

## **Walt Adamson**

**Institution:** University of Glasgow, Scotland

**A brief description of my role or project:** My research explores how genetic variation drives differences in disease outcomes. I focus on sub-Saharan Africa and diaspora populations, with particular interest in APOL1 at the interface of infection and chronic disease.

**What do you hope to get out of the course?** I'm really looking forward to meeting and spending time with current and future leaders in the field of African kidney genetics: exchanging ideas and developing new collaborations.





Dalbeattie



Glasgow



Music (+ family!)



Cycling



Travel



Football

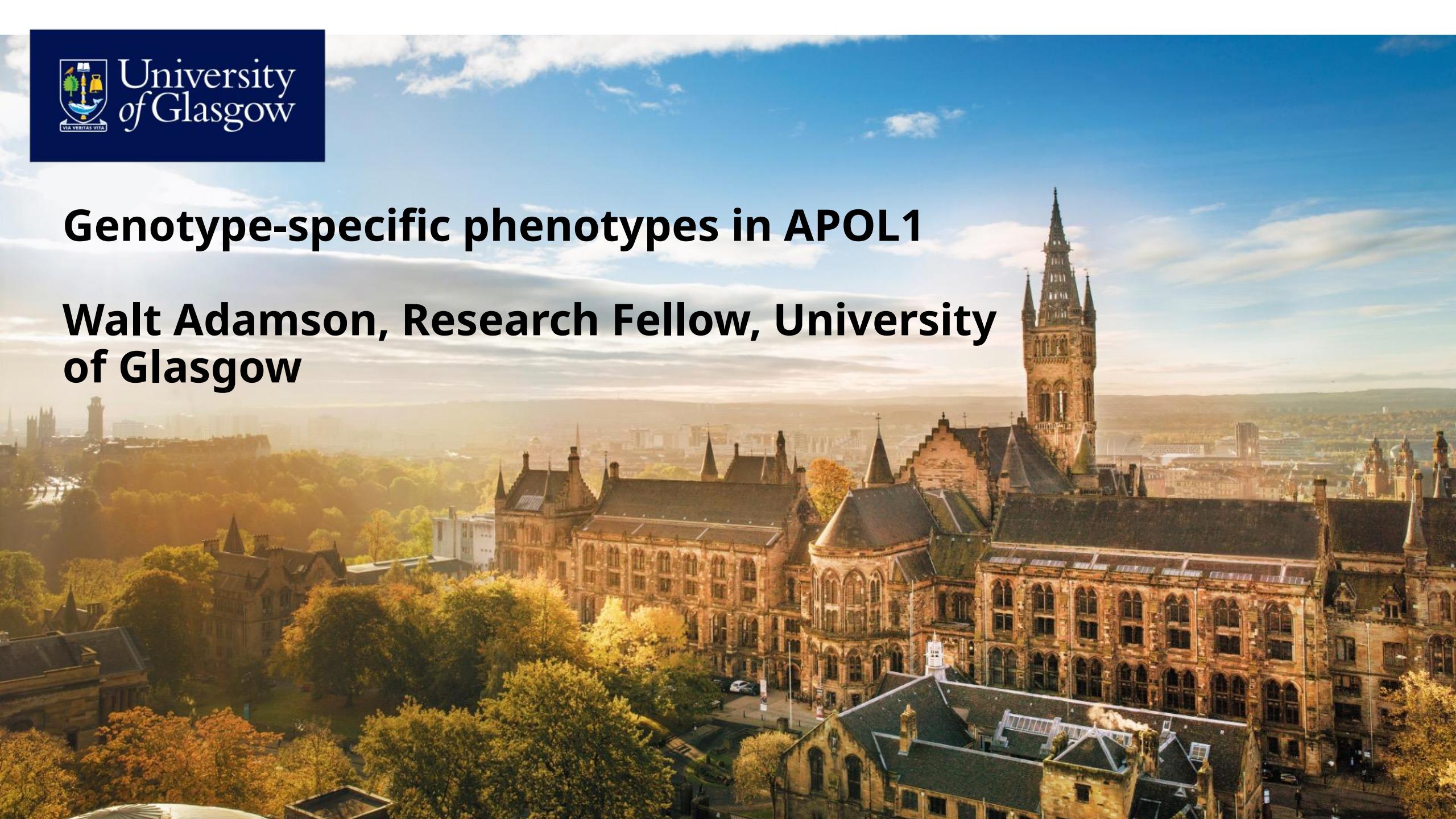




University  
of Glasgow

# Genotype-specific phenotypes in APOL1

**Walt Adamson, Research Fellow, University  
of Glasgow**

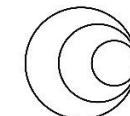


# ANIMAL FARM

GEORGE ORWELL

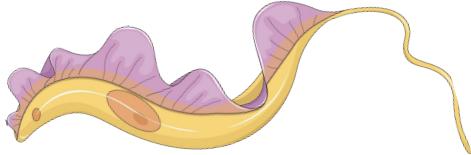


*"All APOL1 variants are equal, but some are more equal than others."*

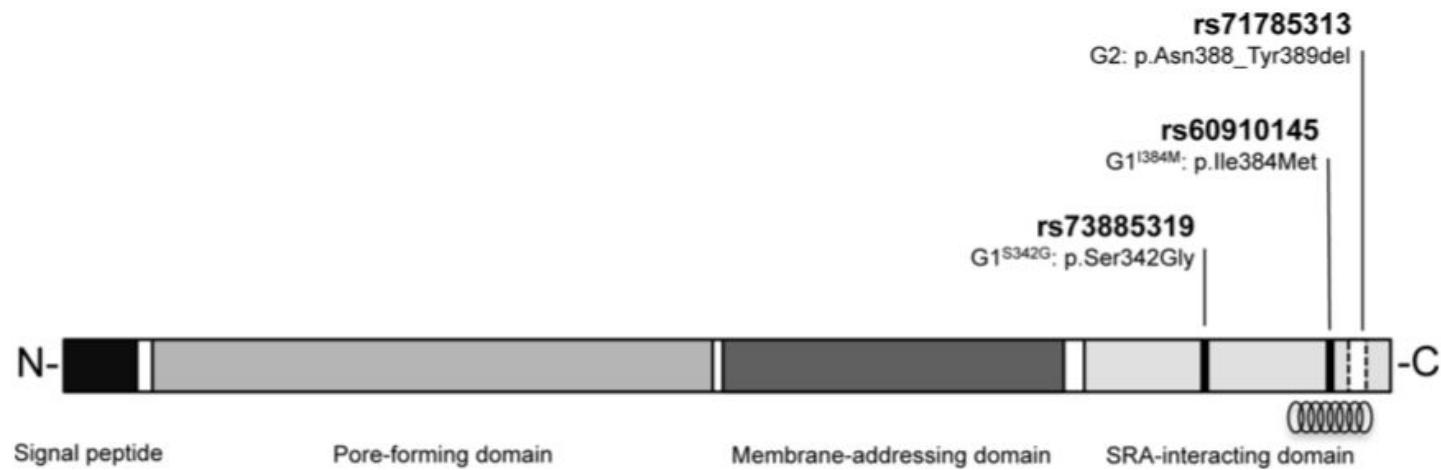


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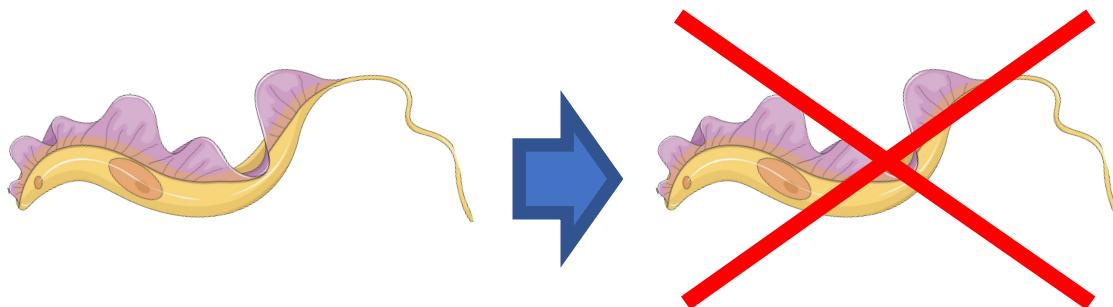
# Humans vs trypanosomes: an evolutionary arms race



Trypanosomes infect  
mammals

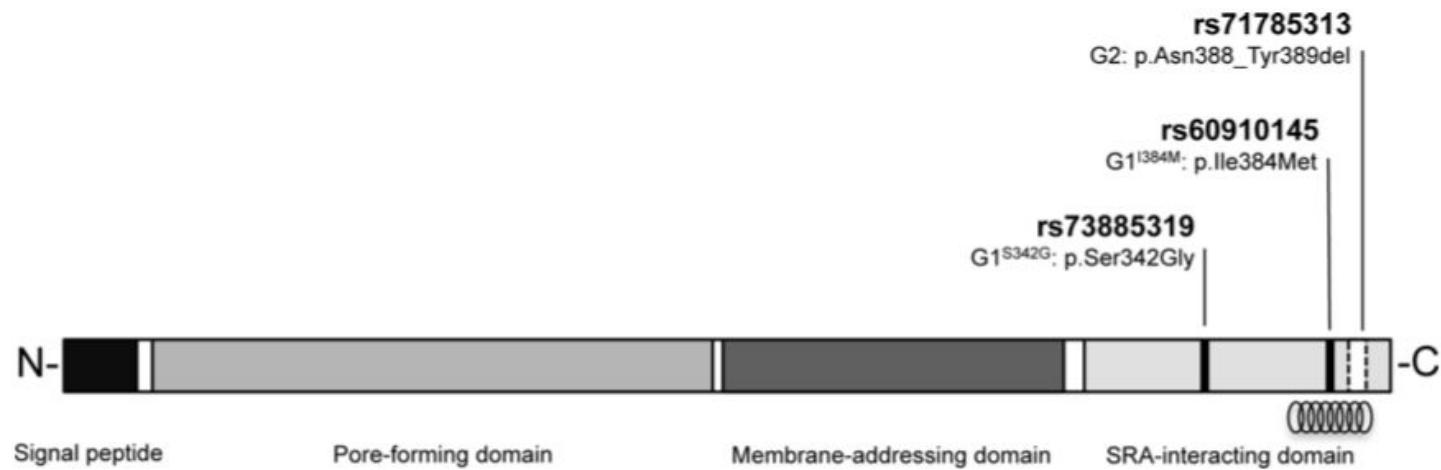


# Humans vs trypanosomes: an evolutionary arms race



Trypanosomes infect mammals

Humans evolve APOL1 to lyse trypanosomes



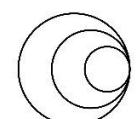
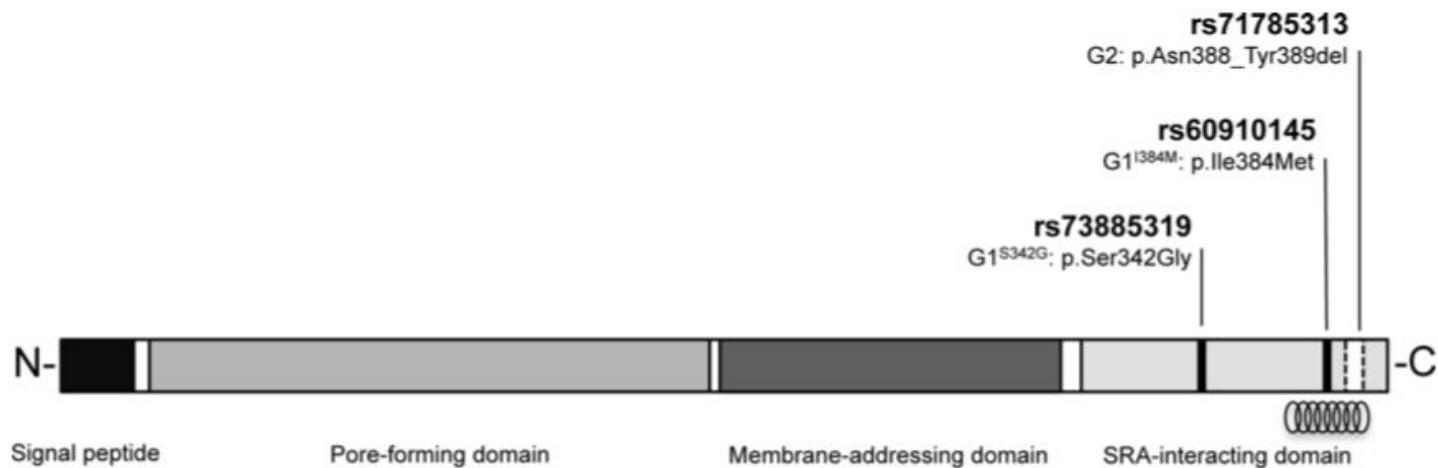
# Humans vs trypanosomes: an evolutionary arms race



Trypanosomes infect mammals

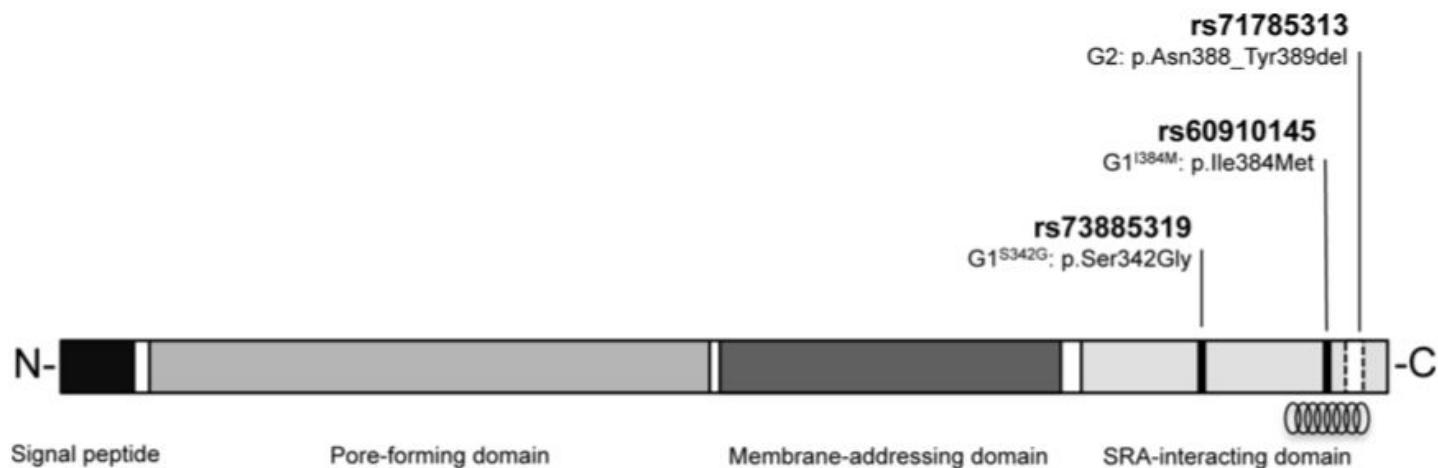
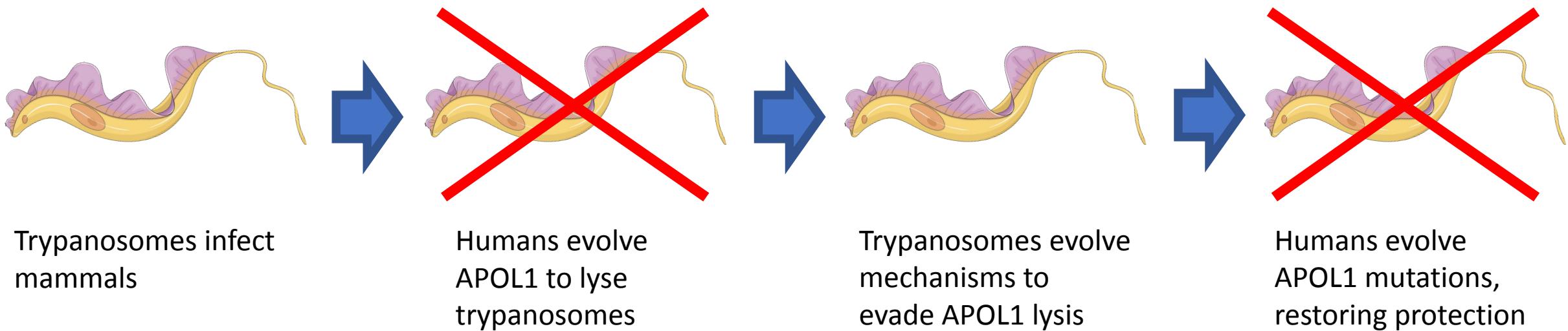
Humans evolve APOL1 to lyse trypanosomes

