M	%G2	N	Source	References
			p.S342 G	p.I384 M	p.N388/Y389			
West Africa								
1	Mandenka	Senegal	5	2.4	21.4	22	HGDP	Kopp et al ²
2	Yoruba	Nigeria	45.2	45.2	7.5	60	HapMap	Kopp et al ²
2	Yoruba	Nigeria	45.2	45.2	16.7	25	HGDP	Kopp et al ²
2	Yoruba	Nigeria	39	39	6	18	—	Ko et al ^B
3	Igbo	Nigeria	30.2	30.2	24.4	43	—	Ulasi et al ¹¹
4	Bulsa	Ghana	11.4	11.4	21.4	22	—	Tzur et al ¹⁰
5	Asante	Ghana	40.9	41.2	12.9	35	—	Tzur et al ¹⁰
West Central Africa								
6	Fulani	Cameroon	0	0	8	19	—	Ko et al ^B
7	Lemande	Cameroon	0	0	3	18	—	Ko et al ^B
8	Mada	Cameroon	3	3	3	19	—	Ko et al ^B
9	Bakola	Cameroon	5	5	5	19	—	Ko et al ^B
10	Somie	Cameroon	16.4	15.3	12.3	65	—	Tzur et al ¹⁰
11	Far North-CMR/Chad	Cameroon	0.8	0	3.3	64	—	Tzur et al ¹⁰
12	COG	Republic of Congo	10.9	9.3	4.5	55	—	Tzur et al ¹⁰
Central Africa								
13	Biaka	Central African Republic	4.2	4	10.0	36	HGDP/Kidd	Kopp et al ²
14	Mbuti	Democratic Republic of Congo	0	0	3.8	15	HGDP/Kidd	Kopp et al ²

Limou et al.

Advances in Chronic Kidney Disease, Vol 21, No 5 (September), 2014: pp 426-433

APOL1 Prevalence across Populations

Map Ref.	Population	Country	%G1 ^G	%G1 ^M	%G2	N	Source	References
			p.S342 G	p.I384 M	p.N388/Y389			
North Africa								
15	Mozabite	Algeria	1.8	1.8	0	30	HGDP	Kopp et al ²
16	Kordofan	Sudan	0	1.7	5	30	—	Tzur et al ¹⁰
17	Afar	Ethiopia	0	0	0	76	—	Tzur et al ¹⁰
18	Amhara	Ethiopia	0	0	0	76	—	Tzur et al ¹⁰
19	Annuak	Ethiopia	2	2	2.7	76	—	Behar et al ⁹
20	Maale	Ethiopia	0	0	0	76	—	Tzur et al ¹⁰
21	Oromo	Ethiopia	0	0	0	76	—	Tzur et al ¹⁰
East Africa								
22	Luhya	Kenya	5.1	5.4	7.1	90	HapMap	Kopp et al ²
23	Borana	Kenya	0	0	3	18	—	Ko et al ⁸
24	Sengwer	Kenya	0	0	3	19	—	Ko et al ⁸
25	Bantu-NE	Kenya	4.5	4.5	4.5	12	HGDP	Kopp et al ²
26	Hadza	Tanzania	5	5	0	19	—	Ko et al ⁸
27	Iraqw	Tanzania	5	5	3	19	—	Ko et al ⁸
28	Sadawe	Tanzania	5	5	0	19	—	Ko et al ⁸
Southeastern Africa								
29	MWI	Malawi	12	12	12	50	—	Tzur et al ¹⁰
30	Sena	Mozambique	12.2	12.0	11.0	51	—	Tzur et al ¹⁰
Southern Africa								
31	San	Namibia	0	0	1	7	HGDP	Kopp et al ²
32	Motswana	Botswana	5.5	5.13	5.5	570	—	Winkler/Wester*
33	Bantu-SA	South African	7.1	7	21.4	8	HGDP	Kopp et al ²
34	Zulu	South African	5.3	5.0	5.5	113	—	Bhimma/Winkler*
Total						2204		

Limou et al.

Advances in Chronic Kidney Disease, Vol 21, No 5 (September), 2014: pp 426-433

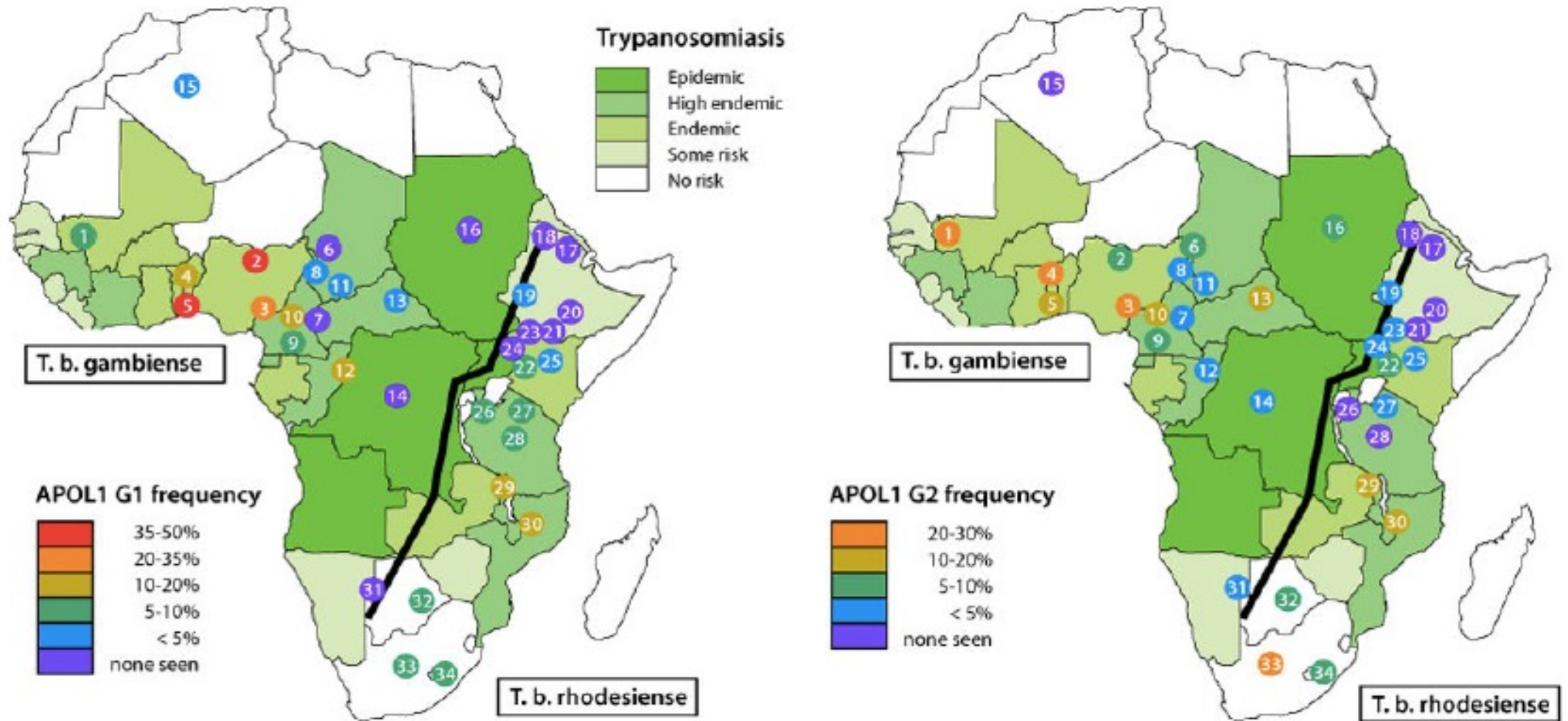
APOL1 Prevalence across Populations

Map Ref.	Population	Country	%G1 ^G	%G1 ^M	%G2	N	Source	References
			p.S342 G	p.I384 M	p.N388/Y389			
South and Central Asia								
	Balochi	Pakistan	0	0	2.1	25	HGDP	Kopp et al ²
	Other	8 Populations	0	0	0	195	HGDP	Kopp et al ²
	Eastern Asia	18 Populations	0	0	0	231	HGDP	Kopp et al ²
	Europe (8 populations)	8 Populations	0	0	0	161	HGDP	Kopp et al ²
	Oceania (2 populations)	2 Populations	0	0	0	39	HGDP	Kopp et al ²
	Europe (8 populations)	8 Populations	0	0	0	161	HGDP	Kopp et al ²
	Native Americans	5 Populations	0	0	0	107	HGDP	Kopp et al ²
North America								
	African Americans	Mid-Atlantic United States	22.1	22.0	13.4	383	—	Kopp et al ²
	African Americans	Southwest United States	19.7	19.7	NR	61	1000GP	1000GP ¹³
	African Americans	—	22.6	22.2	13.4	2200	ESP6500	ESP6500 ¹²
	African Americans	New York	20.9	20.4	15.3	148	—	Tzur et al ¹⁰
	European Americans	—	0	0	0	4000	ESP65000	ESP6500 ¹²
	European Americans	Utah	0	0	0	85	1000GP	1000GP ¹³
	US Hispanic-New York City	New York	1.8	1.8	NR		—	Tzur et al ¹⁰
	US Mexicans-Los Angeles	California	0	0	0	66	1000GP	1000GP ¹³

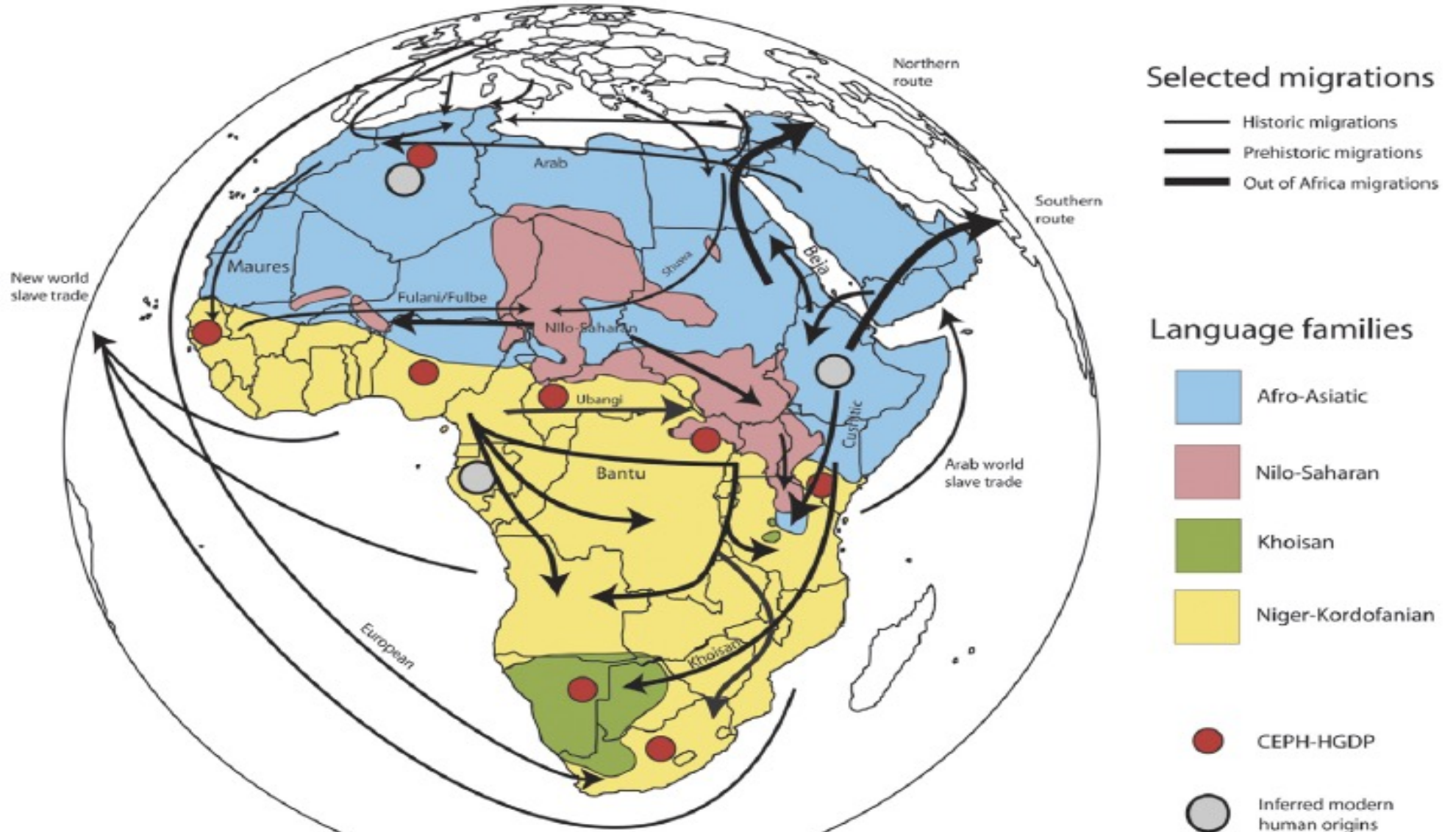
Limou et al.

Advances in Chronic Kidney Disease, Vol 21, No 5 (September), 2014: pp 426-433

Geographic Distribution of *APOL1* Risk Alleles & Trypanosoma



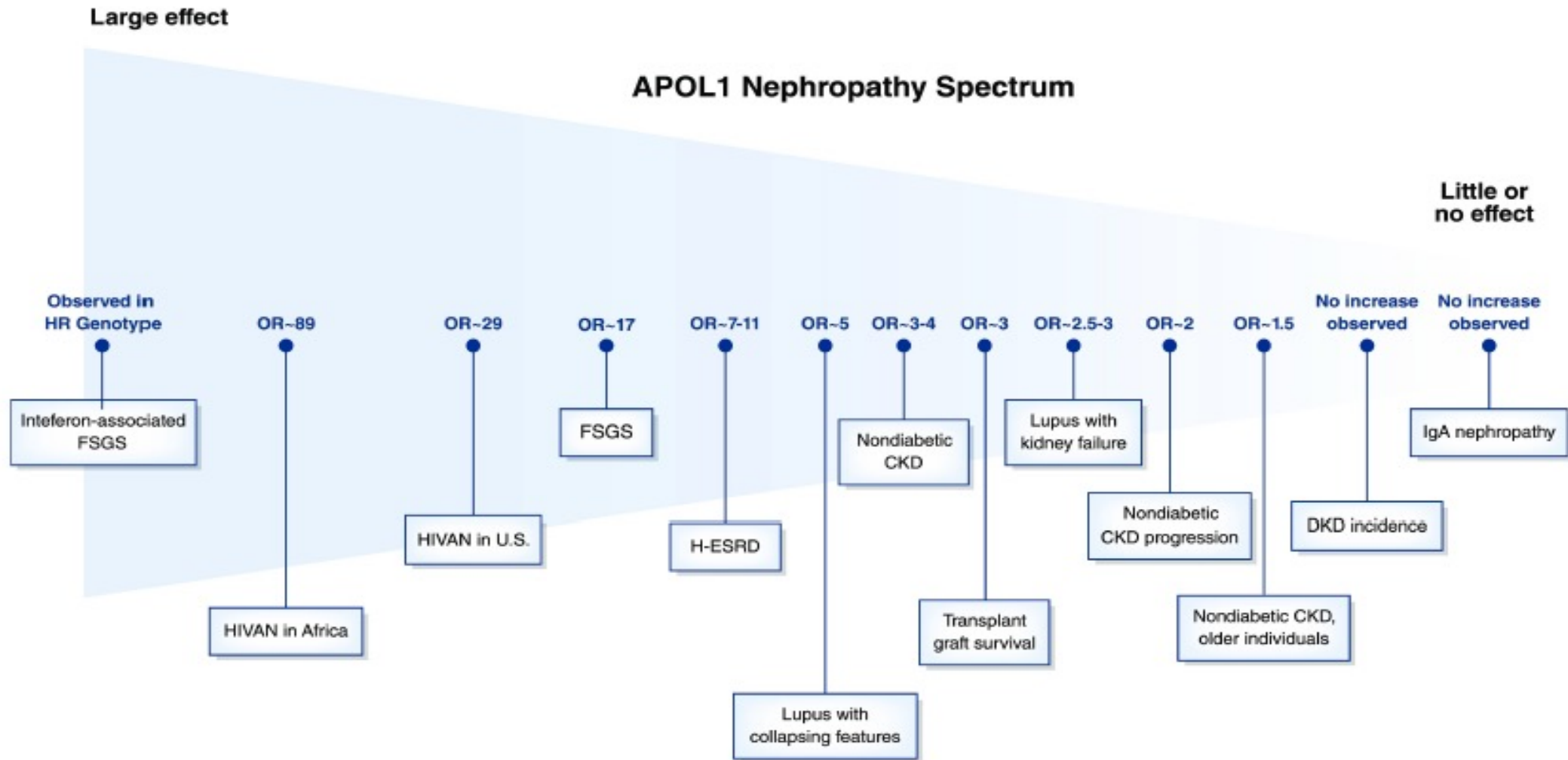
Human Diversity, Migration and Origins



Floyd Reed and Sarah Tishkoff

Current Opinion in Genetics & Development 2006, 16:597-605

Spectrum of *APOL1* Nephropathy



Friedman DJ & Pollak MR

Clin J Am Soc Nephrol. 2021 Feb 8; 16(2): 294–303.