Trypanosomes evolve mechanisms to evade APOL1 lysis

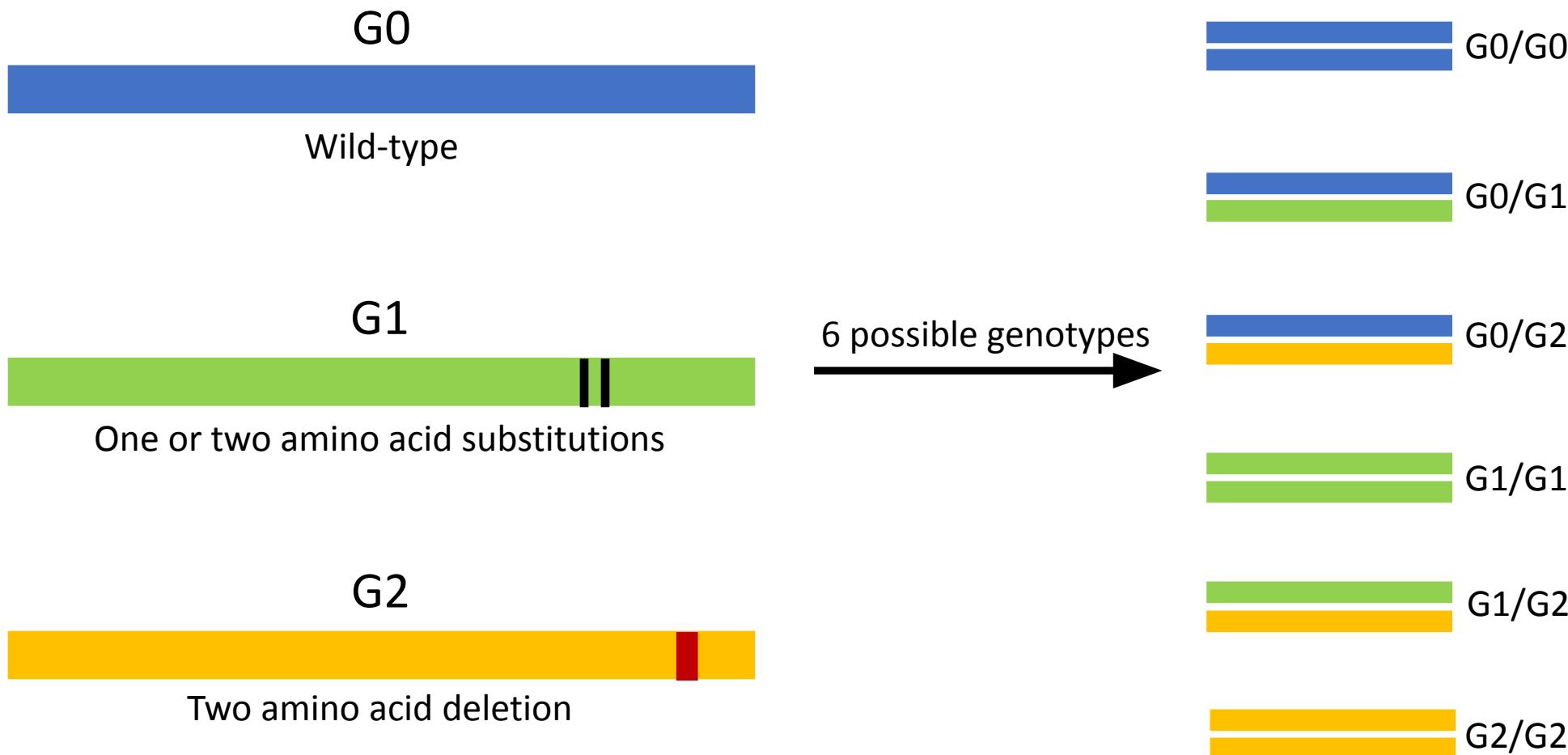


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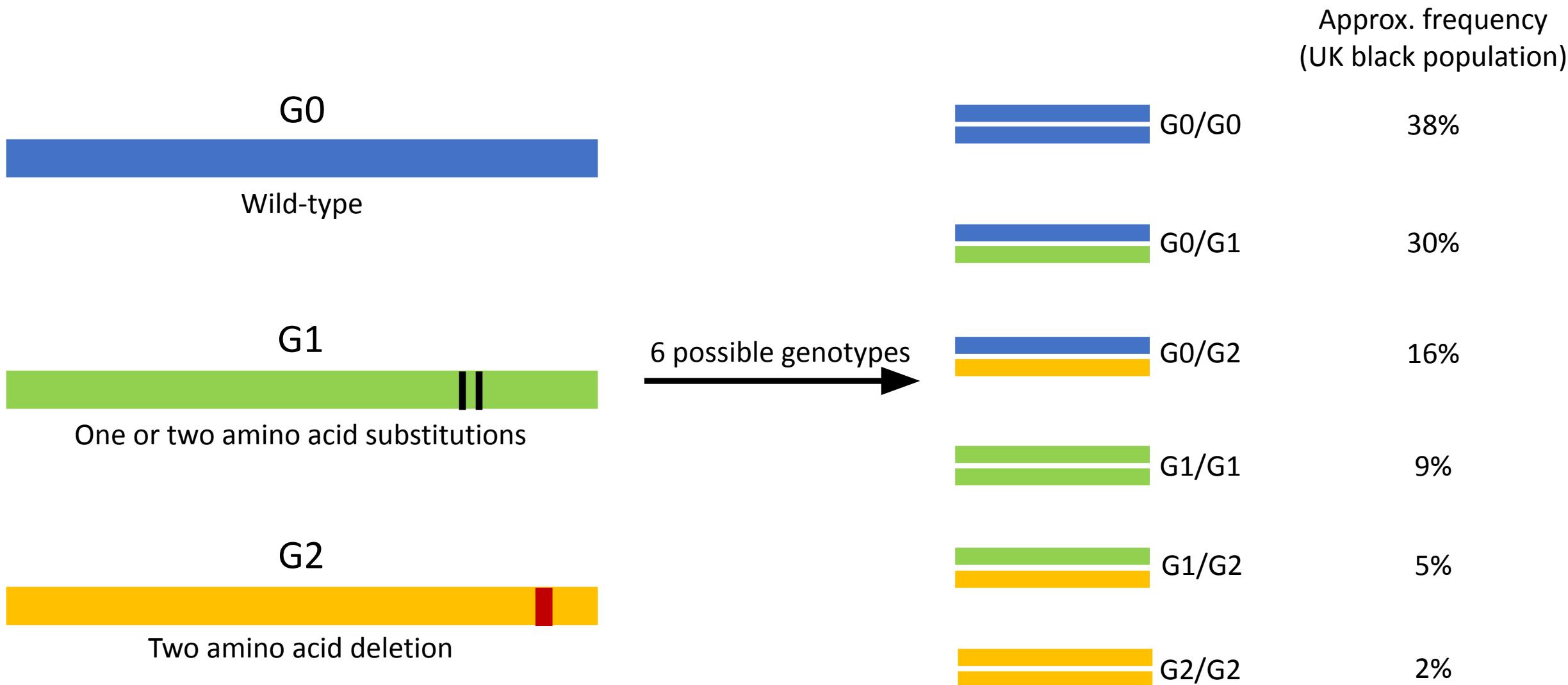
# Humans vs trypanosomes: an evolutionary arms race

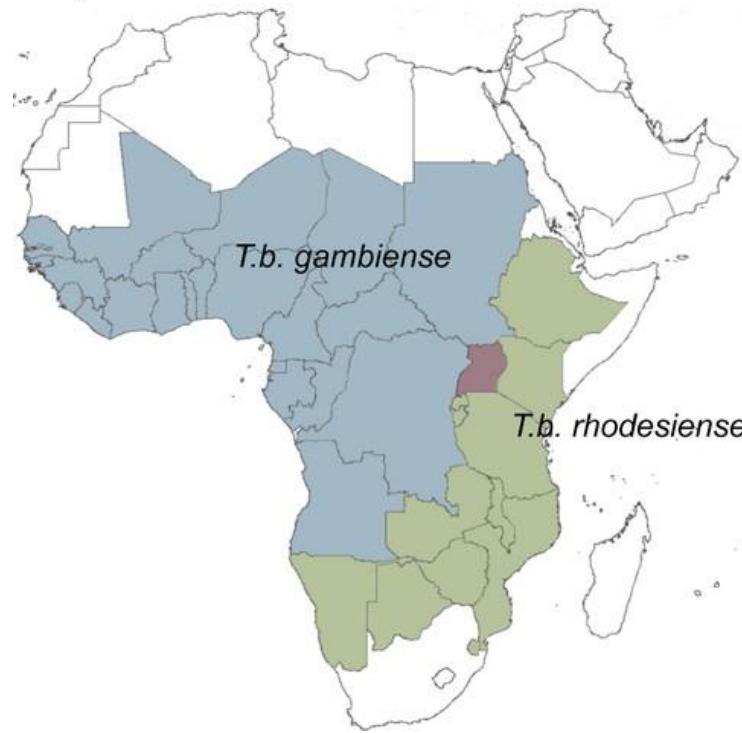


# APOL1 variants



# APOL1 variants





	G0/G0	G0/G1	G1/G1	G0/G2	G2/G2
T.b. gambiense		↓ RISK (severe HAT)	↓ RISK (severe HAT)	↑ RISK (severe HAT)	↑ RISK (severe HAT)
T.b. rhodesiense				↓ RISK (infection)	↓ RISK (infection)

# The relationship between malaria susceptibility and sickle cell anaemia

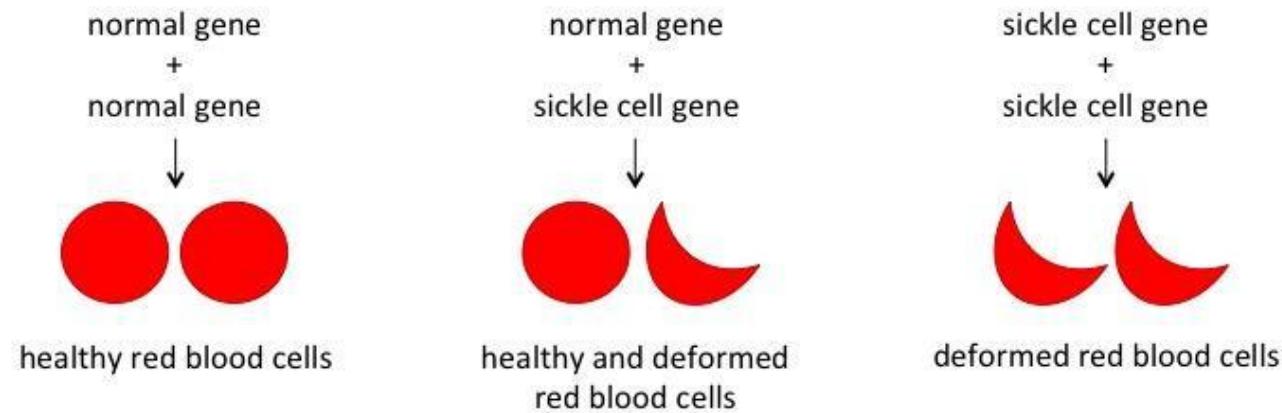
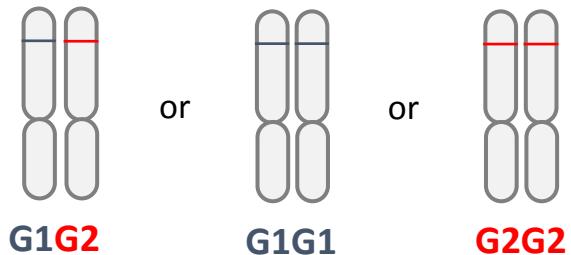


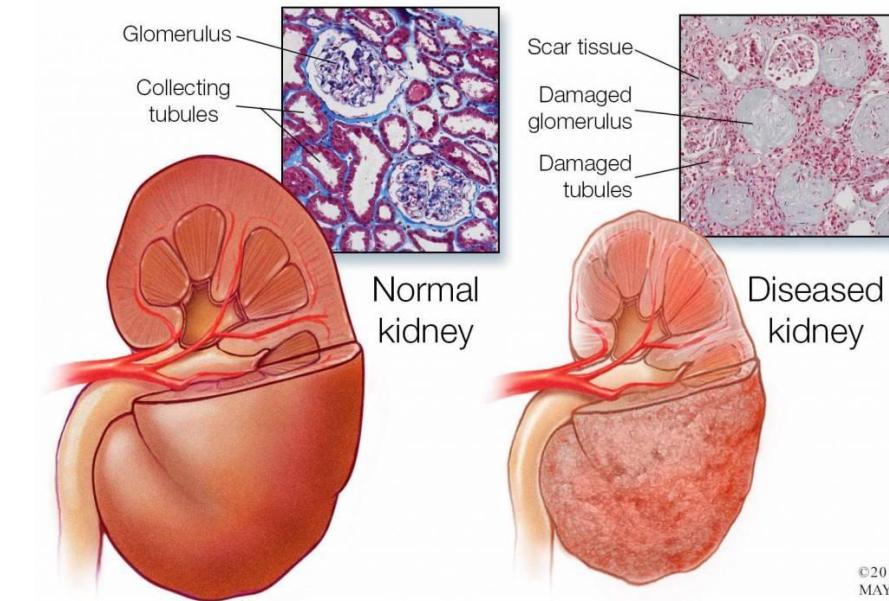
Image: Arizona State University

# Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans

Giulio Genovese,<sup>1,2\*</sup> David J. Friedman,<sup>1,3\*</sup> Michael D. Ross,<sup>4</sup> Laurence Lecordier,<sup>5</sup>



**G1G1, G2G2 and G1G2** are higher odds  
(5 – 24x) of developing a spectrum of  
CKD



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MAYO

## ***APOL1 Nephropathy Risk Alleles and Mortality in African American Adults: A Cohort Study***



*Orlando M. Gutiérrez, Marguerite R. Irvin, Neil A. Zakai, Rakhi P. Naik, Ninad S. Chaudhary, Michelle M. Estrella, Sophie Limou, Suzanne E. Judd, Mary Cushman, Jeffrey B. Kopp, and Cheryl A. Winkler*

AJKD

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Sophie



## HHS Public Access

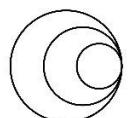
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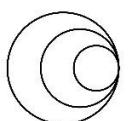
# Apolipoprotein L1 Variants and Blood Pressure Traits in African Americans

Girish N. Nadkarni, MD, MPH, CPH<sup>a</sup>, Geneviève Galarneau, PhD<sup>a</sup>, Stephen B. Ellis, MS<sup>a</sup>, Rajiv Nadukuru, MS<sup>a</sup>, Jinglan Zhang, PhD<sup>a</sup>, Stuart A. Scott, PhD<sup>a</sup>, Claudia Schurmann, PhD<sup>a</sup>, Rongling Li, MD, PhD, MPH<sup>b</sup>, Laura J. Rasmussen-Torvik, PhD<sup>c</sup>, Abel N. Kho, MD<sup>c</sup>, M. Geoffrey Hayes, PhD<sup>d</sup>, Jennifer A. Pacheco, MS<sup>c</sup>, Teri A. Manolio, MD, PhD<sup>b</sup>, Rex L. Chisholm, PhD<sup>c</sup>, Dan M. Roden, MD<sup>e</sup>, Joshua C. Denny, MD, MS<sup>e</sup>, Eimear E. Kenny, PhD<sup>a</sup>, and Erwin P. Bottinger, MD<sup>a</sup>

M. Estrella,



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2017.01.040.

its in African

Vis, MS<sup>a</sup>,  
Tann,  
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a.

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Author manuscript  
*Arterioscler Thromb Vasc Biol.* Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:  
*Arterioscler Thromb Vasc Biol.* 2017 September ; 37(9): 1765–1769. doi:10.1161/ATVBAHA.117.309384.

## *APOL1 Risk Variants and Cardiovascular Disease: Results from the African American Study of Kidney Disease and Hypertension (AASK)*

Apolipoprote  
Americans

Girish N. Nadkarni, MD, M  
Rajiv Nadukuru, MS<sup>a</sup>, Jingla  
PhD<sup>a</sup>, Rongling Li, MD, PhD, M  
Geoffrey Hayes, PhD<sup>d</sup>, Jennifer  
Chisholm, PhD<sup>c</sup>, Dan M. Roden, M  
and Erwin P. Bottinger, MD<sup>a</sup>



An

Orlando  
Sophie



Published in  
J Am Coll C



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## ***APOL1 renal risk variants are associated with obesity and body composition in African ancestry adults***

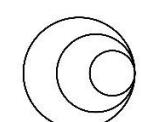
### **An observational genotype–phenotype association study**

Girish N. Nadkarni, MD, MPH<sup>a</sup>, Kezhen Fei, MS<sup>b</sup>, Genevieve Galarneau, PhD<sup>c</sup>, Yan Gao, MPH<sup>d</sup>, James G. Wilson, MD<sup>d</sup>, Richard Cooper, MD<sup>e</sup>, Ebony B. Madden, PhD<sup>f</sup>, Joshua C. Denny, MD, MS, FACMI<sup>g</sup>, Lynne D. Richardson, MD<sup>h</sup>, Martin Pollak, MD<sup>i</sup>, Ruth J. F. Loos, PhD<sup>j</sup>, Carol R. Horowitz, MD, MPH<sup>k,\*</sup>, Orlando Sophie, Publ. J Am Med Inf Assoc<sup>l</sup>,  

Apolipoprotein  
Americans

Girish N. Nadkarni, MD, MPH<sup>a</sup>, Rajiv Nadukuru, MS<sup>a</sup>, Jingtao PhDa, Rongling Li, MD, PhD<sup>a</sup>, Geoffrey Hayes, PhD<sup>d</sup>, Jennifer Chisholm, PhD<sup>c</sup>, Dan M. Roden, MD<sup>a</sup> and Erwin P. Bottinger, MD<sup>a</sup>

Disease: Results from  
“Daney Disease and Hypertension



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***APOL1, obesity & adults***

An observational

Girish N. Nadkarni, MD,  
James G. Wilson, MD<sup>a</sup>,  
Lynne D. Richardson, MD<sup>a</sup>,

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J Am Soc Nephrol.