Published online 2020 Jul 2. doi: 10.2215/CJN.15161219: 10.2215/CJN.15161219

Prevalence of *APOL1* HR Genotypes in Different African Populations

Histology in PLWH	Population (n)	<i>APOL1</i> high-risk genotype frequency (%)			Odds ratios (95% CI) for 2 versus 1 or 0 risk alleles	Ref.
		HIV negative no CKD	HIV positive no CKD	HIV positive with specific histology		
HIVAN	African American (n=54)	NR	NR	72	29.2 (13.1-68.5)	77
	African American (n=60)	NR	NR	NR	3.01 (1.2-7.59)	79
	South African (n=38)	1.9	3.7	79	89 (17.7-912)	78
	Northern Nigerian (n=17)	5.8	0	12.5 ^a	5.5 (0.83-36.29)	80
FSGS	South African (n=22)	1.9	3.7	8	2.1 (0.03-44)	78
	Northern Nigerian (n=20)	5.8	0	12.5 ^a	9.0 (1.62-50.12)	80
ICD	South African (n=12)	1.9	3.7	25	5.6 (0.4-86)	78

CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; ICD, immune complex-mediated disease; NR, not reported; PLWH, people living with HIV. ^a*APOL1* high-risk genotype frequency of 12.5% among those with HIV-associated kidney disease in the Northern Nigerian cohort.

Diana, N.E., Naicker, S. The changing landscape of HIV-associated kidney disease. *Nat Rev Nephrol* (2024). <https://doi.org/10.1038/s41581-023-00801-1>

APOL1 High Risk Genotypes associated with Kidney Disease in USA and SSA

Phenotype	Country	Setting	No. of cases	No. of controls	OR	Ref.
Non-diabetic ESKD	USA	Adults on dialysis	1002	923	7.3	(21)
ESKD	Brazil	Adults on dialysis	106	106	10.95	(48)
Stage 5 CKD	SA	Adults, mean eGFR 8 (4–12)	70	58	0.85 ^a	(98)
CKD	DRC	Adults, hypertensive CKD	79	83	7.7	(65)
CKD	Nigeria	Adults	44	43	4.8	(42)
FSGS	USA	Adults	192	176	10.5	(21)
FSGS	USA	Mostly adults	217	383	17	(46)
FSGS	SA	Adults	22	108	2.1 ^a	(68)
HIVAN	USA	Adults, HIV+	54	237	29	(46)
HIVAN	SA	Adults, HIV+	78	108	89	(68)
Albuminuria	USA	Young to middle-aged adults	2.9		2.9	(64)
Albuminuria	DRC	Pediatric population	2.1	40	412	(66)
Albuminuria	DRC	Pediatric population, HIV+	22.0	72	329	(66)

^aNot statistically significant. SA, South Africa; USA, United States of America; DRC, Democratic Republic of the Congo.

Aminu Abba Yusuf, Melanie A Govender, Jean-Tristan Brandenburg, Cheryl A Winkler, Kidney disease and APOL1, *Human Molecular Genetics*, Volume 30, Issue R1, 1 March 2021, Pages R129–R137, <https://doi.org/10.1093/hmg/ddab024>

APOL1 in CKD

Hypertension

OR 7 [Genovese et al. Science 2010]

2.57 in AASK Study (incr to 6.29 in advanced CKD) [Lipkowitz et al. Kidney Int 2012]

FSGS : OR 17 [Kopp et al. JASN 2011]

HIVAN: OR 29 [Kopp et al. JASN 2011]

OR 89 in our SA Study [Kasembeli et al. JASN 2015]

Children with perinatal HIV infection:

3X incr odds of CKD with high risk genotype

median age of 8.8 vs 14.3 years in those with 0 or 1 risk allele

[Purswani et al. JAIDS 2016]

Lupus nephropathy: OR 2.7-5.4

Sickle cell nephropathy: OR 3.4 [Limou et al. Adv in Chr Kidney Dis. 2014]

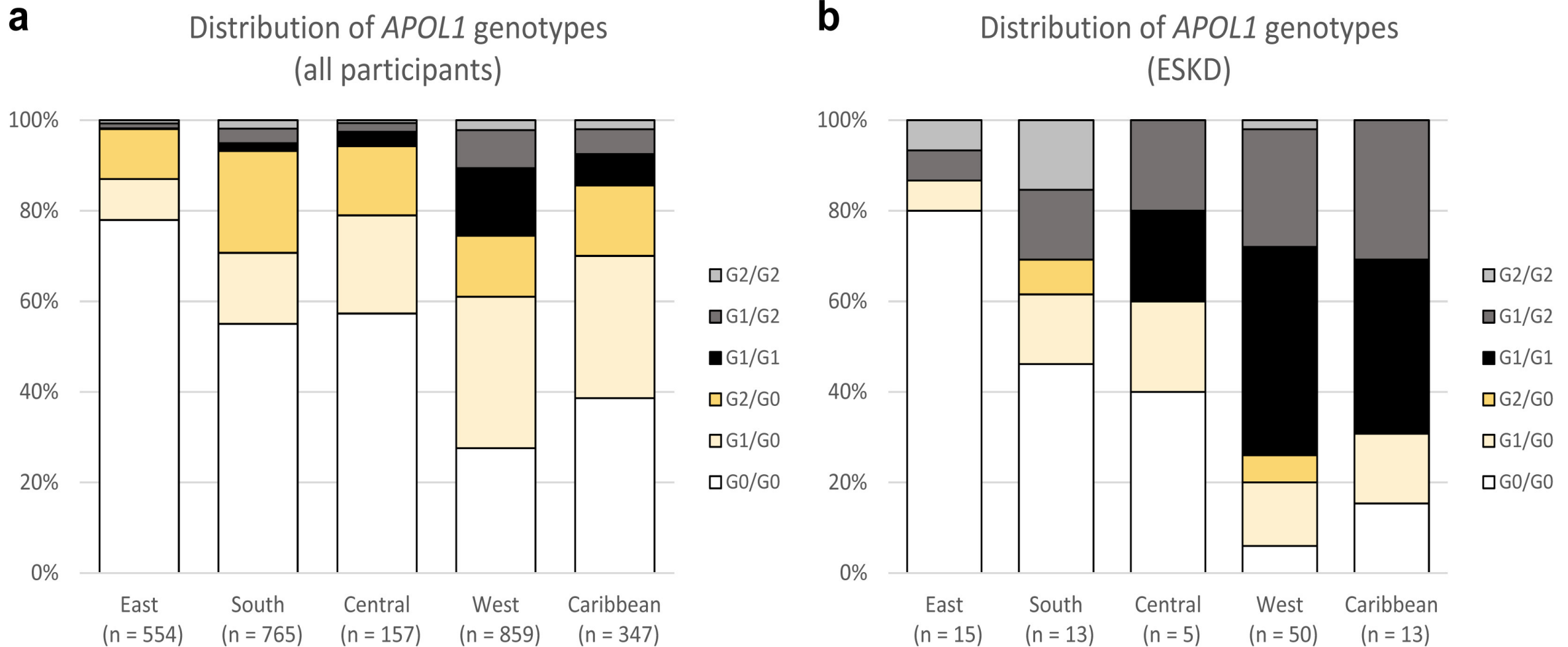
APOL1 in HIVAN, CKD and Controls

78.9% of HIVAN were homozygous (G1/G1 or G2/G2) or compound heterozygotes (G1/G2), compared to 3.7% of the HIV (+) controls ($P=1.2 \times 10^{-14}$) and 1.9% of population controls ($P=8.9 \times 10^{-16}$)

GENOTYPE	HIV (+) Cases and Controls			HIV (-) Cases and Controls	
	HIVAN N (%)	CKD N (%)	Controls N (%)	CKD N (%)	Controls N (%)
0 risk allele	2 (5.3)	22 (56.4)	34 (63.0)	26(66.7)	36 (66.7)
1 risk allele	6 (15.8)	12 (30.8)	18 (33.3)	12(30.8)	17 (31.5)
G0/G1	5 (13.2)	4 (10.3)	4 (7.4)	6 (15.4)	7 (13.0)
G0/G2	1 (2.6)	8 (20.5)	14 (25.9)	6 (15.4)	10 (18.5)
2 risk alleles	30 (78.9)	5 (12.8)	2 (3.7)	1 (2.6)	1 (1.9)
G1/G1	8 (21.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
G1/G2	19 (50.0)	2 (5.1)	0 (0.0)	1 (2.6)	0 (0.0)
G2/G2	3 (7.9)	2 (5.1)	2 (3.7)	0 (0.0)	1 (1.9)
Total	38	39	54	39	54

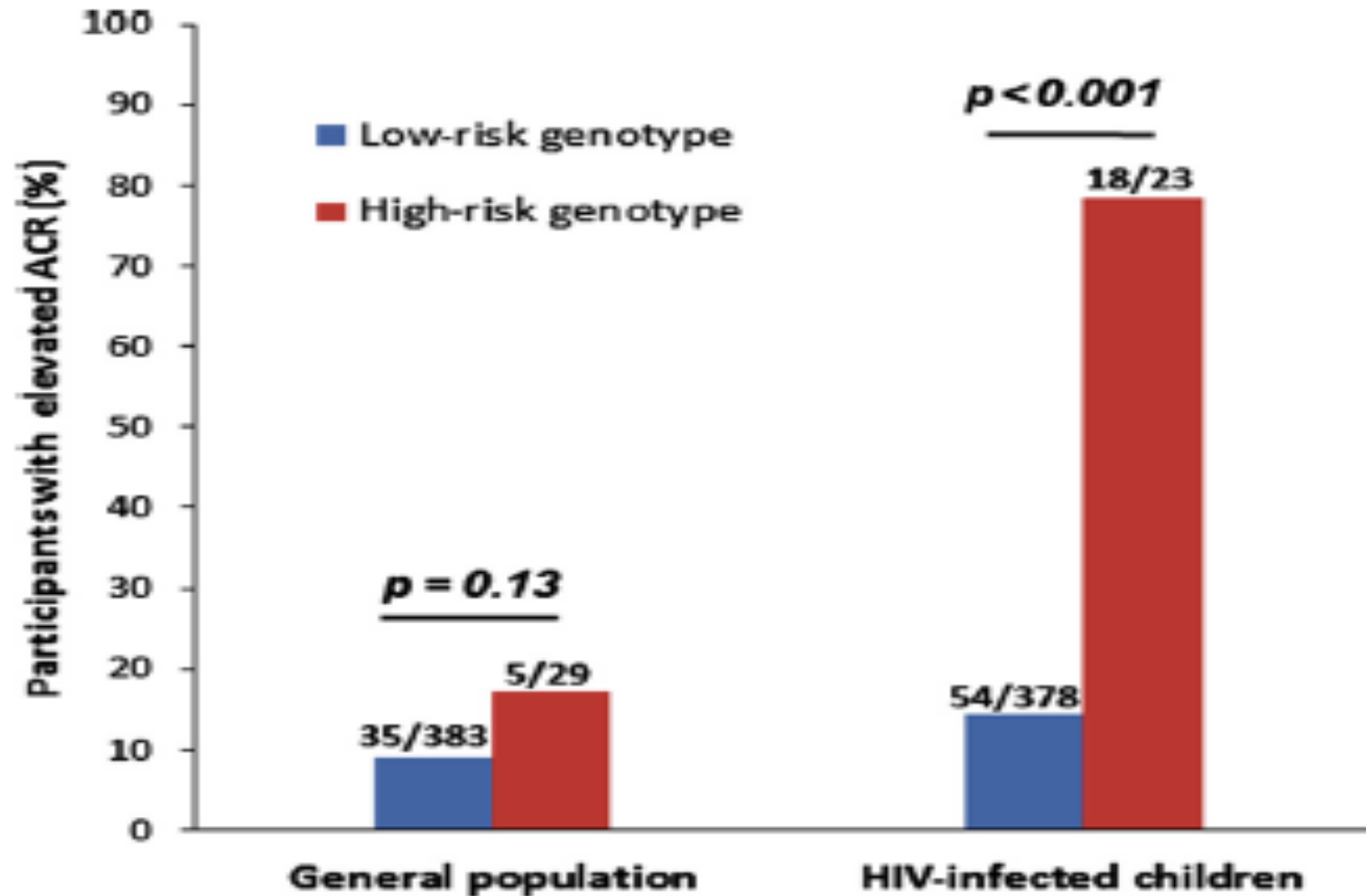
*The single HIV (+) CKD patient carrying the G1^M (A-G-I) haplotype is excluded from the table.

Distribution of *APOL1* GENOTYPES IN UK



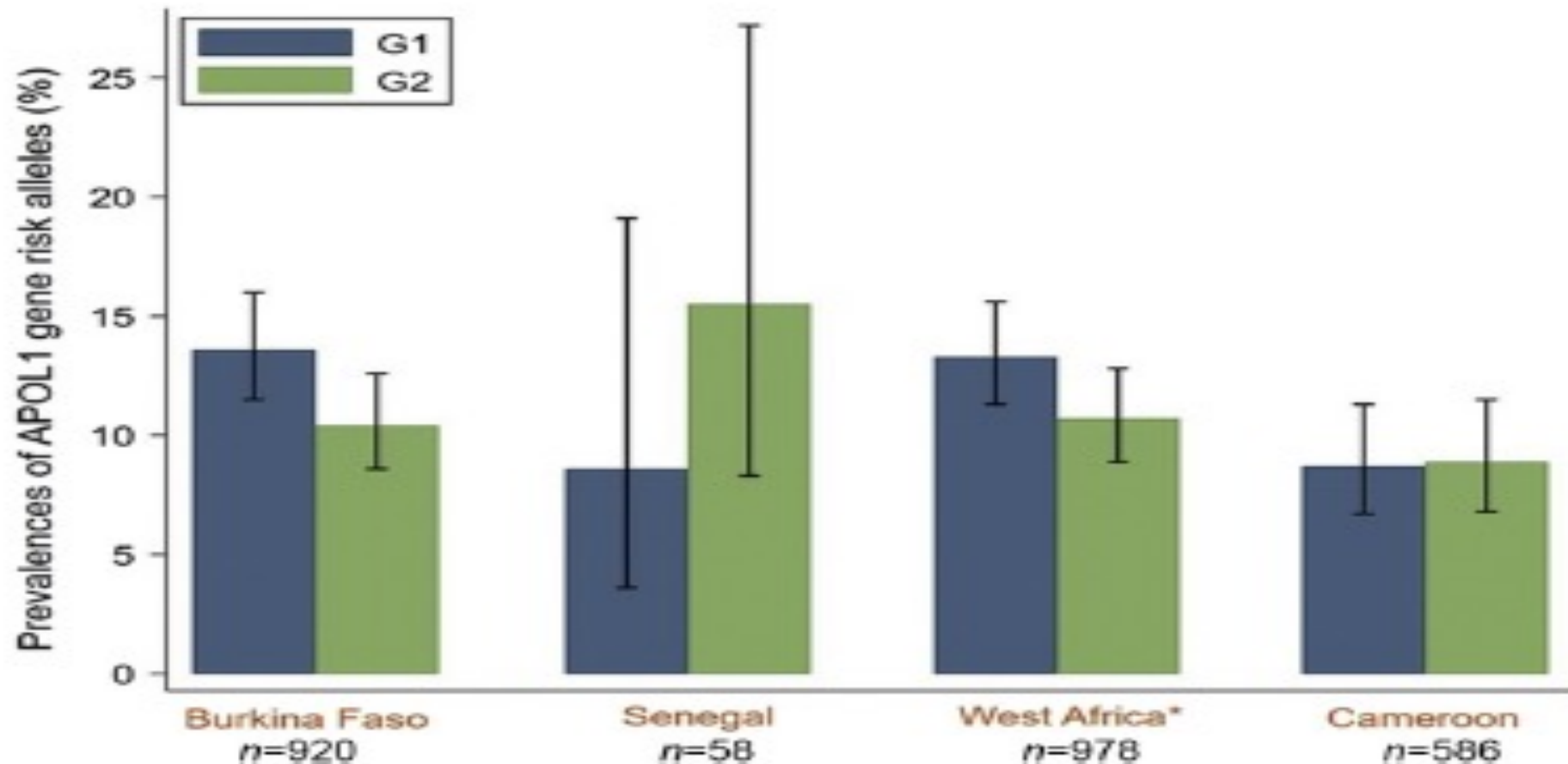
Hung RKY et al. GEN-AFRICA Study Group. Sickle Cell Trait and Kidney Disease in People of African Ancestry With HIV. *Kidney Int Rep.* 2021 Dec 13;7(3):465-473. doi: 10.1016/j.ekir.2021.12.007. PMID: 35257059; PMCID: PMC8897676.

APOL1 and Kidney Disease In Children in the DRC



Ekulu PM, Nseka NM, Aloni MN, Gini JL, Makulo JR, Lepira FB, Sumaili EK, Mafuta EM, Nsibu CN, Shiku JD. Prévalence de la protéinurie et son association avec le VIH/sida chez l'enfant à Kinshasa, Congo [Prevalence of proteinuria and its association with HIV/AIDS in Congolese children living in Kinshasa, Democratic Republic of Congo]. *Nephrol Ther.* 2012 Jun;8(3):163-7. French. doi: 10.1016/j.nephro.2011.09.004. Epub 2011 Nov 3. PMID: 22056079.