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Alex N. Kasembeli\*, Raquel Duarte\*, Michèle Ramsay†, Pulane Mosiane‡, Caroline Dickens\*, Thérèse Dix-Peek\*, Sophie Limou§, Efe Sezgin§||, George W. Nelson§, Agnes B. Fogo||, Stewart Goetsch\*\*, Jeffrey B. Kopp††, Cheryl A. Winkler§, Saraladevi Chishowana‡‡, Ger Naicker\*\* and Erwin P. Bottingy\*

# Journal of the American Society of Nephrology : JASN

J Am Soc Nephrol. 26(11): 2882-2890

**APOL1 Risk Variants Are Strongly Associated with HIV-Associated Nephropathy in Black South Africans**

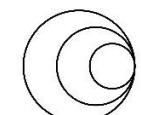
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udy

MPH<sup>d</sup>,  
MD, MS, FACMI<sup>g</sup>,  
D, MPH<sup>k,\*</sup>



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# Causes of APOL1-induced cell injury

- Autophagy
- Lysosomal permeability
- Pyroptosis
- Mitochondrial dysfunction
- Impairment of vacuolar acidification
- Activation of stress-activated kinases
- ER stress
- Mitophagy
- Influx of  $\text{Na}^+$  and  $\text{Ca}^{2+}$  ions

= a lack of consensus

# Previous association studies have focus on number of risk alleles carried

> N Engl J Med. 2013 Dec 5;369(23):2183-96. doi: 10.1056/NEJMoa1310345. Epub 2013 Nov 9.

## APOL1 risk variants, race, and progression of chronic kidney disease

Afshin Parsa <sup>1</sup>, W H Linda Kao, Dawei Xie, Brad C Astor, Man Li, Chi-yuan Hsu, Harold I Feldman, Rulan S Parekh, John W Kusek, Tom H Greene, Jeffrey C Fink, Amanda H Anderson, Michael J Choi, Jackson T Wright Jr, James P Lash, Barry I Freedman, Akinlolu Ojo, Cheryl A Winkler, Dominic S Raj, Jeffrey B Kopp, Jiang He, Nancy G Jensvold, Kaixiang Tao, Michael S Lipkowitz, Lawrence J Appel, AASK Study Investigators; CRIC Study Investigators

### Abstract

**Background:** Among patients in the United States with chronic kidney disease, black patients are at increased risk for end-stage renal disease, as compared with white patients.

**Methods:** In two studies, we examined the effects of variants in the gene encoding apolipoprotein L1 (APOL1) on the progression of chronic kidney disease. In the African American Study of Kidney Disease and Hypertension (AASK), we evaluated 693 black patients with chronic kidney disease attributed to hypertension. In the Chronic Renal Insufficiency Cohort (CRIC) study, we evaluated 2955 white patients and black patients with chronic kidney disease (46% of whom had diabetes) according to whether they had 2 copies of high-risk APOL1 variants (APOL1 high-risk group) or 0 or 1 copy (APOL1 low-risk group). In the AASK study, the primary outcome was a composite of end-stage renal disease or a doubling of the serum creatinine level. In the CRIC study, the primary outcomes were the slope in the estimated glomerular filtration rate (eGFR) and the composite of end-stage renal disease or a reduction of 50% in the eGFR from baseline.

## APOL1 Variants Associate with Increased Risk of CKD among African Americans

Meredith C. Foster,<sup>\*†</sup> Josef Coresh,<sup>\*†‡§</sup> Myriam Fornage,<sup>||</sup> Brad C. Astor,<sup>¶</sup> Morgan Grams,<sup>\*†§</sup> Nora Franceschini,<sup>\*\*</sup> Eric Boerwinkle,<sup>||</sup> Rulan S. Parekh,<sup>\*§††</sup> and W.H. Linda Kao<sup>\*†</sup>

### ABSTRACT

Although case-control studies suggest that African Americans with common coding variants in the APOL1 gene are 5–29 times more likely than those individuals without such variants to have focal segmental glomerulosclerosis, HIV-associated nephropathy, or ESRD, prospective studies have not yet evaluated the impact of these variants on CKD in a community-based sample of African Americans. Here, we studied whether the APOL1 G1 and G2 risk alleles associate with the development of CKD and progression to ESRD by analyzing data from 3067 African Americans in the Atherosclerosis Risk in Communities Study who did not have CKD at baseline. Carrying two risk alleles associated with a 1.49-fold increased risk of CKD (95% CI=1.02 to 2.17) and a 1.88-fold increased risk of ESRD (95% CI=1.20 to 2.93) compared with zero or one risk allele; associations persisted after adjusting for European ancestry. Among participants who developed CKD, those participants

## Race, APOL1 Risk, and eGFR Decline in the General Population

Morgan E Grams <sup>1</sup>, Casey M Rebholz <sup>2</sup>, Yuan Chen <sup>2</sup>, Andreea M Rawlings <sup>2</sup>, Michelle M Estrella <sup>3</sup>, Elizabeth Selvin <sup>4</sup>, Lawrence J Appel <sup>4</sup>, Adrienne Tin <sup>2</sup>, Josef Coresh <sup>5</sup>

### Abstract

The APOL1 high-risk genotype, present in approximately 13% of blacks in the United States, is a risk factor for kidney function decline in populations with CKD. It is unknown whether genetic screening is indicated in the general population. We evaluated the prognosis of APOL1 high-risk status in participants in the population-based Atherosclerosis Risk in Communities (ARIC) study, including associations with eGFR decline, variability in eGFR decline, and related adverse health events (AKI, ESRD, hypertension, diabetes, cardiovascular disease, pre-ESRD and total hospitalization rate, and mortality). Among 15,140 ARIC participants followed from 1987–1989 (baseline) to 2011–2013, 75.3% were white, 21.5% were black/APOL1 low-risk, and 3.2% were black/APOL1 high-risk. In a demographic-adjusted analysis, blacks had a higher risk for all assessed adverse health events; however, in analyses adjusted for comorbid conditions and socioeconomic status, blacks had a higher risk for hypertension, diabetes, and ESRD only. Among blacks, the APOL1 high-risk genotype associated only with higher risk of ESRD in a fully adjusted analysis. Black race and APOL1 high-risk status were associated with faster eGFR decline ( $P<0.001$  for each). However, we detected substantial overlap among the groups: median (10th–90th percentile) unadjusted eGFR decline was 1.5 (1.0–2.2) ml/min per 1.73 m<sup>2</sup> per year for whites, 2.1 (1.4–3.1) ml/min per 1.73 m<sup>2</sup> per year for blacks with APOL1 low-risk status, and 2.3 (1.5–3.5) ml/min per 1.73 m<sup>2</sup> per year for blacks with APOL1 high-risk status. The high variability in eGFR decline among blacks with and without the APOL1 high-risk genotype suggests that population-based screening is not yet justified.

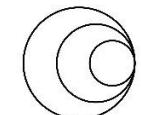
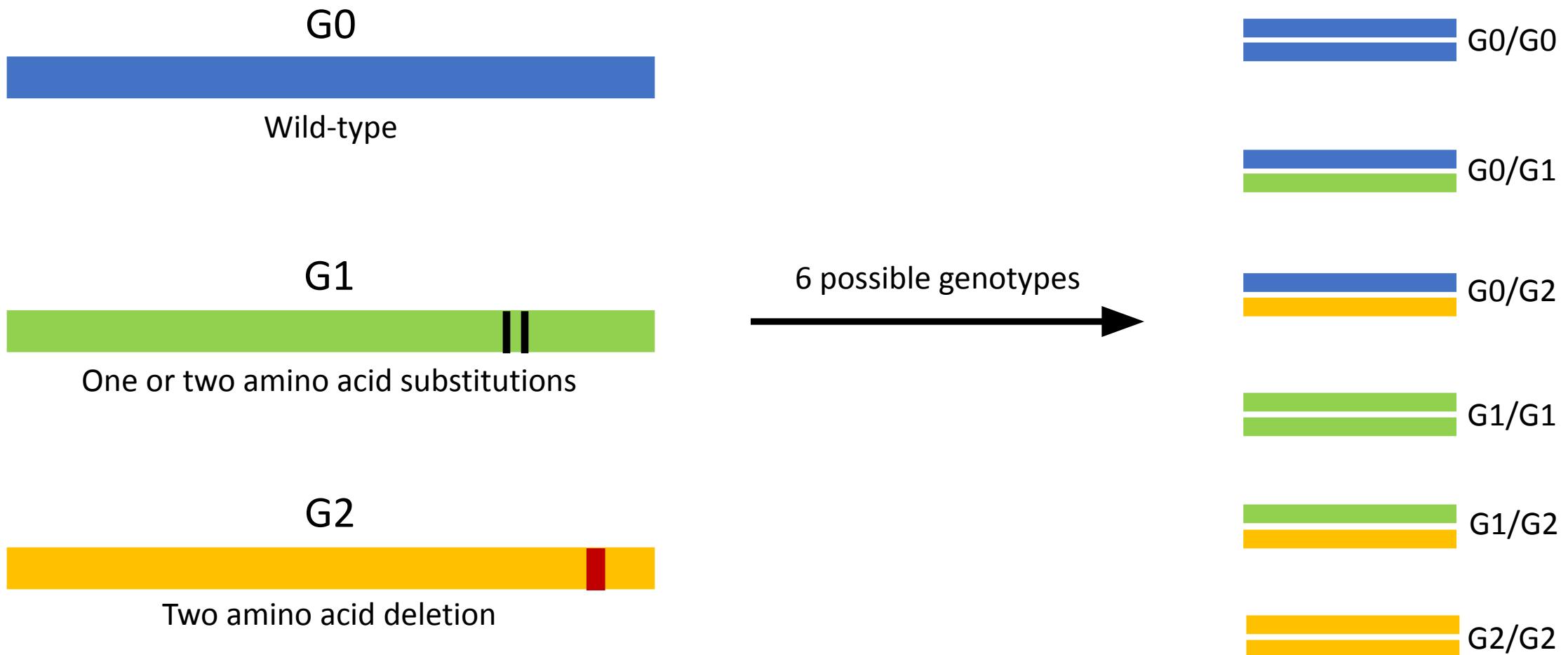
## Apolipoprotein L1 gene variants associate with prevalent kidney but not prevalent cardiovascular disease in the Systolic Blood Pressure Intervention Trial

Carl D Langefeld <sup>1</sup>, Jasmin Divers <sup>1</sup>, Nicholas M Pajewski <sup>1</sup>, Amret T Hawfield <sup>2</sup>, David M Rebourcier <sup>3</sup>, Diane E Bild <sup>4</sup>, George A Kaysen <sup>5</sup>, Paul L Kimmel <sup>6</sup>, Dominic S Raj <sup>7</sup>, Ana C Ricardo <sup>8</sup>, Jackson T Wright Jr <sup>9</sup>, John R Sedor <sup>10</sup>, Michael V Rocco <sup>2</sup>, Barry I Freedman <sup>2</sup>, Systolic Blood Pressure Intervention Trial (SPRINT)

### Abstract

Apolipoprotein L1 gene (APOL1) G1 and G2 coding variants are strongly associated with chronic kidney disease (CKD) in African Americans (AAs). Here APOL1 association was tested with baseline estimated glomerular filtration rate (eGFR), urine albumin:creatinine ratio (UACR), and prevalent cardiovascular disease (CVD) in 2571 AAs from the Systolic Blood Pressure Intervention Trial (SPRINT), a trial assessing effects of systolic blood pressure reduction on renal and CVD outcomes. Logistic regression models that adjusted for potentially important confounders tested for association between APOL1 risk variants and baseline clinical CVD (myocardial infarction, coronary, or carotid artery revascularization) and CKD (eGFR under 60 ml/min per 1.73 m<sup>2</sup>) and/or UACR over 30 mg/g). AA SPRINT participants were 45.3% female with a mean (median) age of 64.3 (63) years, mean arterial pressure 100.7 (100) mm Hg, eGFR 76.3 (77.1) ml/min per 1.73 m<sup>2</sup>, and UACR 49.9 (9.2) mg/g, and 8.2% had clinical CVD. APOL1 (recessive inheritance) was positively associated with CKD (odds ratio 1.37, 95% confidence interval 1.08–1.73) and log UACR estimated slope ( $\beta$ ) 0.33) and negatively associated with eGFR ( $\beta$  -3.58), all significant. APOL1 risk variants were not significantly associated with prevalent CVD (1.02, 0.82–1.27). Thus, SPRINT data show that APOL1 risk variants are associated with mild CKD but not with prevalent CVD in AAs with a UACR under 1000 mg/g.

# APOL1 variants



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# APOL1 variants

	<i>T.b. gambiense</i> infection	<i>T.b.rhodesiense</i> infection	Chronic kidney disease
	Wild-type	Wild-type	Wild-type
	Protective	No effect	No effect
	Deleterious	Protective	No effect
	Protective	No effect	Deleterious
	Unclear	Unclear	Deleterious
	No effect	Protective	Deleterious

# APOL1 variants

	<i>T.b. gambiense</i> infection	<i>T.b.rhodesiense</i> infection	Chronic kidney disease
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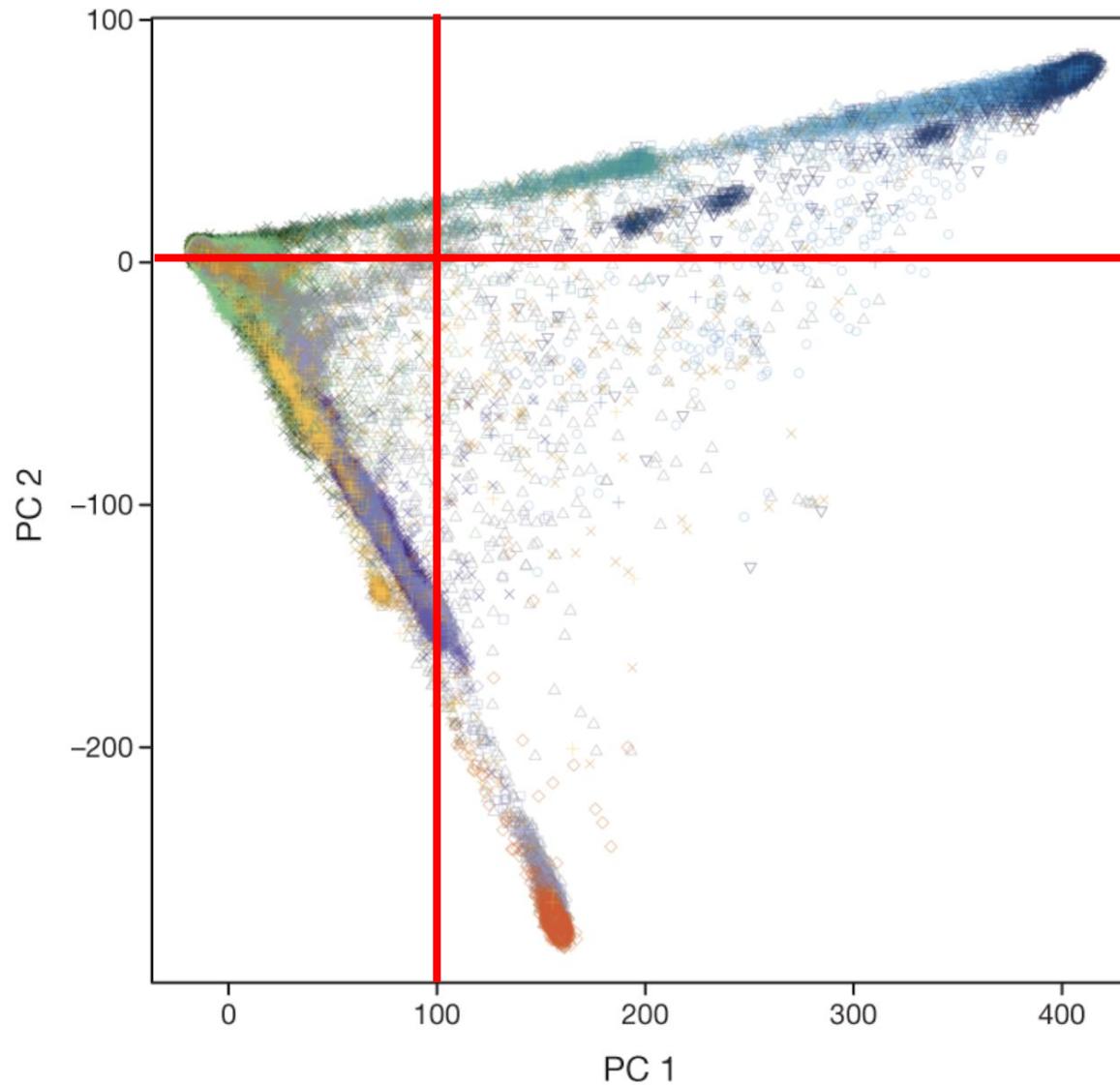
## Key messages

- G1 and G2 are *different* – and not just in sleeping sickness.
- $G1 \neq G2$ , and  $G1/G1 \neq G1/G2 \neq G2/G2$ .
- The G1/G2 genotype is particularly deleterious.
- APOL1 protein concentration also influences health and disease.



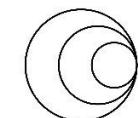
- ~500,000 healthy participants aged 40-69, enrolled 2006-2010, to be followed for 30 years.
- HUGE collection of data on each participant (clinical measurements, indicators of health, lifestyle, medications, etc, etc).
- ~850,000 SNPs examined for each participant, whole-genome sequencing recently completed.
- Olink protein concentration data recently available
- Blood and urine samples available on request.
- Regular follow-ups to examine changes to health.

# Cohort selection: PCA analysis



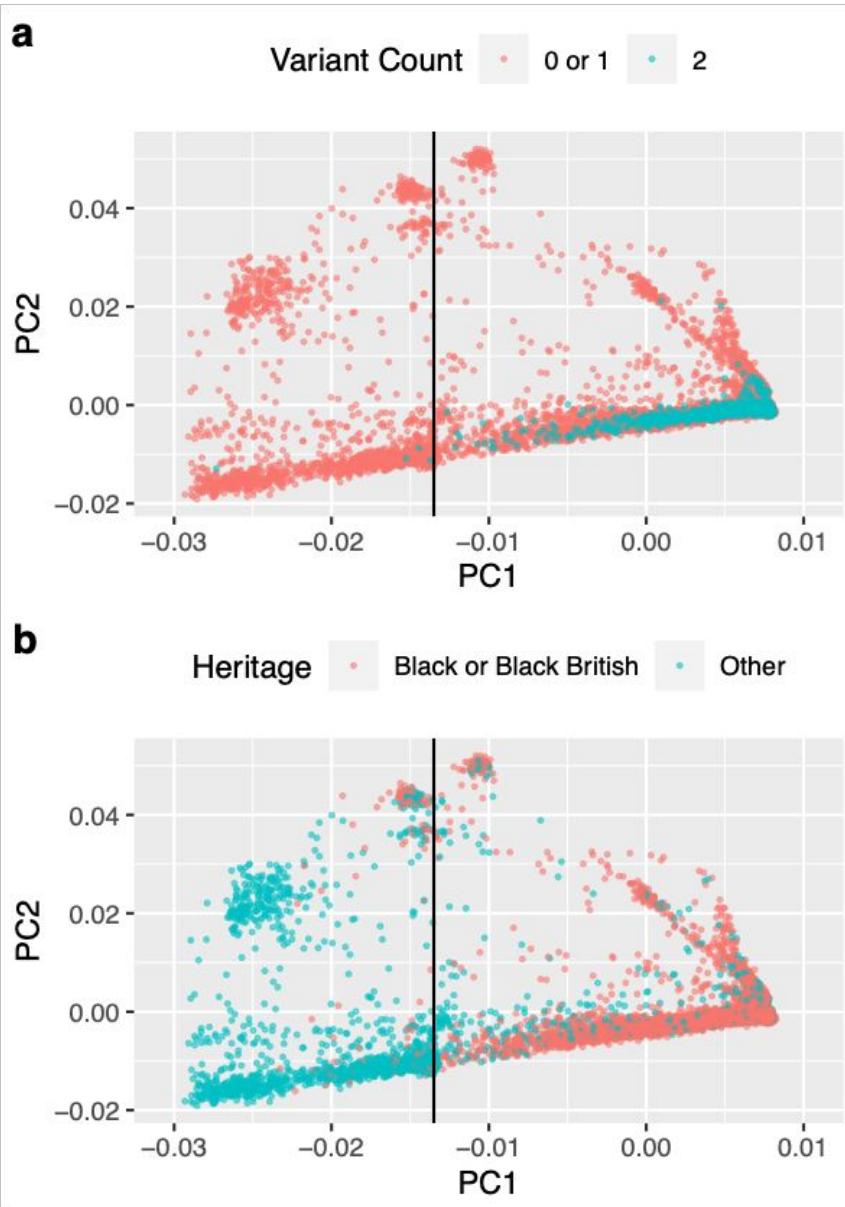
## Self-reported ethnic background

- ✖ British (white)
- ✖ Irish
- ▲ Any other white background
- ✖ Indian
- ✖ Pakistani
- ✖ Bangladeshi
- ✖ Any other Asian background
- ✖ Chinese
- ▼ African
- Caribbean
- ✚ Any other black background
- ✖ White and Asian
- ◻ White and black African
- ▲ White and black Caribbean
- ✖ Any other mixed background
- △ Other/unknown



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# Cohort selection: PCA analysis



Genotype	n	%
G0/G0	4,299	44.8%
G0/G1	2,665	27.7%
G0/G2	1,435	14.9%
G1/G1	695	7.2%
G1/G2	349	3.6%
G2/G2	161	1.7%

# Indicators of chronic kidney disease

## Reduced glomerular filtration rate (GFR)

- The rate at which blood passes through the kidney's glomeruli.
- Measured in mL/min/1.73m<sup>2</sup>
- Healthy individuals: ~90 mL/min/1.73m<sup>2</sup>
- GFR < 60 mL/min/1.73m<sup>2</sup> indicates chronic kidney disease

## Albumin:creatinine ratio (ACR) - proteinuria

- The presence of excess proteins in urine
- Can indicate kidneys with impaired ability to absorb serum proteins
- Defined by the albumin:creatinine ratio (ACR) in urine.
- ACR >3 mg/mmol indicates chronic kidney disease

## Progression to end stage kidney disease (ESKD)

- Defined by the UK Biobank
- Based on hospital admission and operation data

## Definition of chronic kidney disease

- Reduced GFR (269 cohort members)  
**OR**
- Elevated ACR (611 cohort members)  
**OR**
- Progression to ESKD (81 cohort members)

**In our cohort, 822/7969 individuals (10.3%) had chronic kidney disease.**

# Carriage of two APOL1 variants is associated with CKD

Number of variants	n (cohort)	n (CKD)	Odds ratio (95% CI)	p-value
0	4,299	388 (9.0%)	-	-
1	4,090	416 (10.2%)	1.1 (0.9-1.3)	0.43
2	1,205	<b>169 (14.0%)</b>	<b>1.5 (1.2-1.8)</b>	<b>0.0006</b>

Covariates: age, sex, body mass index, Townsend deprivation index, diabetes, hypertension, principal components 1-4

# Elevated ACR is associated only with the G1/G1 genotype

Genotype	n (cohort)	n (elevated ACR)	Odds ratio (95% CI)	p-value
G0/G0	4,299	302 (7.0%)	-	-
G0/G1	2,665	209 (7.9%)	1.0 (0.8-1.3)	0.67
G0/G2	1,435	115 (8.0%)	1.2 (0.9-1.5)	0.20
<b>G1/G1</b>	<b>695</b>	<b>81 (11.7%)</b>	<b>1.6 (1.2-2.2)</b>	<b>0.002</b>
G1/G2	349	39 (11.2%)	1.3 (0.9-2.0)	0.15
G2/G2	161	11 (6.8%)	1.1 (0.5-2.0)	0.88

Covariates: age, sex, body mass index, Townsend deprivation index, diabetes, hypertension, principal components 1-4

# Low filtration rate is associated with G1/G2 and G2/G2

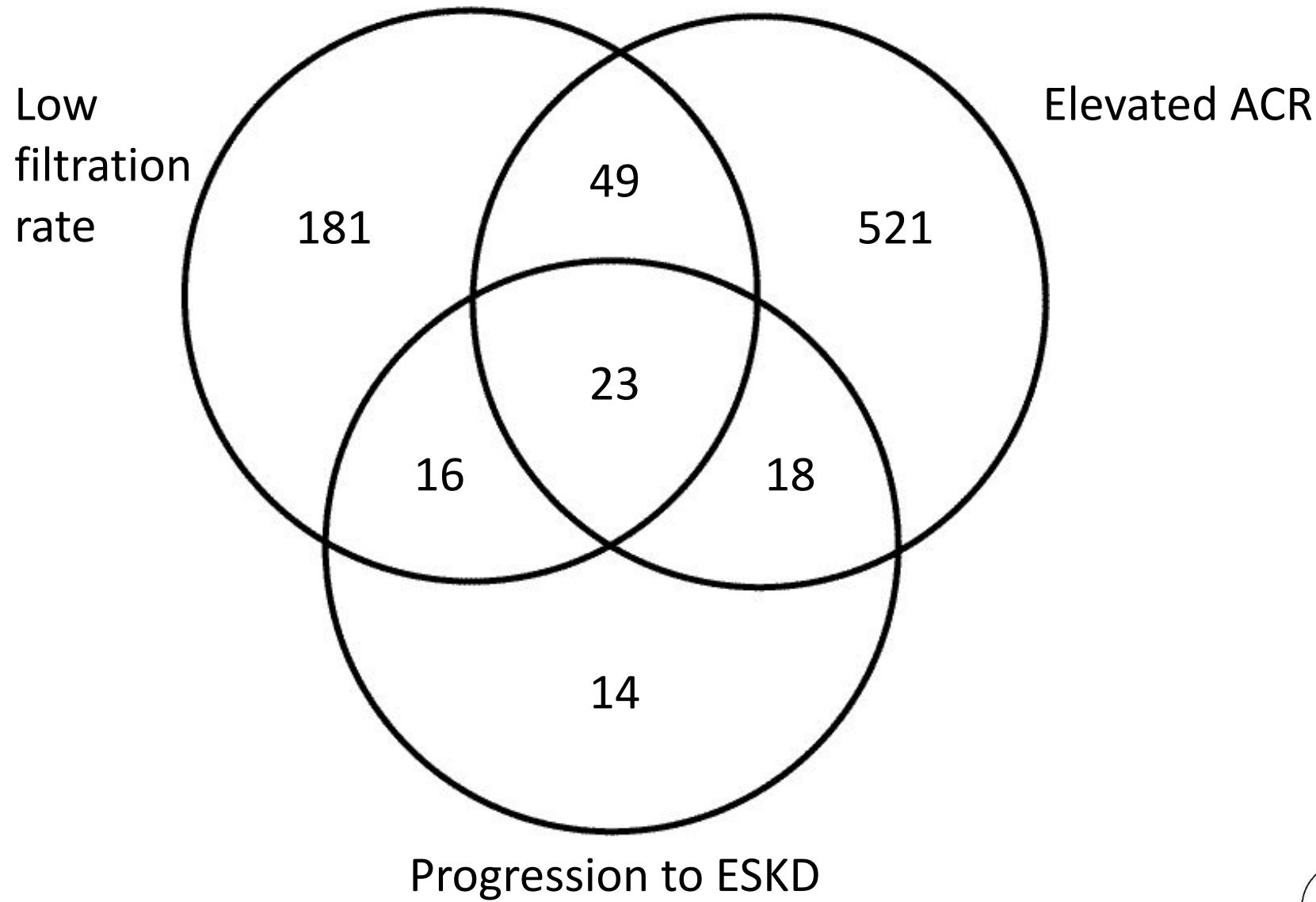
Genotype	n (cohort)	n (elevated ACR)	Odds ratio (95% CI)	p-value
G0/G0	4,299	115 (2.7%)	-	-
G0/G1	2,665	80 (3.0%)	0.9 (0.7-1.3)	0.65
G0/G2	1,435	46 (3.2%)	1.1 (0.7-1.5)	0.70
G1/G1	695	29 (4.2%)	1.3 (0.8-2.0)	0.29
<b>G1/G2</b>	<b>349</b>	<b>19 (5.4%)</b>	<b>1.8 (1.0-2.9)</b>	<b>0.04</b>
<b>G2/G2</b>	<b>161</b>	<b>12 (7.5%)</b>	<b>2.6 (1.3-4.9)</b>	<b>0.01</b>

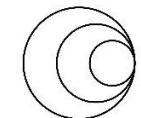
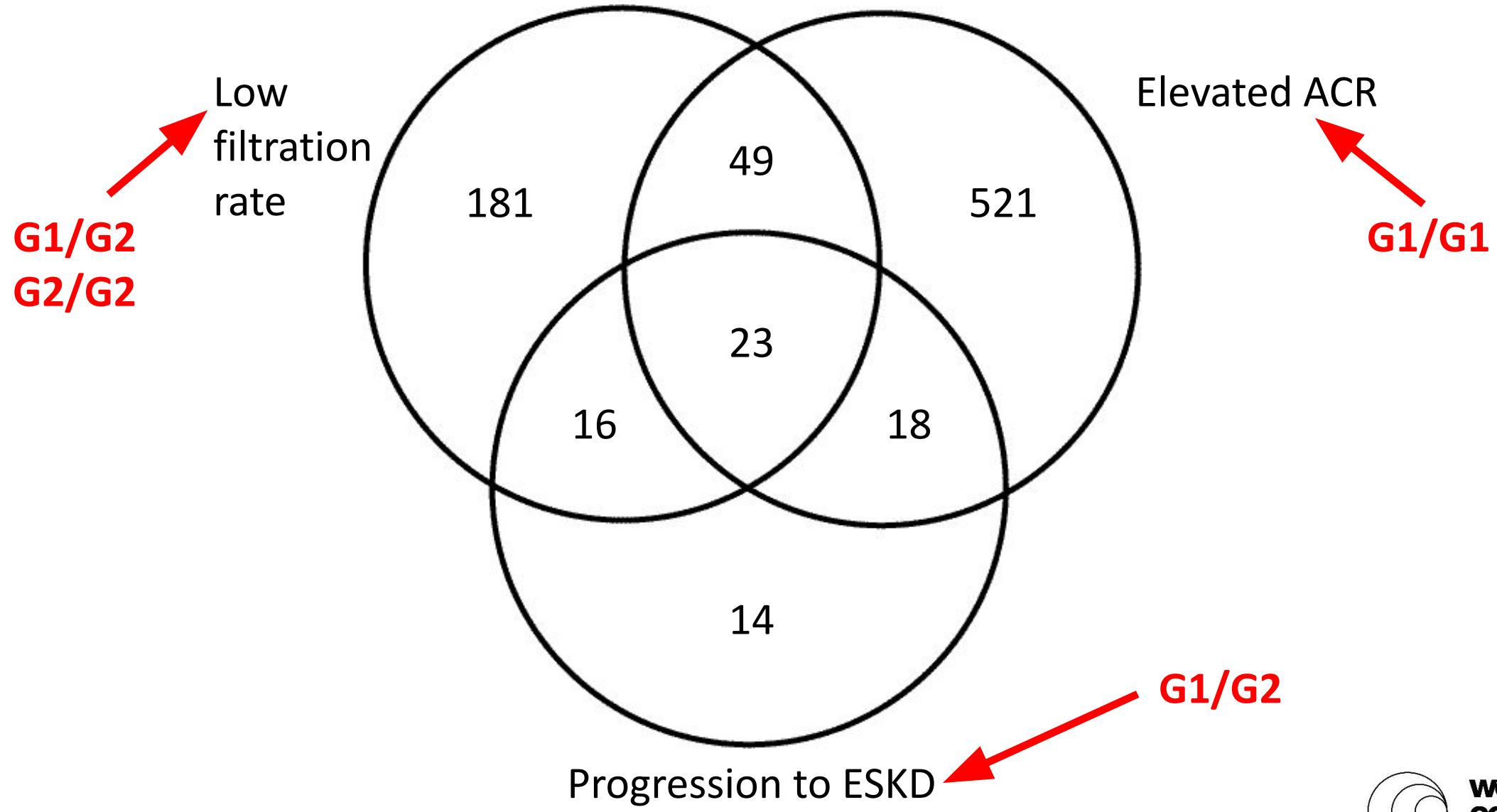
Covariates: age, sex, body mass index, Townsend deprivation index, diabetes, hypertension, principal components 1-4

# Progression to end-stage kidney disease is associated with G1/G2

Genotype	n (cohort)	n (elevated ACR)	Odds ratio (95% CI)	p-value
G0/G0	4,299	31 (0.7%)	-	-
G0/G1	2,665	20 (0.8%)	1.0 (0.6-1.9)	0.94
G0/G2	1,435	11 (0.8%)	1.1 (0.5-2.1)	0.88
G1/G1	695	9 (1.3%)	1.5 (0.7-3.2)	0.30
<b>G1/G2</b>	<b>349</b>	<b>10 (2.9%)</b>	<b>3.4 (1.5-7.2)</b>	<b>0.004</b>
G2/G2	161	1 (0.6%)	1.3 (0.2-5.3)	0.75

Covariates: age, sex, body mass index, Townsend deprivation index, diabetes, hypertension, principal components 1-4