APOL1 Risk Variants in PWH in West Africa & Cameroon



No direct association between *APOL1* HR and eGFR change over time.

Among the 2LADY cohort participants, those with both *APOL1* HR and high baseline viral load had a faster eGFR progression ($\beta = -3.9[-7.7 \text{ to } -0.1]$ ml/min per 1.73 m^2 per year, $P < 0.05$) than those with LR genotype and low VL.

Apolipoprotein L1 high-risk genotypes and albuminuria in Sub-Saharan African Populations

Design and Methods



Cross-sectional population-based study in 4 Sub-Saharan African countries



APOL1 risk allele and genotype frequencies determined and genetic associations assessed for kidney disease



N=10,769

G1 allele frequencies



Highest in South and West Africa (~7-13%)



G2 allele frequencies



South Africa 15-24%



West Africa 9-12%

Association between APOL1 risk variants and albuminuria and eGFR <60 mL/min/1.73 m²



Albuminuria

OR 1.63

(additive model)

OR 1.39

(recessive model)



eGFR <60

NS

(additive model)

NS

(recessive model)

Association between APOL1 risk variants and albuminuria, compared to G0/G0, stronger for

G1/G1

OR 3.87

(95% CI: 2.16-6.93)

Compared to

G2/G2

OR 1.65

(95% CI: 1.09-2.51)

Or

G1/G2

OR 1.24

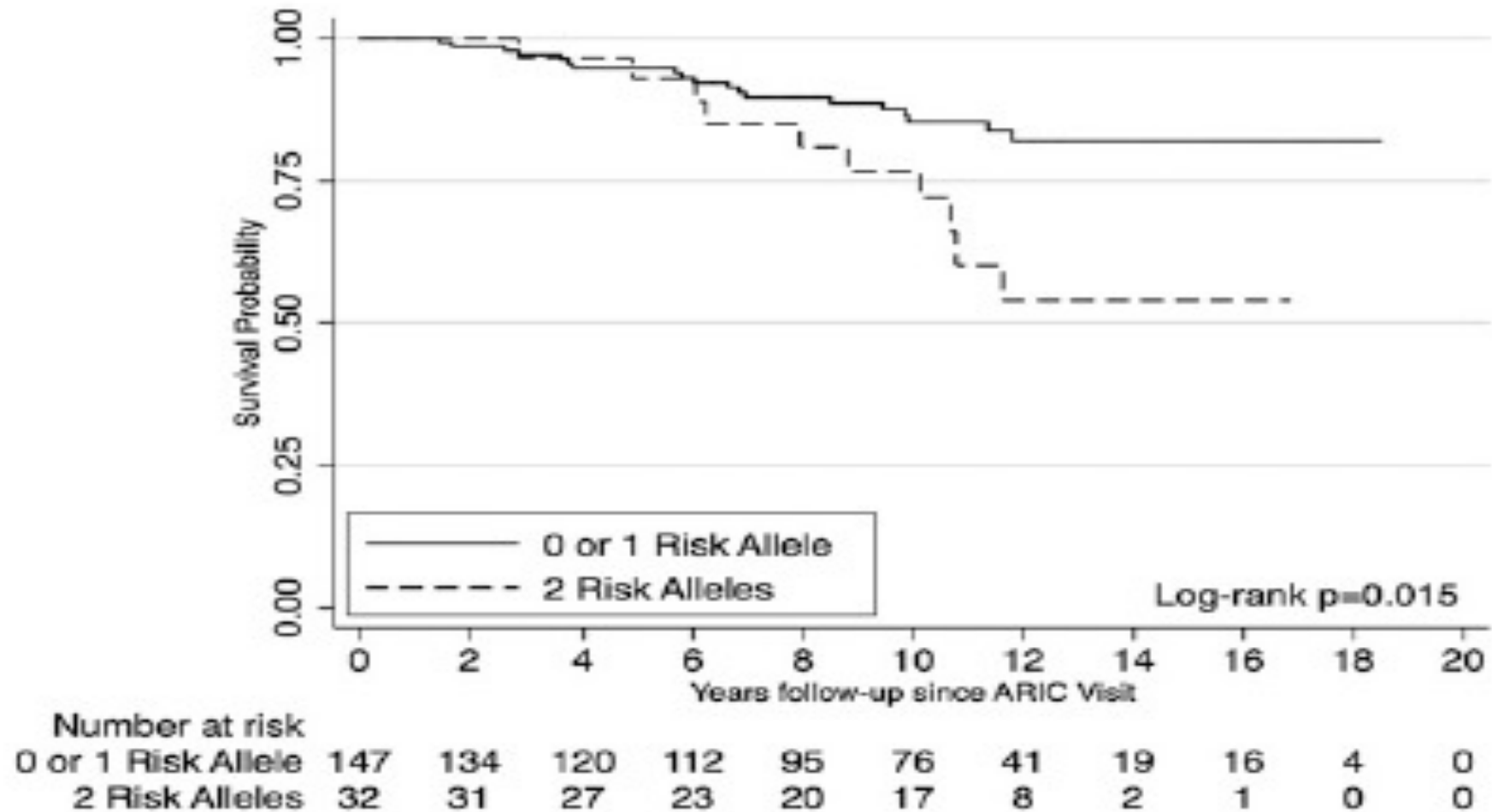
(95% CI: 0.83-1.87)

Results

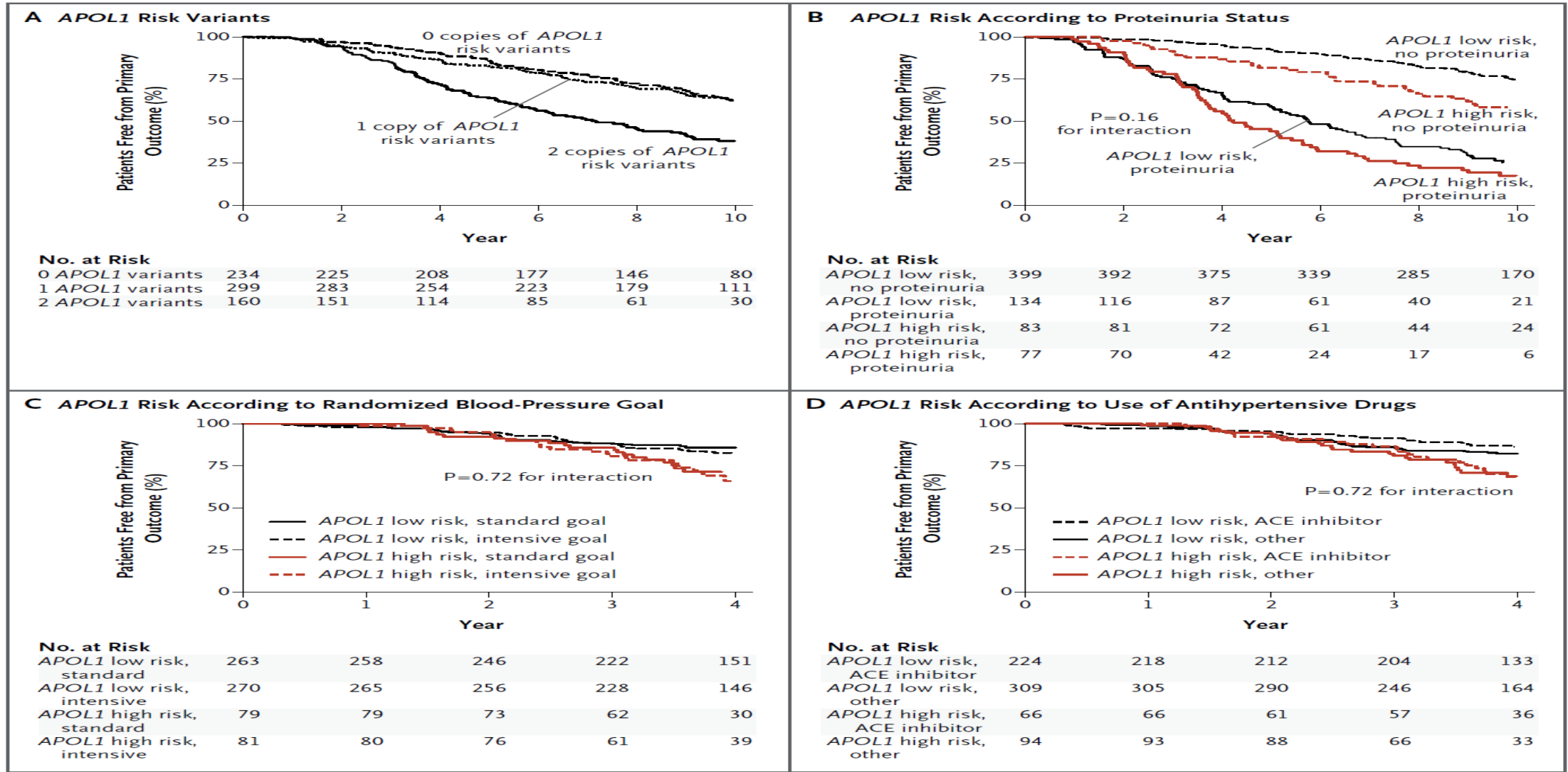
Conclusions: APOL1 G1 and G2 alleles and high-risk genotype frequencies differed between and within different African regions. APOL1 risk variants were associated with albuminuria, but not eGFR <60 mL/min/1.73 m². There may be differential effects of different APOL1 high-risk genotypes on albuminuria.

Jean-Tristan Brandenburg, Melanie A. Govender, Cheryl A. Winkler, et al., *Apolipoprotein L1 High-Risk Genotypes and Albuminuria in Sub-Saharan African Populations*. CJASN doi: 10.2215/CJN.14321121. Visual Abstract by Nayan Arora, MD

Progression to ESKD according to *APOL1* Status



APOL1 and CKD progression in AASK Cohort



Associations between *APOL1* HR Genotypes & Renal Outcomes

Participant characteristics	N	Univariable			Multivariable		
		OR	95% CI	P value	OR	95% CI	P value
Primary outcome							
End-stage kidney disease	99	10.31	6.81–15.60	<0.001	10.58	6.22–17.99	<0.001 ^a
Secondary outcomes							
Proteinuria (PCR >100 mg/mmol)	67	1.83	0.97–3.46	0.06			
Albuminuria (ACR >30 mg/mmol)	99	2.57	1.59–4.17	<0.001	3.34	2.00–5.56	<0.001 ^b
eGFR <60 ml/min per 1.73 m ²	221	5.65	4.19–7.61	<0.001	5.50	3.81–7.95	<0.001 ^c
FSGS/HIVAN/hypertensive nephropathy (clinical diagnosis)	19	14.64	5.46–39.27	<0.001	12.77	4.46–36.59	<0.001 ^d
FSGS (biopsy confirmed)	15	11.81	4.17–33.39	<0.001	12.86	4.04–40.99	<0.001 ^d
HIVAN (biopsy confirmed)	37	24.49	11.45–52.36	<0.001	30.16	12.48–72.88	<0.001 ^d

APOL1 and CKD

- 3030 young adults with preserved GFR in the Coronary Artery Risk Development in Young Adults (CARDIA) study.
- Study population: white (n=1700), high-risk black (two *APOL1* risk alleles, n=176), and low-risk black (zero/one risk allele, n=1154).
 - Mean age 35 years,
 - mean eGFR_{cys} was 107 ml/min per 1.73 m²
- 13.2% of blacks had two *APOL1* alleles.
- OR (95% confidence interval) for **incident albuminuria**
 - 5.71 (3.64-8.94) for high-risk blacks
 - 2.32 (1.73-3.13) for low-risk blacks.
 - 1.21 for whites (0.86-1.71).
- high-risk blacks had a 0.45% **faster yearly eGFR_{cys} decline** over 9.3 years compared with whites.
- Low-risk blacks also had a faster yearly eGFR_{cys} decline compared with whites
- blacks with two *APOL1* risk alleles had the highest risk for albuminuria and eGFR_{cys} decline in young adulthood, whereas disparities between low-risk blacks and whites were related to differences in traditional risk factors.

FSGS and *APOL1* in Children

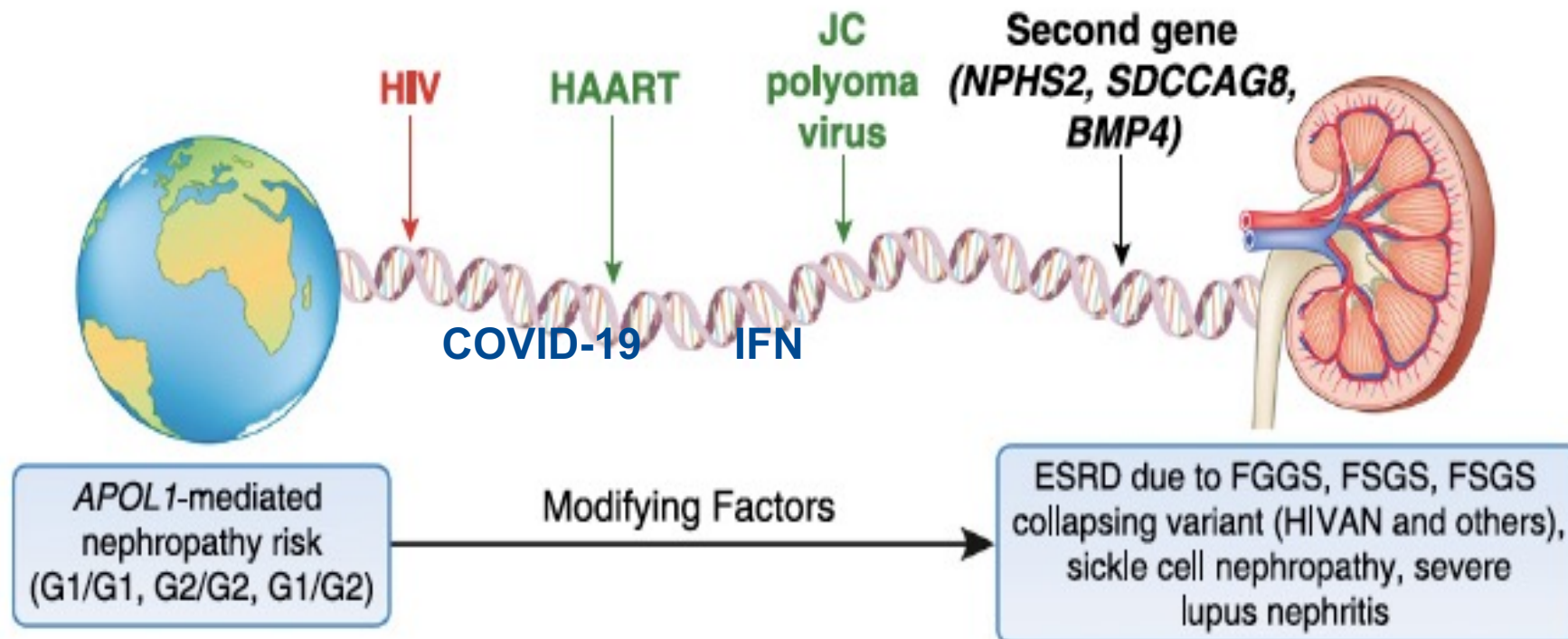
- The FSGS Clinical Trial involving 138 children and young adults
- Randomized to cyclosporin or mycophenolate mofetil plus pulse oral dexamethasone with a primary outcome of proteinuria remission.
- Two *APOL1* risk alleles were present in 27 subjects [four did not self-identify as African American, and 23 of 32 (72%) self-identified African Americans].
- ***APOL1* risk genotype**
 - tended to present at an older age
 - had significantly lower baseline eGFR
 - more segmental glomerulosclerosis and total glomerulosclerosis,
 - more tubular atrophy/interstitial fibrosis
 - more collapsing variants in those with the risk genotype ($P=0.02$), although this association was confounded by age.
- *APOL1* risk genotype did not affect response to either treatment regimen.
- Individuals with the risk genotype were more likely to progress to ESKD ($P<0.01$).