wellcome  
connecting  
science

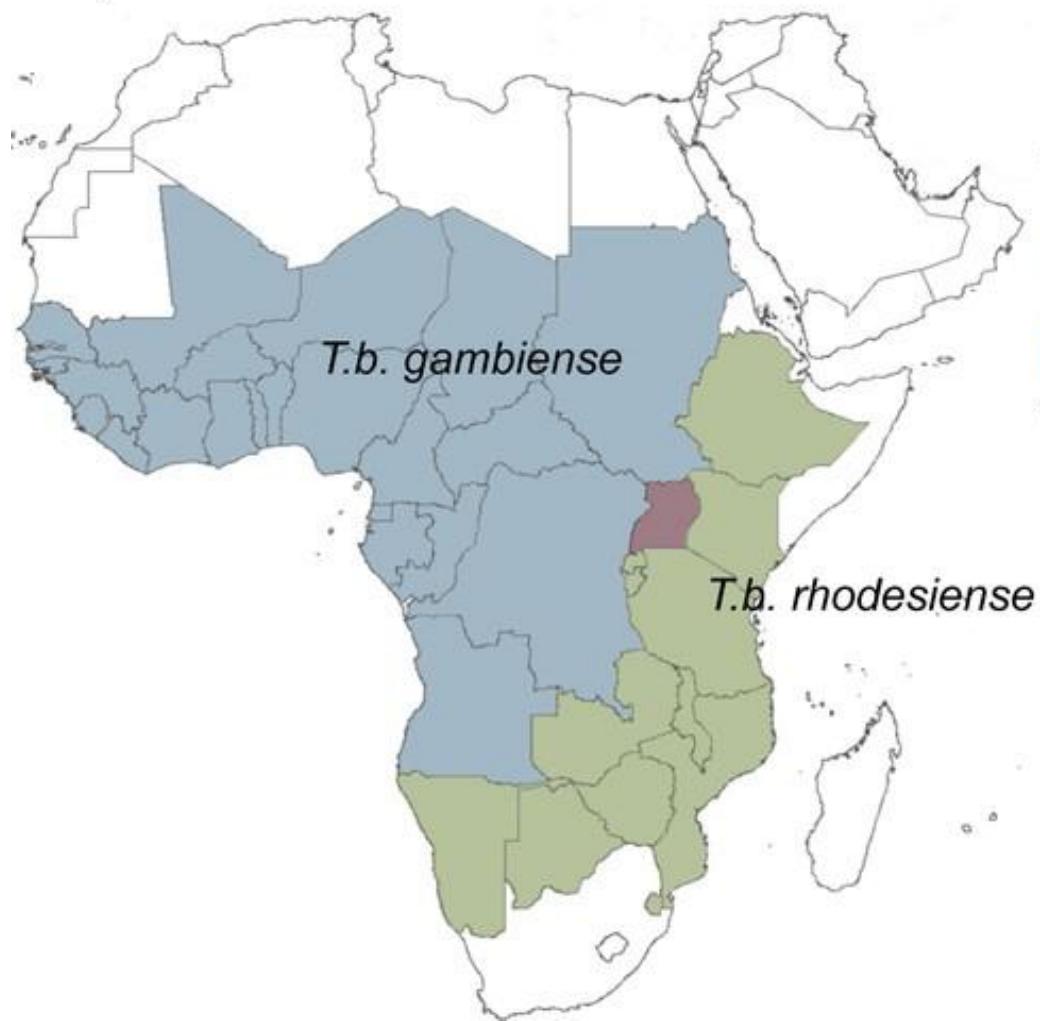
# Causes of APOL1-induced cell injury

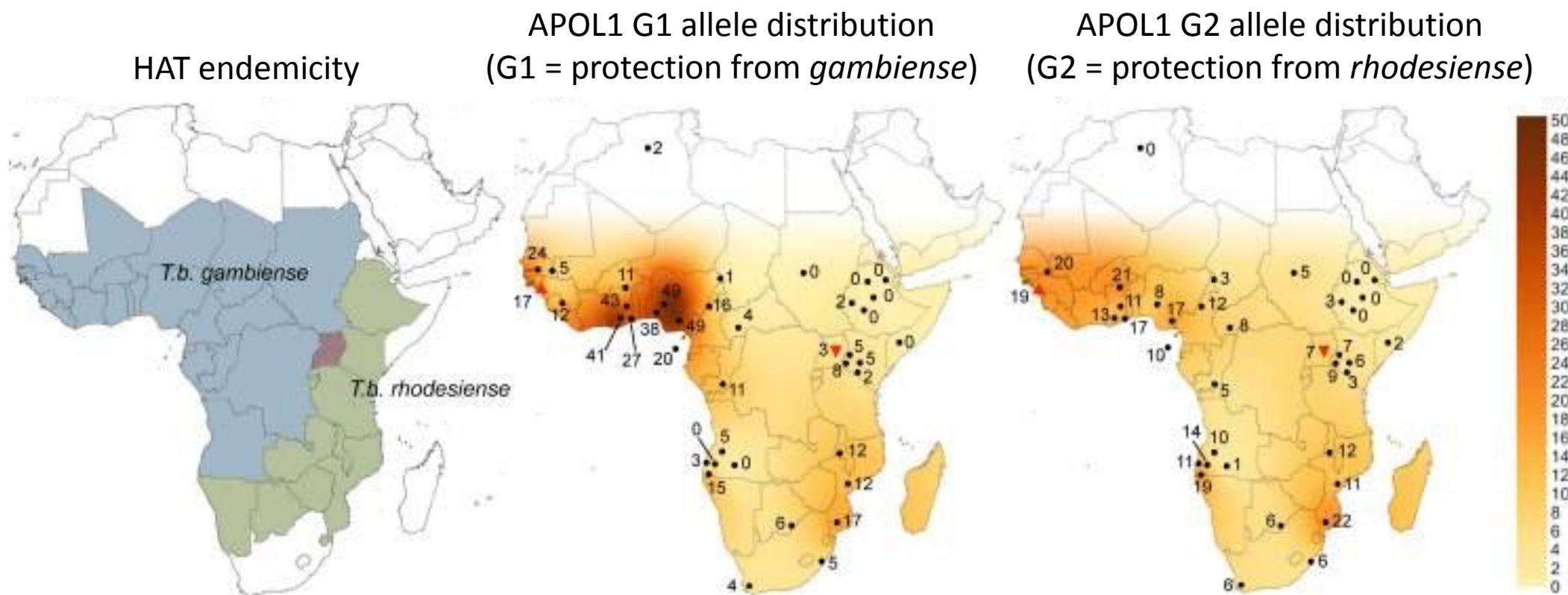
- Autophagy
- Lysosomal permeability
- Pyroptosis
- Mitochondrial dysfunction
- Impairment of vacuolar acidification
- Activation of stress-activated kinases
- ER stress
- Mitophagy
- Influx of  $\text{Na}^+$  and  $\text{Ca}^{2+}$  ions

= a lack of consensus

## Key messages

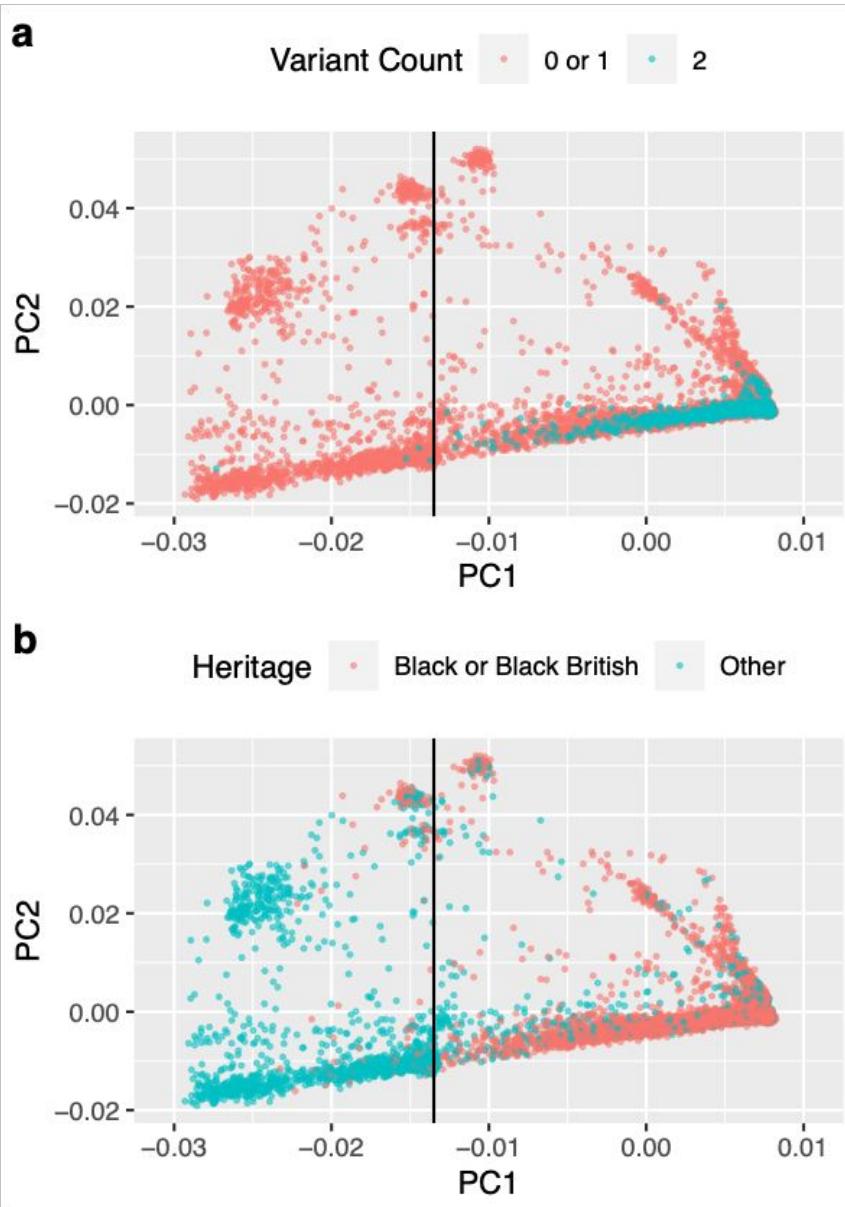
- G1 and G2 are *different* – and not just in sleeping sickness.
- $G1 \neq G2$ , and  $G1/G1 \neq G1/G2 \neq G2/G2$ .





	G0/G0	G0/G1	G1/G1	G0/G2	G2/G2
T.b. <i>gambiense</i>		↓ RISK (severe HAT)	↓ RISK (severe HAT)	↑ RISK (severe HAT)	↑ RISK (severe HAT)
T.b. <i>rhodesiense</i>				↓ RISK (infection)	↓ RISK (infection)

# Cohort selection: PCA analysis



Genotype	n	%
G0/G0	4,299	44.8%
G0/G1	2,665	27.7%
G0/G2	1,435	14.9%
G1/G1	695	7.2%
G1/G2	349	3.6%
G2/G2	161	1.7%

# APOL1 G1/G2 genotype is associated with poor outcomes in COVID-19

Genotype	N	Hospitalised N	Hospitalised OR (95% CI)	Hospitalised p-value	Death N	Death OR	Death p-value
G0/G0	3,982	59 (1.5%)	-	-	15 (0.4%)	-	-
G0/G1	2,460	51 (2.1%)	1.1 (0.8-1.7)	0.5	13 (0.5%)	1.6 (0.7-3.7)	0.3
G0/G2	1,317	25 (1.9%)	1.0 (0.6-1.6)	0.9	6 (0.5%)	1.2 (0.4-3.1)	0.7
G1/G1	639	9 (1.4%)	0.8 (0.4-1.5)	0.5	2 (0.3%)	1.2 (0.2-4.4)	0.8
<b>G1/G2</b>	<b>319</b>	<b>15 (4.7%)</b>	<b>2.4 (1.3-4.3)</b>	<b>0.008</b>	<b>8 (2.5%)</b>	<b>6.8 (2.5-18.3)</b>	<b>0.0004</b>
G2/G2	150	2 (1.3%)	0.8 (0.2-2.4)	0.7	1 (0.7%)	2.4 (0.2-10.6)	0.4

# ICD-10



- International system of coding for health and disease
- Information on infections, diseases, symptoms, social circumstances, external causes of injury/disease, etc.
- ICD-10 hospital admission records available for all UK Biobank participants



Thousands of disease phenotypes



**Which phenotypes are associated with APOL1 genotypes?**

# Conditions associated with APOL1: previous studies

**Phenome-wide association analysis suggests the APOL1 linked disease spectrum primarily drives kidney-specific pathways.**

Archna Bajaj, MD, MSCE<sup>1,\*</sup>, Andrea Ihegword, MD, MPH<sup>2,\*</sup>, Chengxiang Qiu, MS<sup>1,3,4,\*</sup>, Aeron M. Small, MD, MTR<sup>4,5</sup>, Wei-Qi Wei, MD, PhD<sup>6</sup>, Lisa Bastarache, MS<sup>6</sup>, QiPing Feng, PhD<sup>2</sup>, Rachel L Kember, PhD<sup>7,8</sup>, Marjorie Risman, MA<sup>1</sup>, Roy D. Bloom, MD<sup>1,3</sup>, David L. Birtwell, MS<sup>9</sup>, Heather Williams, MS<sup>9</sup>, Christian M. Shaffer, MS<sup>2</sup>, Jinbo Chen, PhD<sup>10</sup>, Regeneron Genetics Center<sup>11</sup>, Joshua C. Denny, MD, MS<sup>2,6</sup>, Daniel J. Rader, MD<sup>1,4</sup>, C. Michael Stein, MBChB<sup>2,12</sup>, Scott M. Damrauer, MD<sup>13,14,\*\*</sup>, Katalin Susztak, MD, PhD<sup>1,3,4,\*\*</sup>

# Differences between our study and previous work

	Bajaj <i>et al.</i>	Our study
Comparison	Carriage of two APOL1 variants vs wild type	Each APOL1 variant genotype (G0/G1, G0/G2, G1/G1, G1/G2, G2/G2) vs wild type
Population	African Americans	UK residents with recent African ancestry
Cohort size	6,579	9,594
Conditions analysed	233 (>5% prevalence in cohort)	1100 (30+ instances in cohort)
Multiple testing correction	Bonferroni (very conservative)	False Discovery Rate (less conservative)
Covariates	Age, sex, CKD, principal components	Age, sex, Townsend deprivation index, CKD, principal components

# Phenome screening: results

Genotype	Number of ICD-10 codes associated
G0/G1	
G0/G2	
G1/G1	
G1/G2	
G2/G2	

Covariates: age, sex, Townsend deprivation index, chronic kidney disease, principal components 1-4

# Phenome screening: results

G0/G0

G0/G1

G0/G2

G1/G1

G1/G2

G2/G2

Genotype	Number of ICD-10 codes associated
G0/G1	0
G0/G2	
G1/G1	0
G1/G2	
G2/G2	0

Covariates: age, sex, Townsend deprivation index, chronic kidney disease, principal components 1-4

# Phenome screening: results

G0/G0

G0/G1

G0/G2

G1/G1

G1/G2

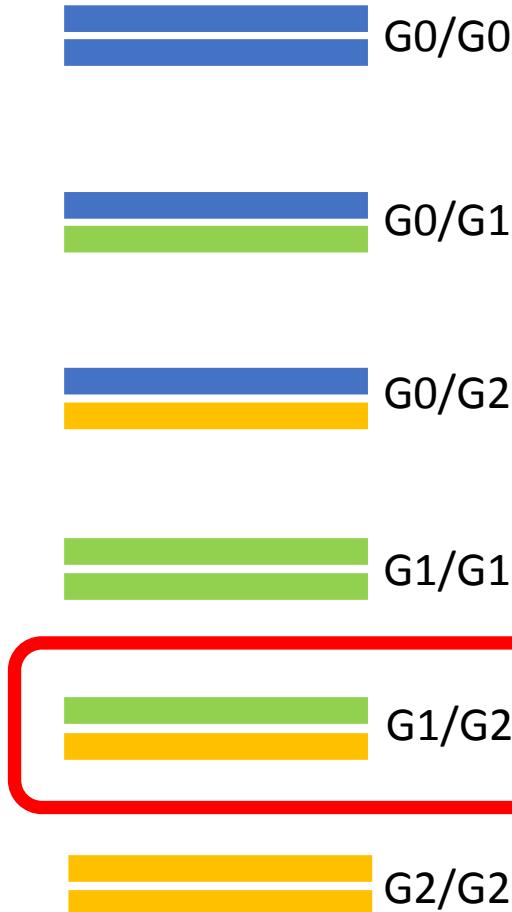
G2/G2

Genotype	Number of ICD-10 codes associated
G0/G1	0
G0/G2	1
G1/G1	0
G1/G2	
G2/G2	0



Covariates: age, sex, Townsend deprivation index, chronic kidney disease, principal components 1-4

# Phenome screening: results



Genotype	Number of ICD-10 codes associated
G0/G1	0
G0/G2	1
G1/G1	0
<b>G1/G2</b>	<b>26</b>
G2/G2	0

All deleterious

Covariates: age, sex, Townsend deprivation index, chronic kidney disease, principal components 1-4

# Phenome screening: results

Genotype	Number of ICD-10 codes associated
G0/G1	0
G0/G2	1
G1/G1	0
<b>G1/G2</b>	<b>26</b>
G2/G2	0
<b>2x APOL1 variants</b>	<b>0</b>

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Covariates: age, sex, Townsend deprivation index, chronic kidney disease, principal components 1-4



# Conditions associated with APOL1 G1/G2

Acute renal failure

Anxiety disorders

Bacterial agents causing disease

Chronic viral hepatitis

Conduction disorders

COVID-19

Foetal problems

Hypoglycaemia

Infectious gastroenteritis

Intestinal disorders

Irritable bowel syndrome

Multiple valve diseases

Nonrheumatic aortic valve disorders

Obstructive/reflux uropathy

Oesophageal disorders

Pancreatic secretion

Paralytic ileus

Peripheral vascular diseases

Peritoneal diseases

Polyarthrosis

Problems in pregnancy

Prostate hyperplasia

Respiratory failure

Viral agents causing disease

Viral pneumonia

Vitamin D deficiency

# Conditions associated with APOL1 G1/G2: poor outcomes in infection

Acute renal failure

Anxiety disorders

Bacterial agents causing disease

Chronic viral hepatitis

Conduction disorders

COVID-19

Foetal problems

Hypoglycaemia

Infectious gastroenteritis

Intestinal disorders

Irritable bowel syndrome

Multiple valve diseases

Nonrheumatic aortic valve disorders

Obstructive/reflux uropathy

Oesophageal disorders

Pancreatic secretion

Paralytic ileus

Peripheral vascular diseases

Peritoneal diseases

Polyarthrosis

Problems in pregnancy

Prostate hyperplasia

Respiratory failure

Viral agents causing disease

Viral pneumonia

Vitamin D deficiency

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G2/G2	150	2 (1.3%)	0.8 (0.2-2.4)	0.7	1 (0.7%)	2.4 (0.2-10.6)	0.4

# APOL1 G1/G2 is associated with hospitalisation due to a non-COVID-19 infectious disease

Genotype	Odds Ratio	p-value
G0/G0	1·0 (ref)	
G0/G1	0·9 (0·8-1·1)	0·35
G0/G2	0·9 (0·8-1·1)	0·27
G1/G1	0·9 (0·7-1·1)	0·37
G1/G2	<b>1·4 (1·1-1·9)</b>	<b>0·007</b>
G2/G2	0·9 (0·6-1·3)	0·55

Covariates: age, sex, Townsend deprivation index, chronic kidney disease, principal components 1-4

# Conditions associated with APOL1 G1/G2: metabolic conditions

Acute renal failure

Anxiety disorders

Bacterial agents causing disease

Chronic viral hepatitis

Conduction disorders

COVID-19

Foetal problems

Hypoglycaemia

Infectious gastroenteritis

Intestinal disorders

Irritable bowel syndrome

Multiple valve diseases

Nonrheumatic aortic valve disorders

Obstructive/reflux uropathy

Oesophageal disorders

Pancreatic secretion

Paralytic ileus

Peripheral vascular diseases

Peritoneal diseases

Polyarthrosis

Problems in pregnancy

Prostate hyperplasia

Respiratory failure

Viral agents causing disease

Viral pneumonia

Vitamin D deficiency

# Conditions associated with APOL1 G1/G2: digestive conditions

Acute renal failure

Anxiety disorders

Bacterial agents causing disease

Chronic viral hepatitis

Conduction disorders

COVID-19

Foetal problems

Hypoglycaemia

Infectious gastroenteritis

Intestinal disorders

Irritable bowel syndrome

Multiple valve diseases

Nonrheumatic aortic valve disorders

Obstructive/reflux uropathy

Oesophageal disorders

Pancreatic secretion

Paralytic ileus

Peripheral vascular diseases

Peritoneal diseases

Polyarthrosis

Problems in pregnancy

Prostate hyperplasia

Respiratory failure

Viral agents causing disease

Viral pneumonia

Vitamin D deficiency

# Conditions associated with APOL1 G1/G2: pregnancy

Acute renal failure

Anxiety disorders

Bacterial agents causing disease

Chronic viral hepatitis

Conduction disorders

COVID-19

Foetal problems

Hypoglycaemia

Infectious gastroenteritis

Intestinal disorders

Irritable bowel syndrome

Multiple valve diseases

Nonrheumatic aortic valve disorders

Obstructive/reflux uropathy

Oesophageal disorders

Pancreatic secretion

Paralytic ileus

Peripheral vascular diseases

Peritoneal diseases

Polyarthrosis

Problems in pregnancy

Prostate hyperplasia

Respiratory failure

Viral agents causing disease

Viral pneumonia

Vitamin D deficiency

# Conditions associated with APOL1 G1/G2: pregnancy

Miller et al. BMC Medical Genetics (2020) 21:110  
<https://doi.org/10.1186/s12881-020-01048-4>

BMC Medical Genetics

RESEARCH ARTICLE

Open Access

## Association of preeclampsia with infant APOL1 genotype in African Americans



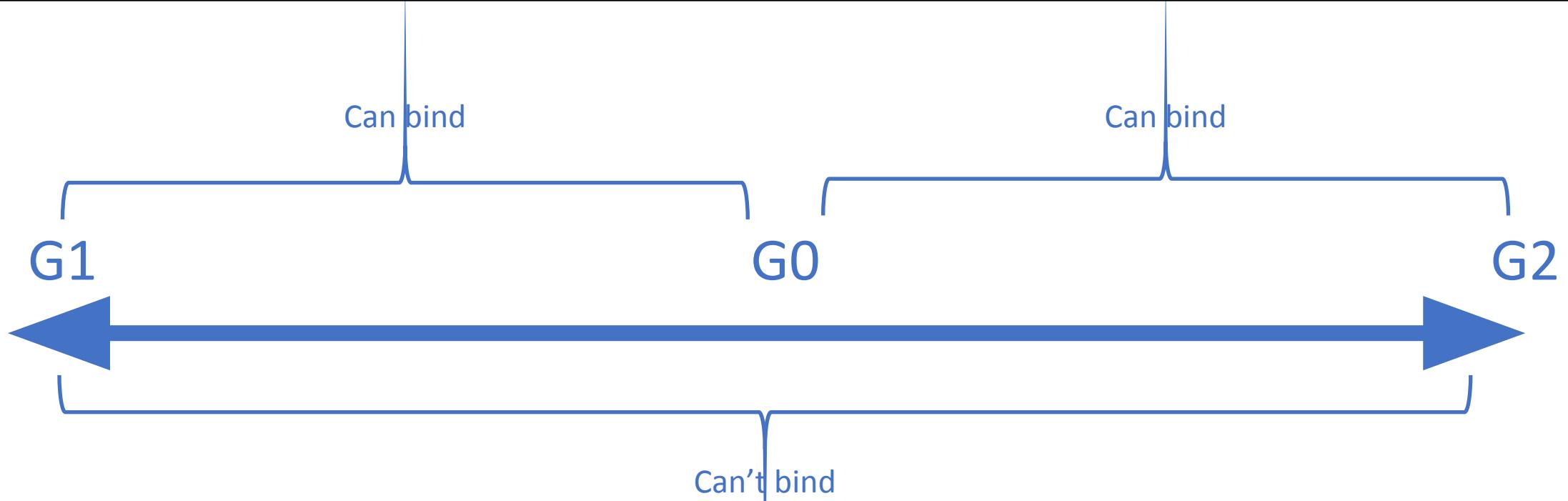
Anna K. Miller<sup>1</sup>, Timur Azhibekov<sup>2</sup>, John F. O'Toole<sup>3</sup>, John R. Sedor<sup>3,4</sup>, Scott M. Williams<sup>1,5</sup>,  
Raymond W. Redline<sup>6</sup> and Leslie A. Bruggeman<sup>3\*</sup> 

# G1/G2 is associated with an increased number of ICD-10 codes

Genotype	Total ICD-10 codes per participant
G0/G0	6.5
G0/G1	7.1
G0/G2	6.8
G1/G1	6.7
G1/G2	8.7
G2/G2	6.3

**p = 0.0003**

# What might the molecular basis of this be?



**Hypothesis:** G1 and G2 are too different: they can't each other properly. G0/G0, G0/G1, G0/G2, G1/G1, and G2/G2 all produce functional pores. In G1/G2:

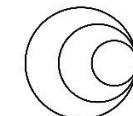
- Pores are made up of G1 and G2, and they are misformed, affecting function.  
OR
- Pores are made up of G1s **or** G2s, with the other type forming harmful aggregates in cells.

# ANIMAL FARM

GEORGE ORWELL



*"All APOL1 variants are equal, but some are more equal than others."*



wellcome  
connecting  
science

# ANIMAL FARM

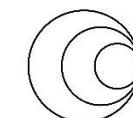
GEORGE ORWELL



APOL1 variants, and the genotypes they produce, are different from each other...

**"~~All APOL1 variants are equal, but some are more equal than others.~~"**

...and the G1/G2 genotype is particularly deleterious.



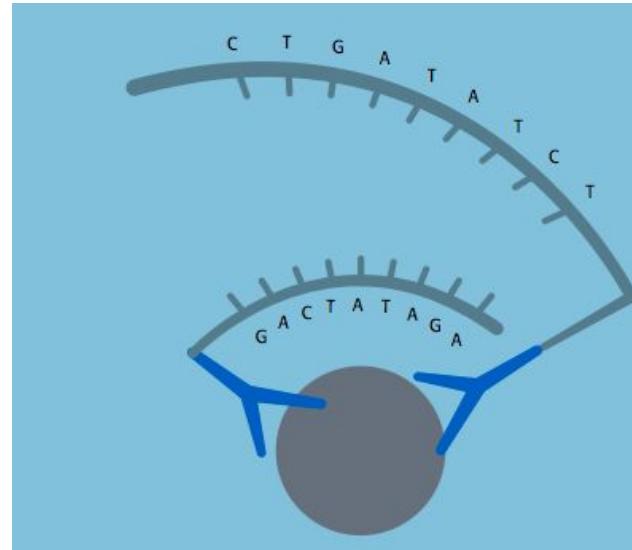
**wellcome**  
connecting  
science



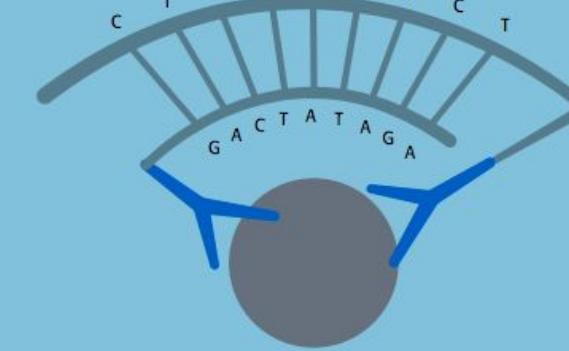
- ~500,000 healthy participants aged 40-69, enrolled 2006-2010, to be followed for 30 years.
- HUGE collection of data on each participant (clinical measurements, indicators of health, lifestyle, medications, etc, etc).
- ~850,000 SNPs examined for each participant, whole-genome sequencing recently completed.
- Olink protein concentration data recently available
- Blood and urine samples available on request.
- Regular follow-ups to examine changes to health.

# Olink: detect and analyse > 3000 proteins simultaneously

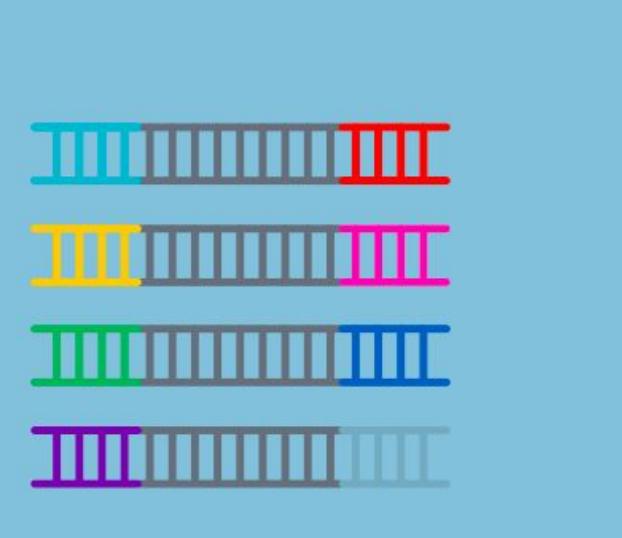
- Performed for 54,219 UK Biobank participants
- (Including 1,050 UK Biobank participants with recent sub-Saharan African ancestry)



Immuno reaction



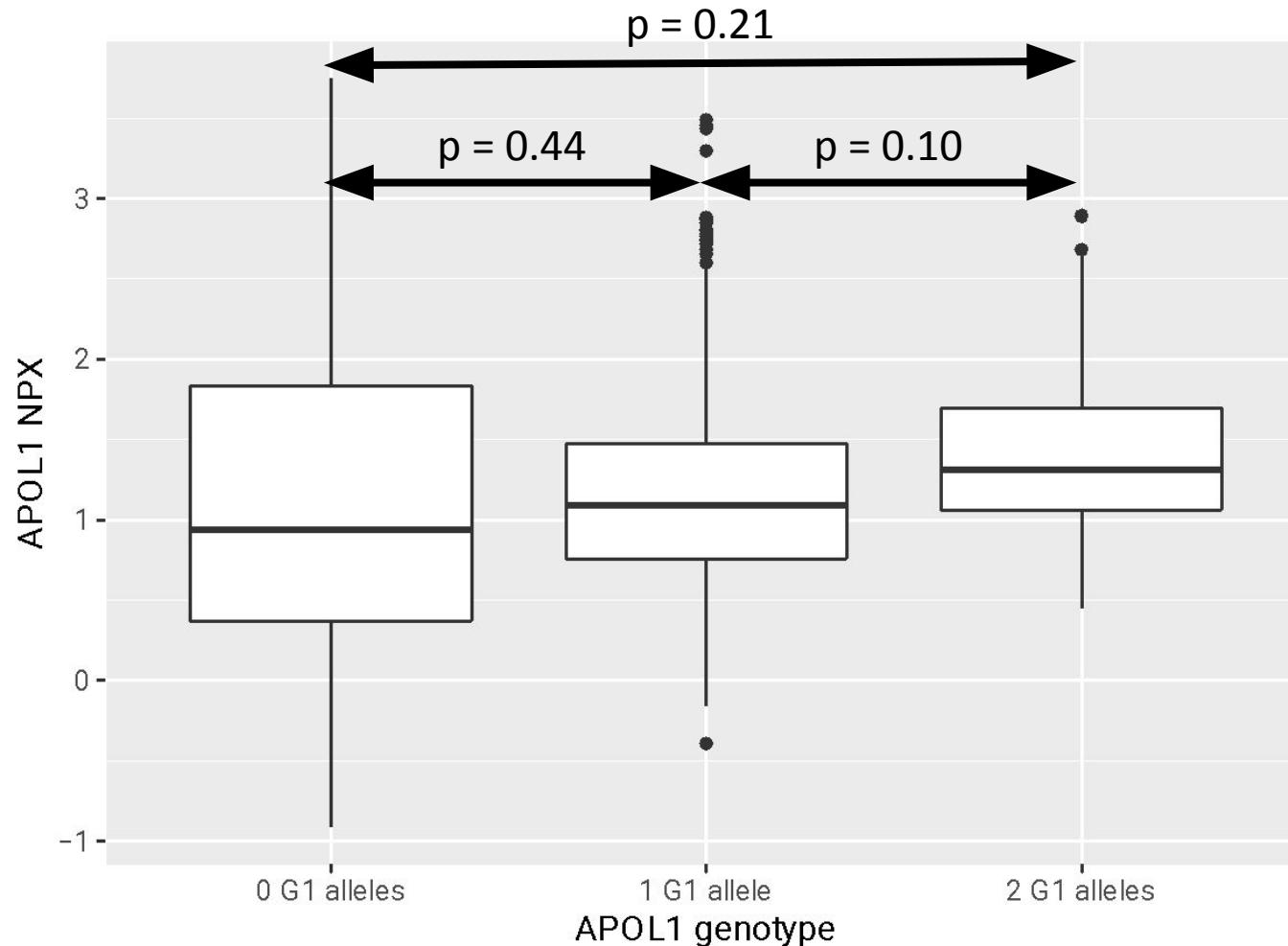
Double-stranded DNA



Quantification by  
real time PCR

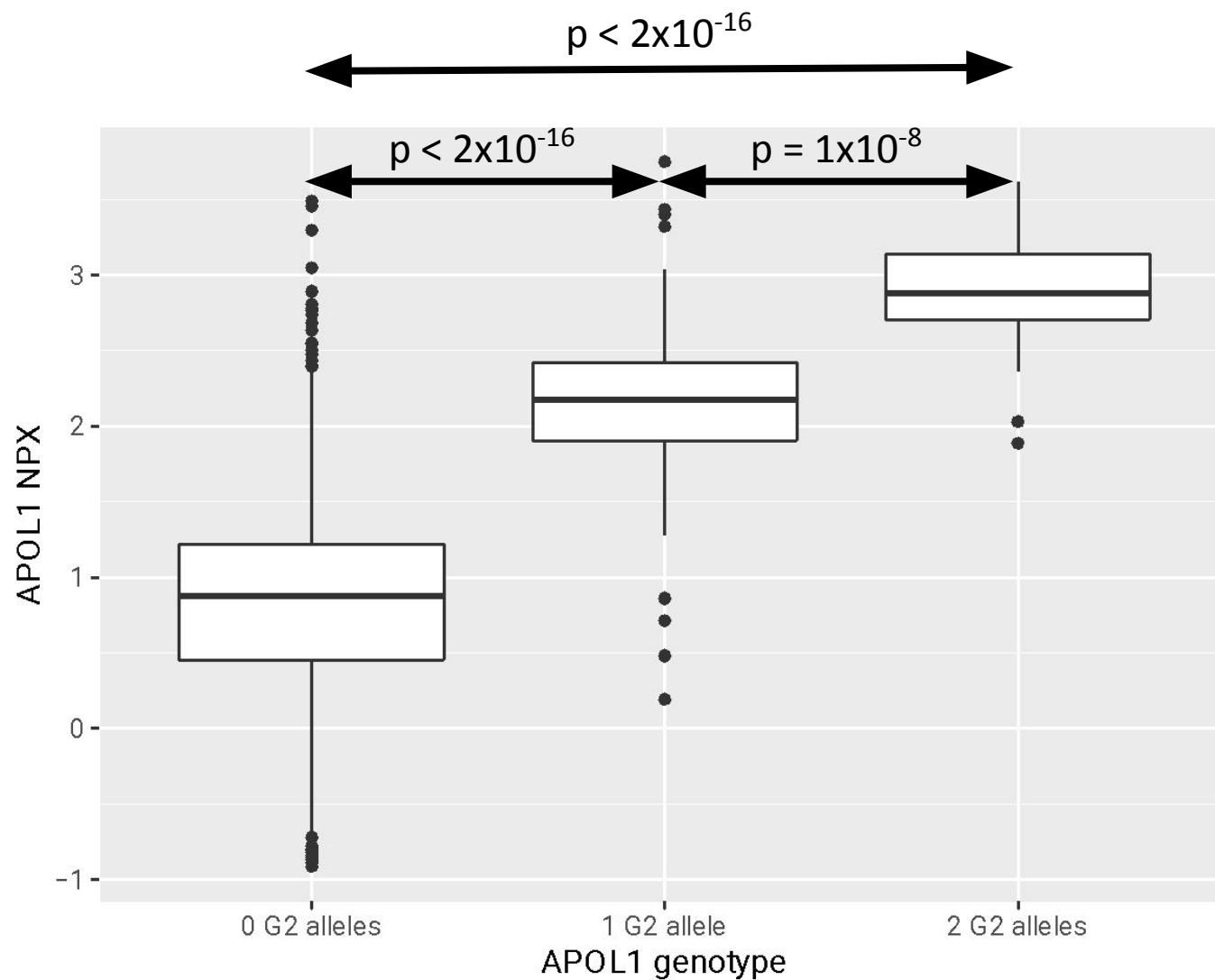
Image from [cellculturedish.com](http://cellculturedish.com)