Children with SRNS/FSGS (Biopsy-proven) and Progression to Advanced CKD

	HR ^d (SE ^e)	95% CI ^f	<i>p</i>
Male sex	0.97 (0.16)	0.69-1.35	0.842
White ethnicity	1.02 (0.17)	0.74-1.41	0.909
<i>APOL1</i> low-risk genotype (<i>n</i> = 197)	1		
<i>APOL1</i> high-risk genotype (<i>n</i> = 16)	2.86 (0.71)	1.75-4.64	< 0.001

117/131 (89%) of FSGS were SRNS and 93/187 (50%) of non-FSGS patients were SRNS

Pathways leading from Genetic Susceptibility to Clinical Kidney Disease



Adapted from Freedman & Skorecki
Clin J Am Soc Nephrol 9: 2006–2013, 2014. doi: 10.2215/CJN.01330214

Response to ART

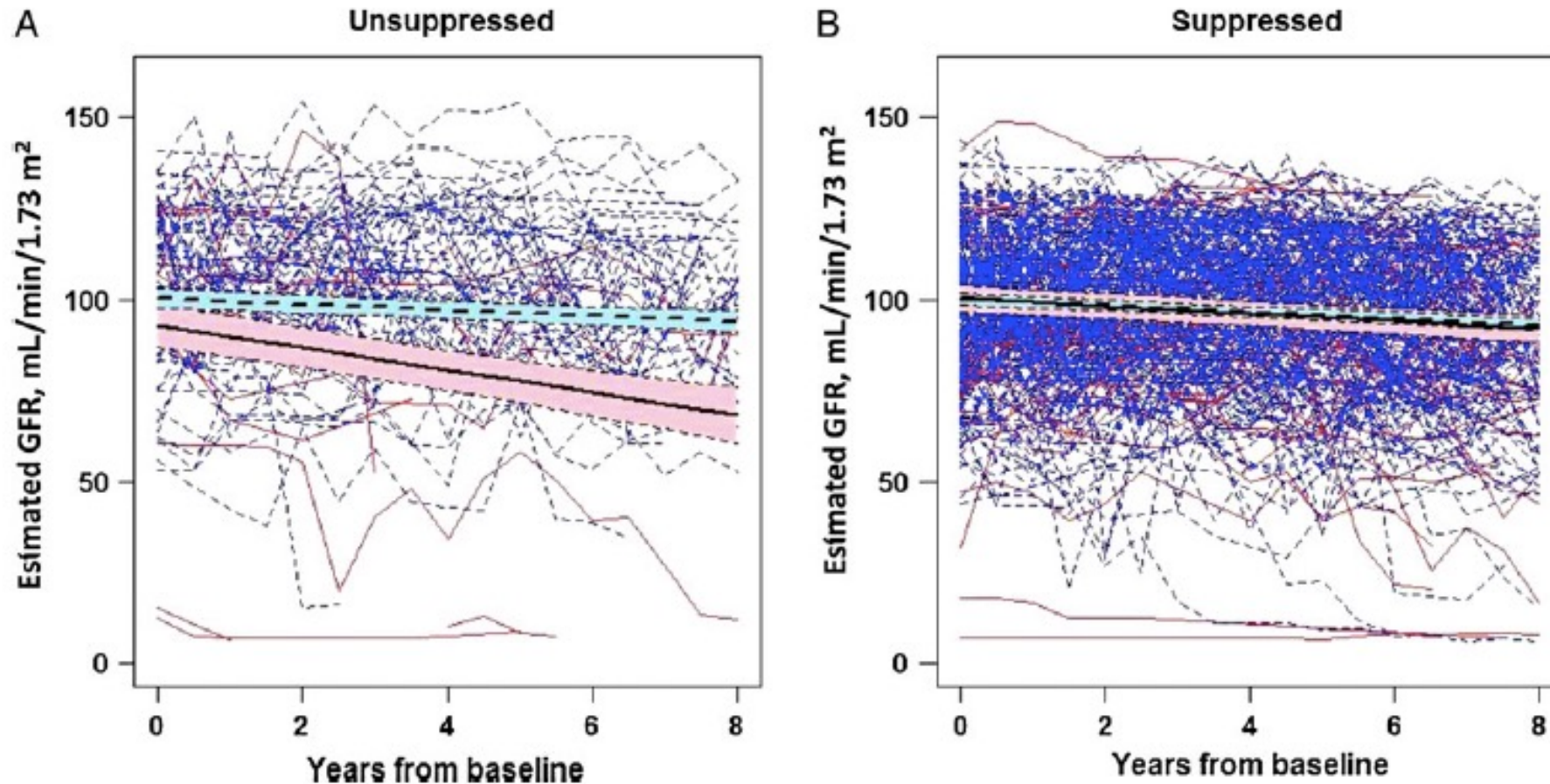
- **Response to ART**

- Rapid progression of HIVAN to ESKD if no/under-Rx [Kalayjian, 2010; Fine, 2012]
- 3x incr risk of ESKD in non-HIVAN in spite of effective ART/RAAS [Fine, 2012]

- ***APOL1* status, viral suppression and kidney function**

- 2.5x decline in eGFR with high risk *APOL1* genotype if poor viral suppression in the Multicenter AIDS Cohort Study [Estrella, CID 2015]

Decline in Renal Function related to Viral Suppression and *APOL1* Risk Genotype



Solid line signifies the *APOL1* high-risk group while the dashed line signifies the low-risk group.

Estrella, CID 2015

Renal Histology in PLWH

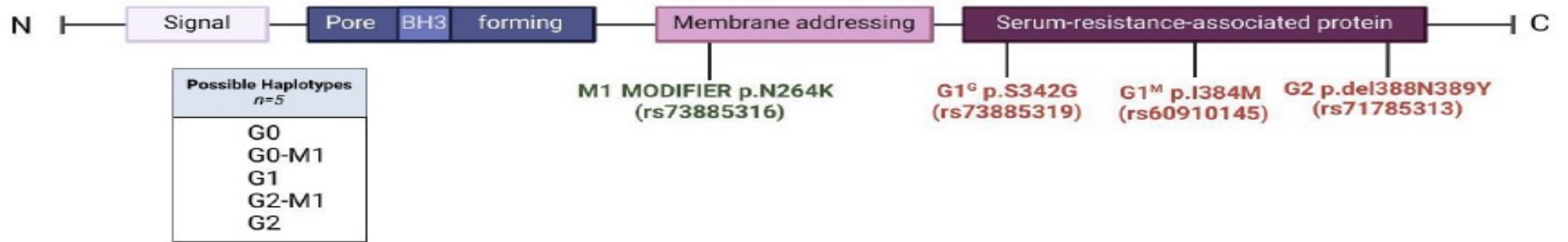
Study details and biopsy findings			South Africa		USA
			Johannesburg (2022) ⁵	Cape Town (2023) ¹²	New York (2020) ⁴
Study details and demographics					
Age in years (IQR)			35 (29–41)	36 (31–44)	53 (45–60)
Black ethnicity (%)			97.5	85 ^a	41 ^b
Number of biopsy samples			690	671	437
Renal histology (%)					
Glomerular dominant	Total		76.2	63.5	44
	Podocytopathies	Total	44.5	46.5	27
Classic HIVAN		25.8	43.7	14	
FSGS (NOS)		13.9	2.1	12	
Other podocytopathy in the setting of HIV		4.8	0.7	2	
Immune complex-mediated glomerular disease		Total	31.7	17	17
	Uncharacterized ICGN with no other aetiology than HIV	11.2	NR	2	
	Membranous nephropathy in the setting of HIV	6.5	2.2	3	
	Membranoproliferative glomerulonephritis in the setting of HIV	6.4	5.2	NR	
	IgA nephropathy in the setting of HIV	0.7	0.5	5	
	Other	6.9	9.1	5	
Tubulointerstitial dominant	Total		10.5	24.7	26
	Tubulo-interstitial nephritis		7	16	3
	Acute tubular injury		3	3.1	8
	Tenofovir nephrotoxicity		NR	3.6	13
	Other		0.5	2.0	2.0
Vascular dominant	Total		1.4	0.3	2
Other	Total		11.9	11.6	28
	Hypertensive nephrosclerosis		6.2	4.0	NR
	Diabetic kidney disease		3.6	4.0	16
	Other		2.1	3.6	12

Data are from the three largest biopsy series utilizing the new KDIGO classification¹¹ and demonstrate the large variety of kidney histology described in PLWH. FSGS (NOS), focal segmental glomerulosclerosis (not otherwise specified); HIVAN, HIV-associated nephropathy; ICGN, immune complex-mediated glomerulonephritis; IQR, interquartile range; NR, not reported. ^aA majority of non-black individuals were of mixed race. ^b30% of the cohort's ethnicity was unknown.