# APOL1 G1 moderately influences protein concentration

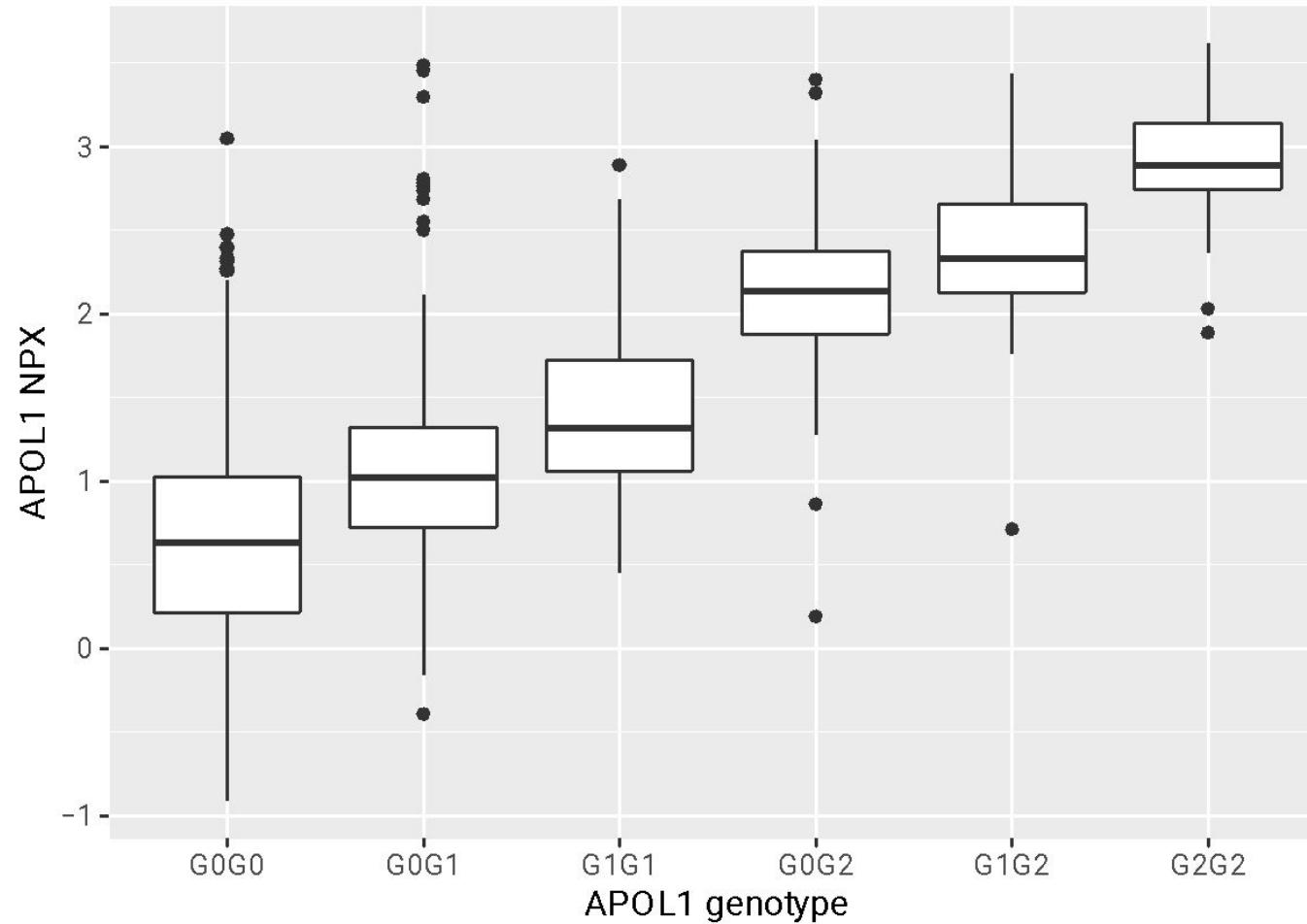


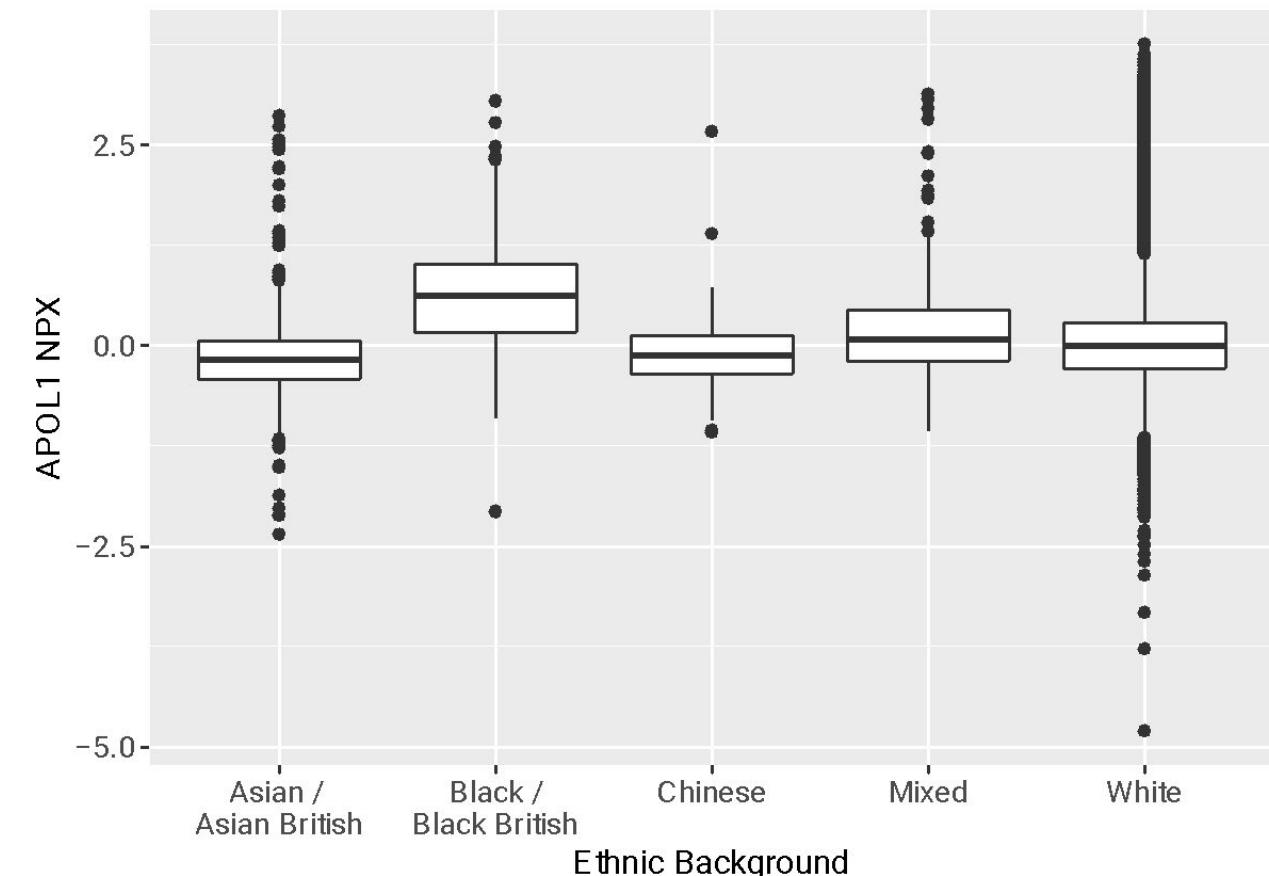
0 G1 alleles  
v  
1 or 2 G1 alleles  
p = 0.0003

# APOL1 G2 strongly influences protein concentration



# APOL1 genotype strongly influences protein concentration





	Asian/Asian British	Black/Black British	Chinese	Mixed	White
Asian/Asian British	-	<2x10 <sup>-16</sup>	0.31	1x10 <sup>-13</sup>	<2x10 <sup>-16</sup>
Black/Black British	<2x10 <sup>-16</sup>	-	<2x10 <sup>-16</sup>	3x10 <sup>-12</sup>	<2x10 <sup>-16</sup>
Chinese	0.31	<2x10 <sup>-16</sup>	-	8x10 <sup>-8</sup>	2x10 <sup>-5</sup>
Mixed	1x10 <sup>-13</sup>	3x10 <sup>-12</sup>	8x10 <sup>-8</sup>	-	<2x10 <sup>-16</sup>
White	<2x10 <sup>-16</sup>	<2x10 <sup>-16</sup>	2x10 <sup>-5</sup>	<2x10 <sup>-16</sup>	-

# ICD-10



- International system of coding for health and disease
- Information on infections, diseases, symptoms, social circumstances, external causes of injury/disease, etc.
- ICD-10 hospital admission records available for all UK Biobank participants



Thousands of disease phenotypes



**Which phenotypes are high or low APOL1 protein concentrations?**

## Phenome screen: APOL1 protein concentration

- 619 conditions examined
- APOL1 genotype taken as a covariate (along with age, sex, Townsend Deprivation index, principal components 1-4.

## Phenome screen: APOL1 protein concentration

- 619 conditions examined
- APOL1 genotype taken as a covariate (along with age, sex, Townsend Deprivation index, principal components 1-4.
- 49 conditions identified as associated with APOL1 concentration:
  - 45 associated with low APOL1 concentration
  - 4 associated with high APOL1 concentration

# Conditions associated with low APOL1 concentration

Type of condition	ICD codes tested	ICD codes associated	Percentage associated	p-value
Infectious diseases	21	1	4.8	0.65
Neoplasms	81	1	1.2	0.04
Immune-related	20	1	5.0	0.70
Metabolic	32	6	18.8	0.02
Mental/behavioral	27	1	3.7	0.48
Nervous system	41	2	4.9	0.56
Eye	33	1	3.0	0.35
Ear	16	1	6.3	0.87
Circulatory	56	22	39.3	<0.00001
Respiratory	44	0	0.0	0.06
Digestive	60	3	5.0	0.52
Skin/subcutaneous	32	1	3.1	0.37
Musculoskeletal	62	1	1.6	0.09
Genitourinary	57	4	7.0	0.94
Pregnancy/childbirth	32	0	0.0	0.11
Codes for special purposes	5	0	0.0	0.53

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Mental/behavioral	27	1	3.7	0.48
Nervous system	41	2	4.9	0.56
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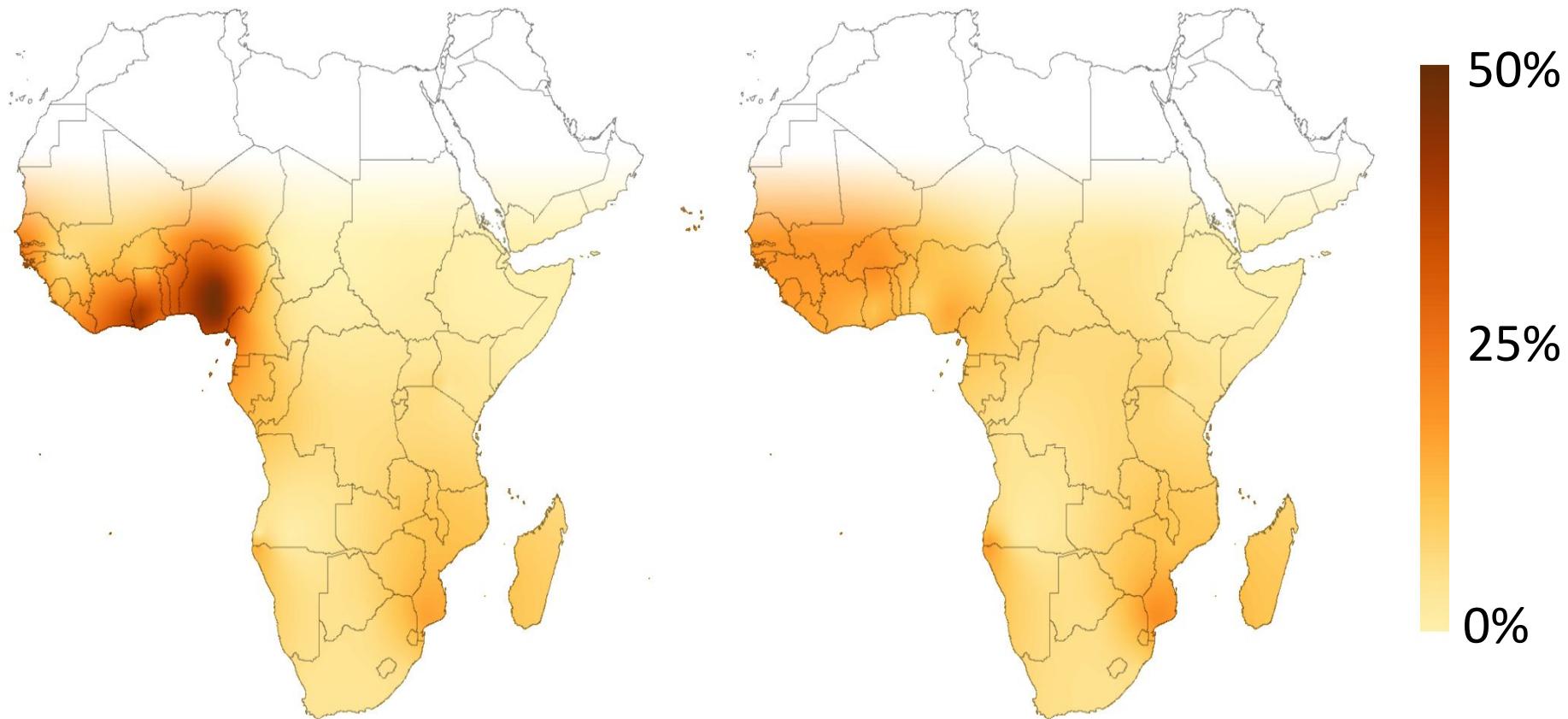
# Circulatory conditions associated with reduced APOL1 concentration

- Acute endocarditis
- Acute ischaemic heart diseases
- Acute myocardial infarction
- Aneurysm and dissection
- Angina pectoris
- Atherosclerosis
- Atrial fibrillation
- Cardiac arrest
- Cardiomyopathy
- Conduction disorders
- Endocarditis
- Haemorrhoids
- Heart failure
- Hypertensive heart disease
- Hypertensive renal disease
- Noninfective disorders of lymphatic vessels and lymph nodes
- Oesophageal varices
- Paroxysmal tachycardia
- Postprocedural disorders of circulatory system
- Pulmonary embolism
- Rheumatic tricuspid valve diseases

## Key messages

- G1 and G2 are *different* – and not just in sleeping sickness.
- $G1 \neq G2$ , and  $G1/G1 \neq G1/G2 \neq G2/G2$ .
- Identified genotype-specific phenotypes within CKD.
- Identified (many) potential new APOL1-associated conditions.
- The G1/G2 genotype is particularly deleterious.
- Low APOL1 protein concentration  $\square$  serious circulatory conditions

# What next?



Allele frequencies of G1 (left) and G2 (right) in Africa.

# Our papers

## Phenome screening of APOL1 genotypes

### Phenome-wide analysis reveals epistatic associations between APOL1 variants and chronic kidney disease and multiple other disorders

Walt E. Adamson,<sup>a,b,c,\*</sup> Harry Noyes,<sup>c,d</sup> Paul Johnson,<sup>a</sup> Anneli Cooper,<sup>a,b</sup> Darren G. Monckton,<sup>e</sup> John Ogunsola,<sup>a,b</sup> Georgia Beckett-Hill,<sup>a</sup> Michael Sullivan,<sup>f</sup> Patrick Mark,<sup>f</sup> Rulan S. Parekh,<sup>g</sup> and Annette MacLeod<sup>a,b,c,\*</sup>

<sup>a</sup>School of Biodiversity, One Health, and Veterinary Medicine, University of Glasgow, United Kingdom

<sup>b</sup>Wellcome Centre for Integrative Parasitology, University of Glasgow, United Kingdom

<sup>c</sup>TrypanoGEN+ Research Group, Uganda, Member of the H3Africa Consortium, South Africa

<sup>d</sup>Centre for Genomic Research, University of Liverpool, United Kingdom

<sup>e</sup>School of Molecular Biosciences, University of Glasgow, United Kingdom

<sup>f</sup>School of Cardiovascular and Metabolic Health, University of Glasgow, United Kingdom

<sup>g</sup>Women's College Hospital, Hospital for Sick Children and University of Toronto, Canada

EBioMedicine, February 2024



## Effect of APOL1 genotype of protein concentration



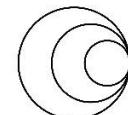
THE PREPRINT SERVER FOR HEALTH SCIENCES

### APOL1 variants G1, G2 and N264K affect APOL1 plasma protein concentration: a UK Biobank study

Walt E. Adamson, Harry Noyes, John Ogunsola, Rulan S. Parekh, Anneli Cooper, Annette MacLeod

doi: <https://doi.org/10.1101/2024.02.28.24303461>

MedRxiv, February 2024



wellcome  
connecting  
science

# COVI-Go Platform

<https://www.covi-go.com>

Immunoassay approved in US





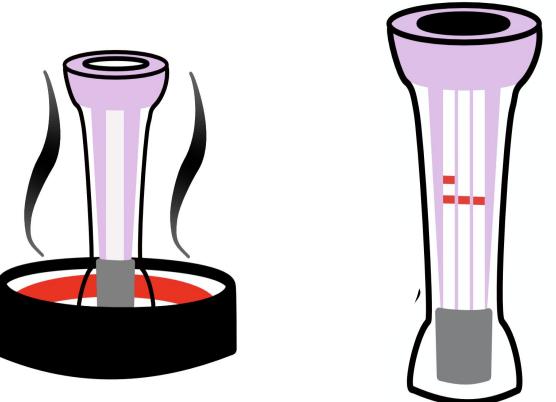
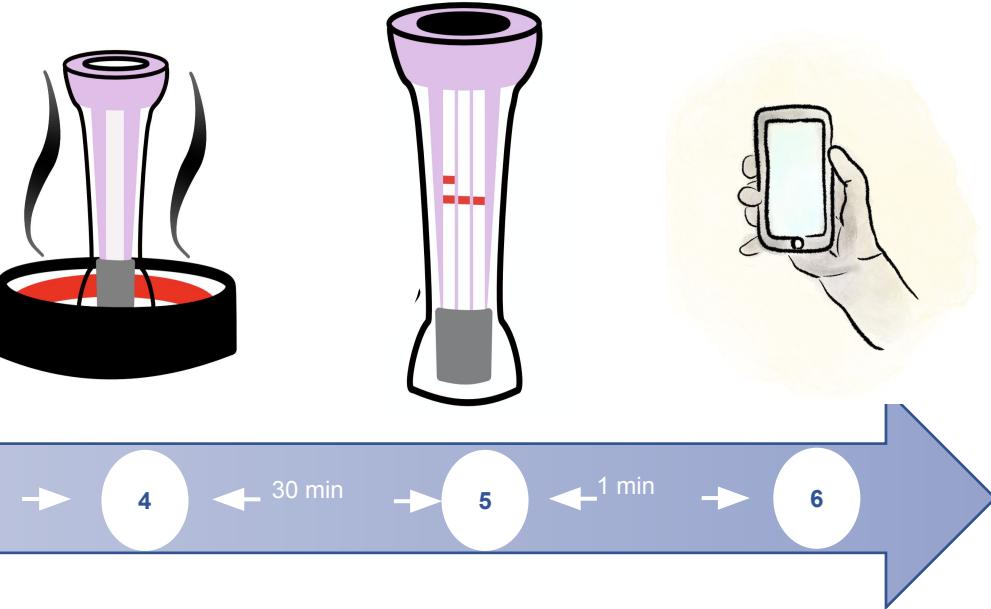
University  
of Glasgow

# Microfluidics Next steps

GLOBAL ACCESS  
**ga** HEALTH

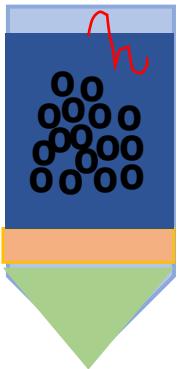


Sample collection  
and insertion





# Integrated sample processing



RNA virus from swab

Magnetic beads

In 1ml of buffer

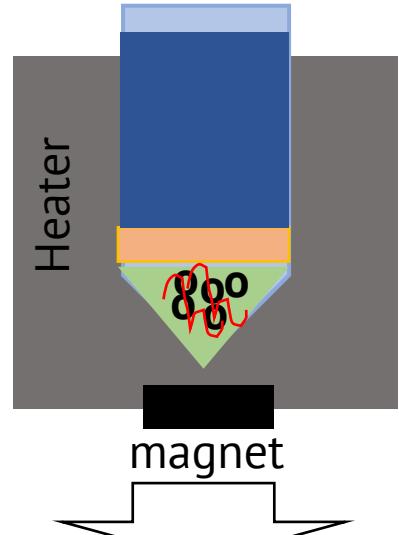
5-10 min  
incubation

200 $\mu$ l immiscible layer

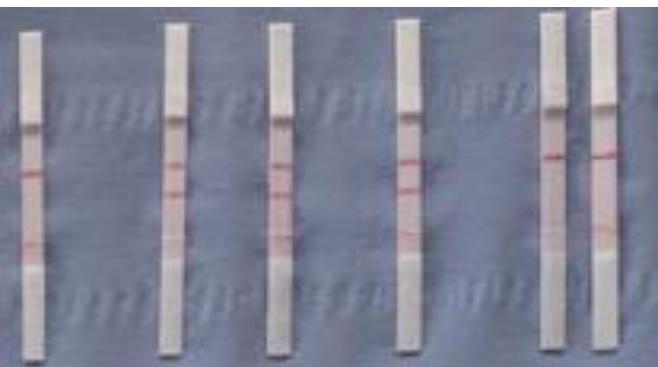
20 $\mu$ l LAMP reaction

COVID-19 copies input

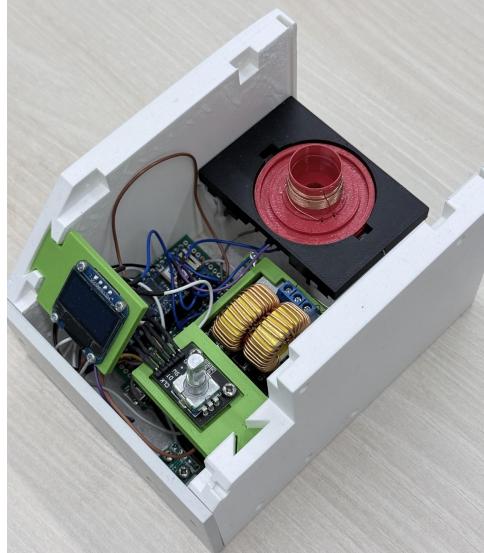
Results after amplification  
shows  
 $100 < \text{LOD} < 1000$  copies



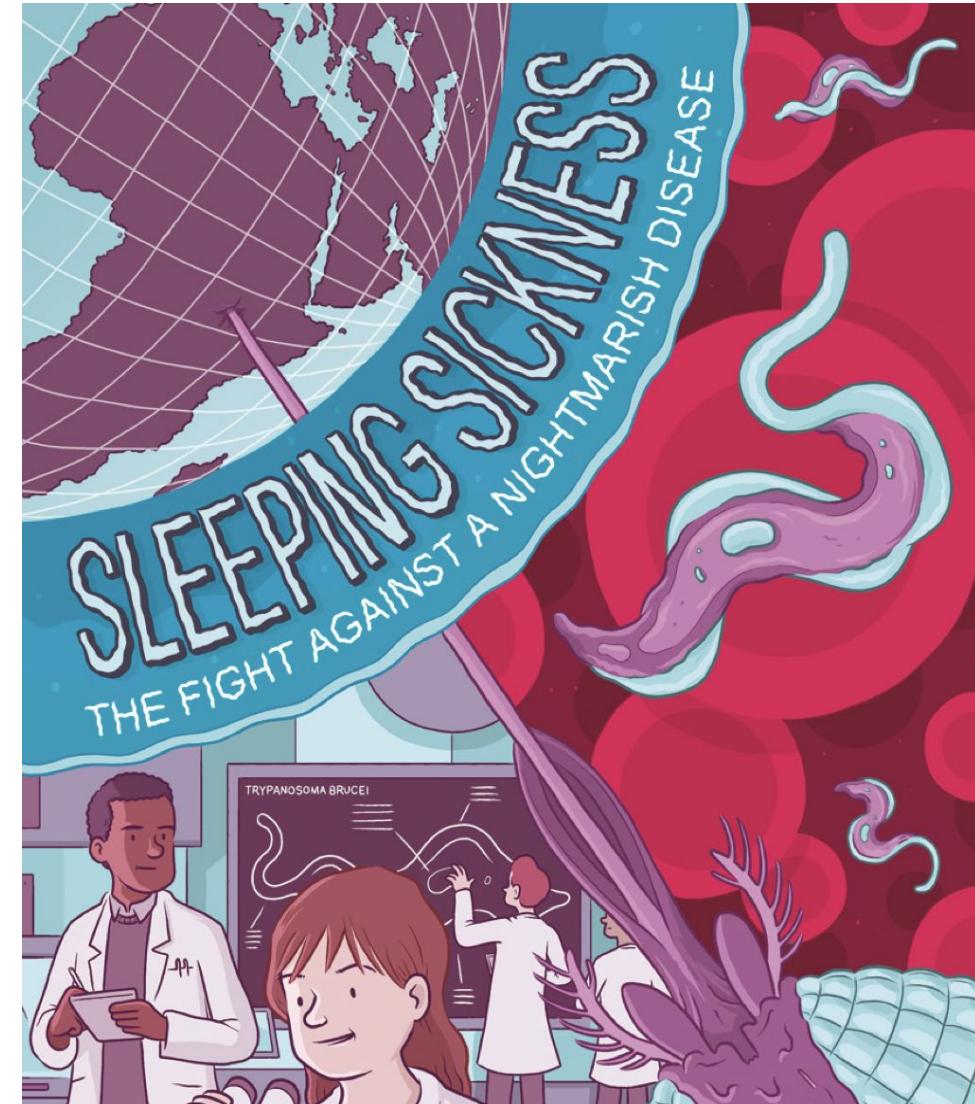
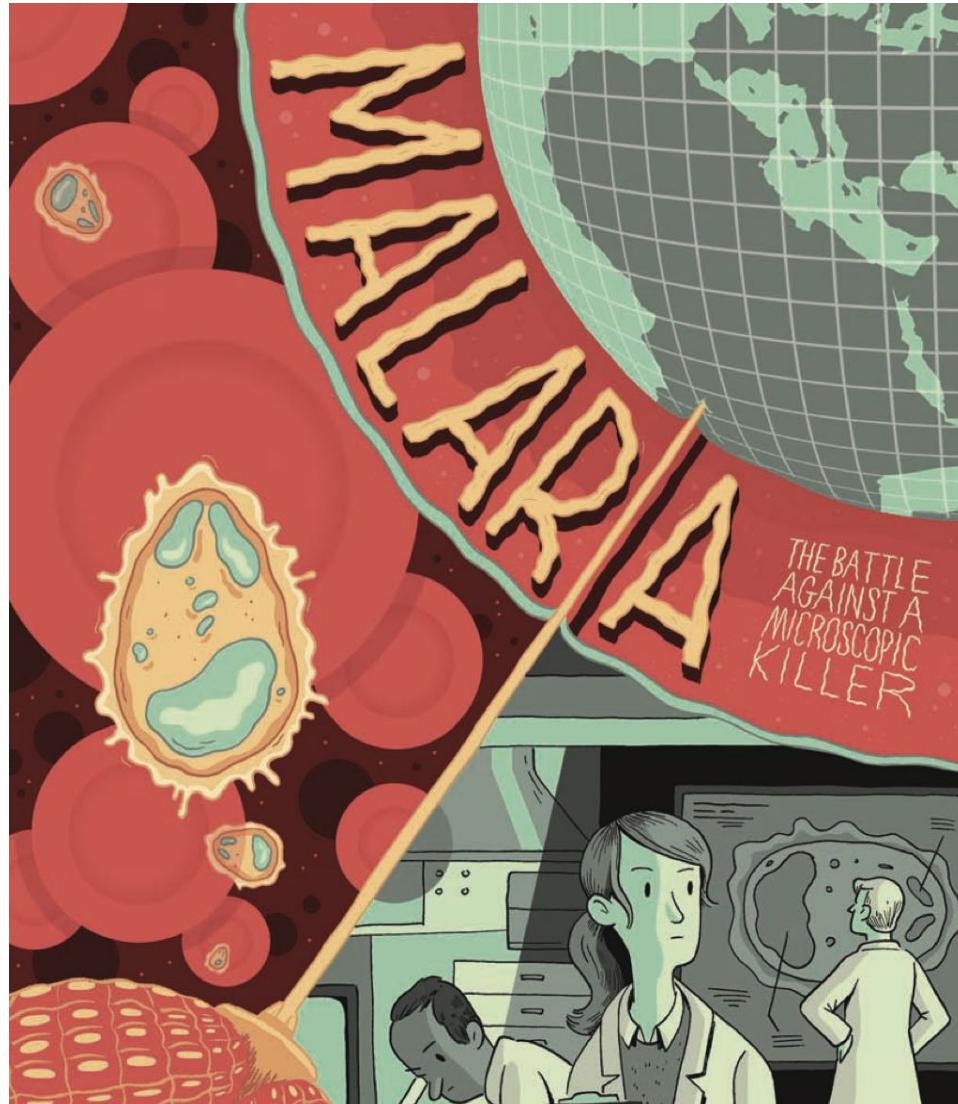
-ve       $10^5$      $10^4$      $10^3$      $10^2$



Control line  
Test line



# Current funding: malaria and human African trypanosomiasis test (MRC Gap fund)



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GAAAAA

G1 (green): in most cases, the A and the T highlighted both become G

G2 (red): these six nucleotides are deleted

G1 (green): in most cases, the A and the T highlighted both become G  
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gattatacagacgcataactggagggtggatccacacagctcagaacacagctggatcttgcctcgtcagtctctgtcaggggaagattccttgaggaggc  
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GAAAAA

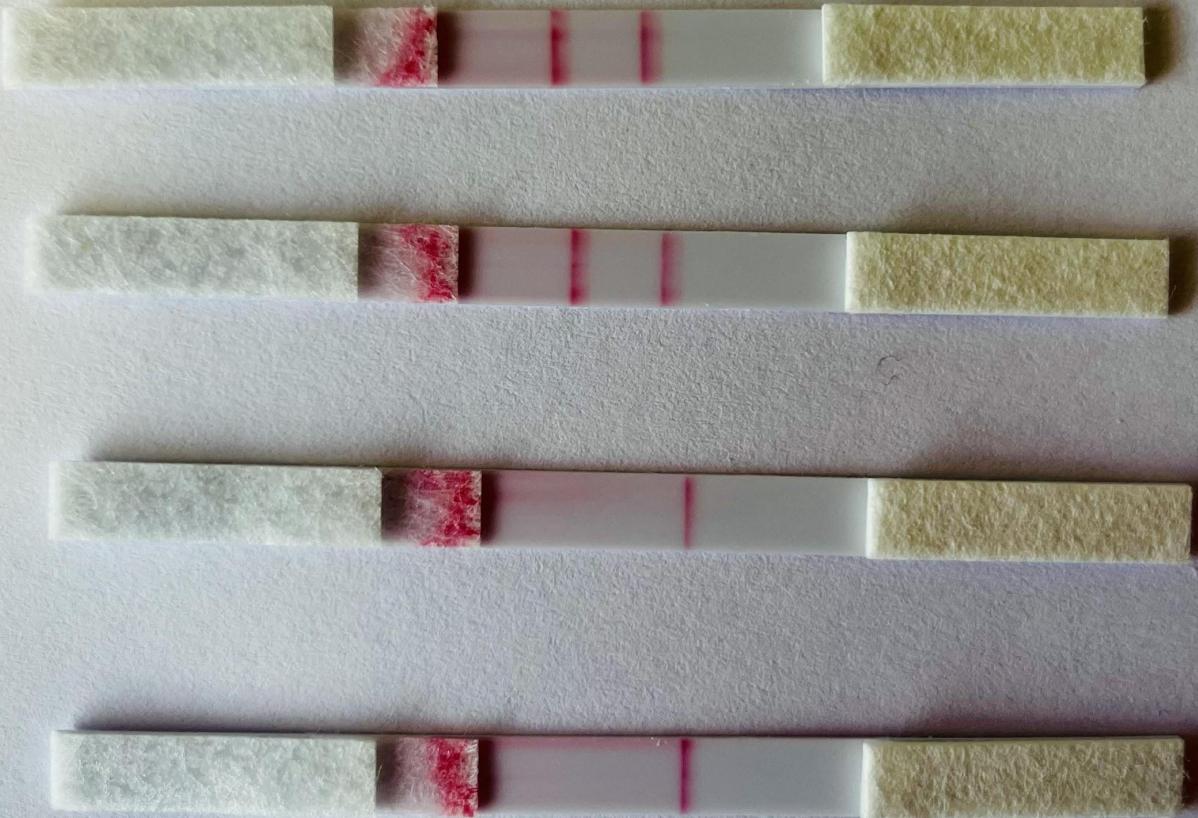
G1 (green): in most cases, the A and the T highlighted both become G

G2 (red): these six nucleotides are deleted

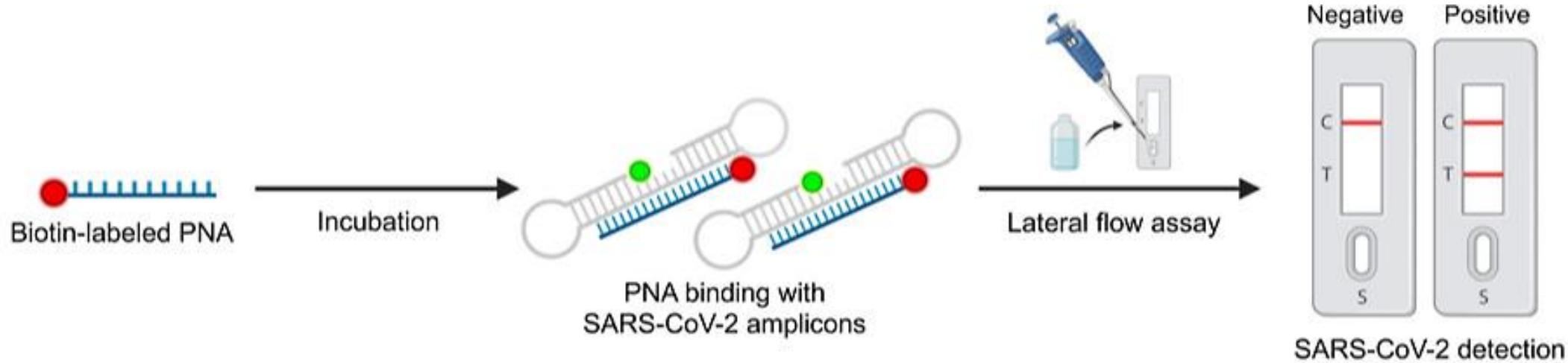
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GAAAAA

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G2 (red): these six nucleotides are deleted



# Peptide Nucleic Acid (PNA) binding



# TCTCAACAATAATT = G0 present = low risk of CKD

gattatacagacgcataactggagggtggatccacacagctcagaacacagctggatcttgcctcgtcagtcgtcaggaaagattcctggaggaggc  
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GAAAAA

# Interpretation of results

APOL1 genotype	PNA binding?
G0/G0	Yes
G0/G1	Yes
G0/G2	Yes
G1/G1	No
G1/G2	No
G2/G2	No



# APOL1 variants

	<i>T.b. gambiense</i> infection	<i>T.b.rhodesiense</i> infection	Chronic kidney disease
	Wild-type	Wild-type	Wild-type
	Protective	No effect	No effect
	Deleterious	Protective	No effect
	Protective	No effect	Deleterious
	Unclear	Unclear	Deleterious
	No effect	Protective	Deleterious

# APOL1 genotyping test

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TCTCAACAATAATT = G0 present

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AACATGCTCA  
= G1 present

CAATAAGATTG  
= G2 present

# Peptide Nucleic Acid (PNA) binding

APOL1 genotype	G0 PNA	G1 PNA	G2 PNA
G0/G0	+	-	-
G0/G1	+	+	-
G0/G2	+	-	+
G1/G1	-	+	-
G1/G2	-	+	+
G2/G2	-	-	+