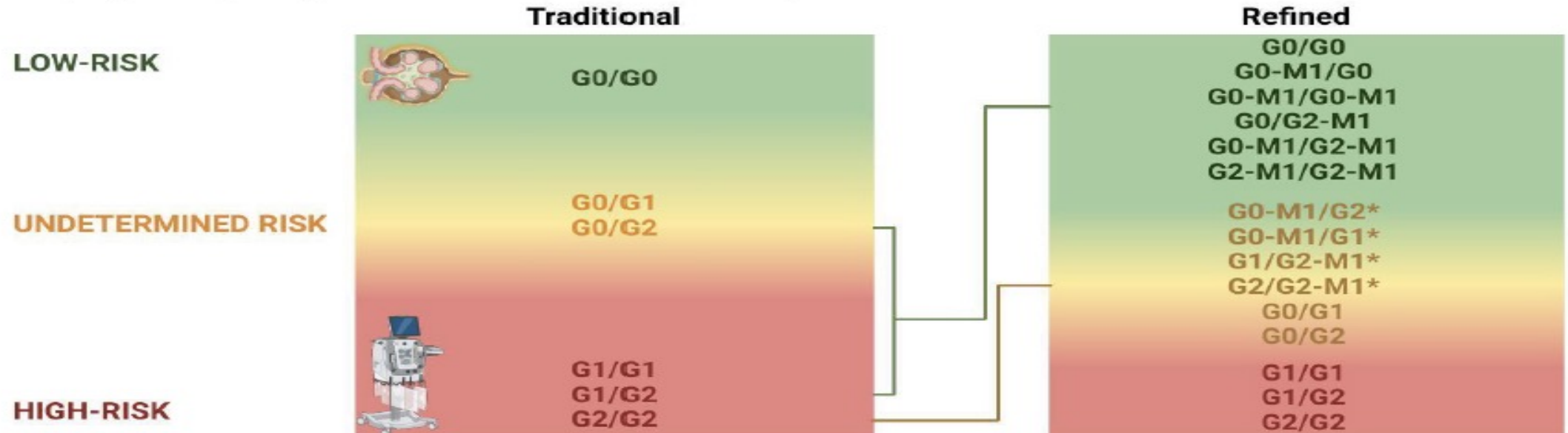
Diana, N.E., Naicker, S. The changing landscape of HIV-associated kidney disease. *Nat Rev Nephrol* (2024). <https://doi.org/10.1038/s41581-023-00801-1>

APOL1 protective M1 p.264K Variant

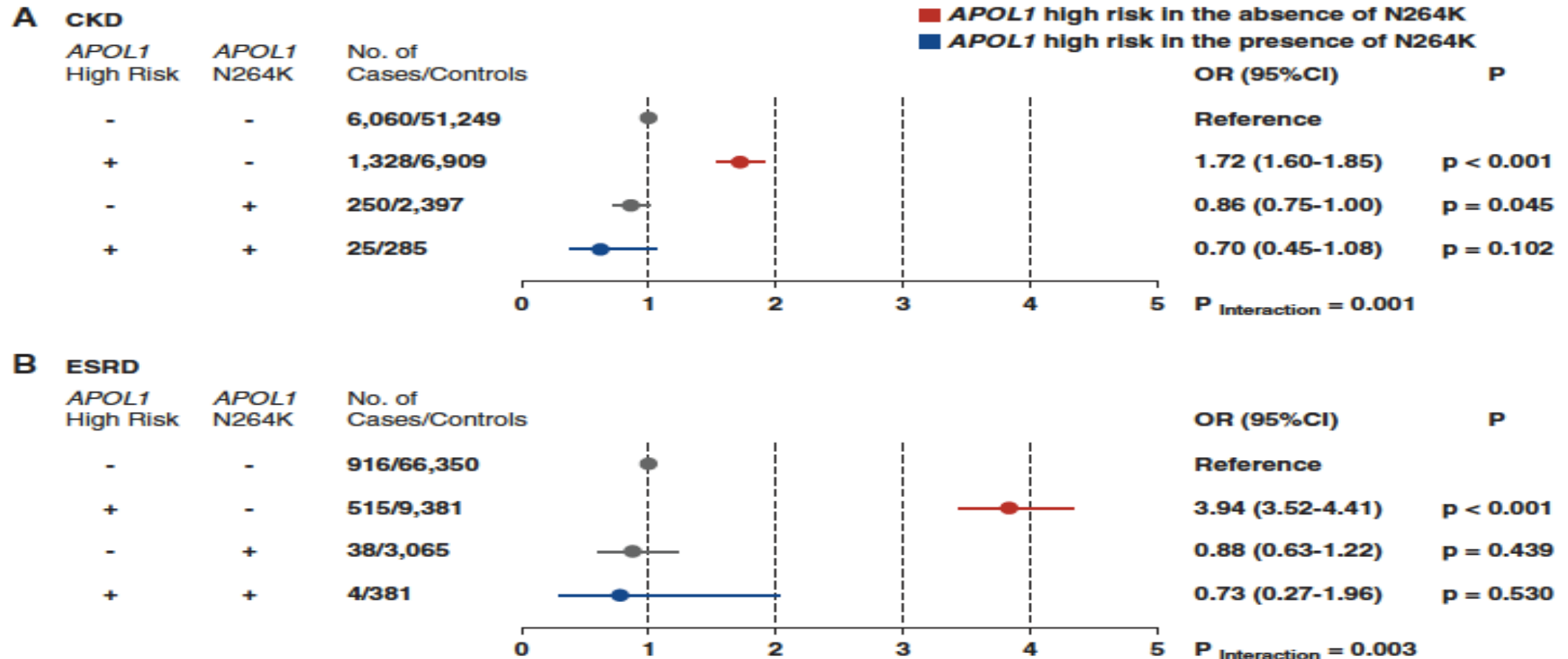
A) APOL1 protein structure, variants and haplotypes



B) Improved genotype risk stratification based on M1 p.N264K



Mitigation of Risk of CKD and ESKD among MVP Participants



Association of Genetic Variants with eGFR Decline (%/yr)

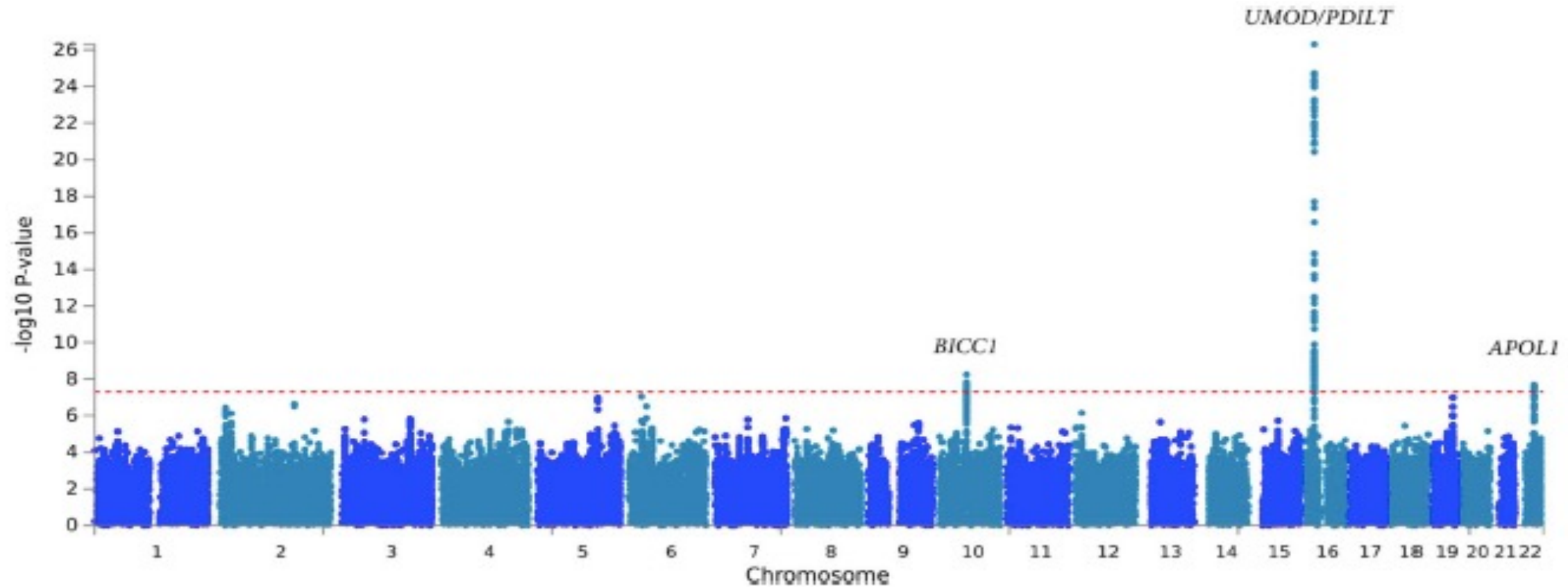


Figure 1. Manhattan plot of the strength of association of genetic variants with eGFR decline (%/yr) in cross-ancestry analyses among individuals with CKD. The y axis represents $-\log_{10}$ P-values for a linear mixed model of genetic variant dosage on repeated log-transformed eGFR measurements, adjusted for age, sex, and first ten principal components of ancestry, stratified by diabetes at baseline and ethnicity, and then meta-analyzed for overall cross-ancestry results. The x axis indicates the chromosomal position of each SNP. A dotted red line marks the $P = 1 \times 10^{-8}$ threshold.

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