

# **Using GWAS to identify functional pathways and therapeutics**

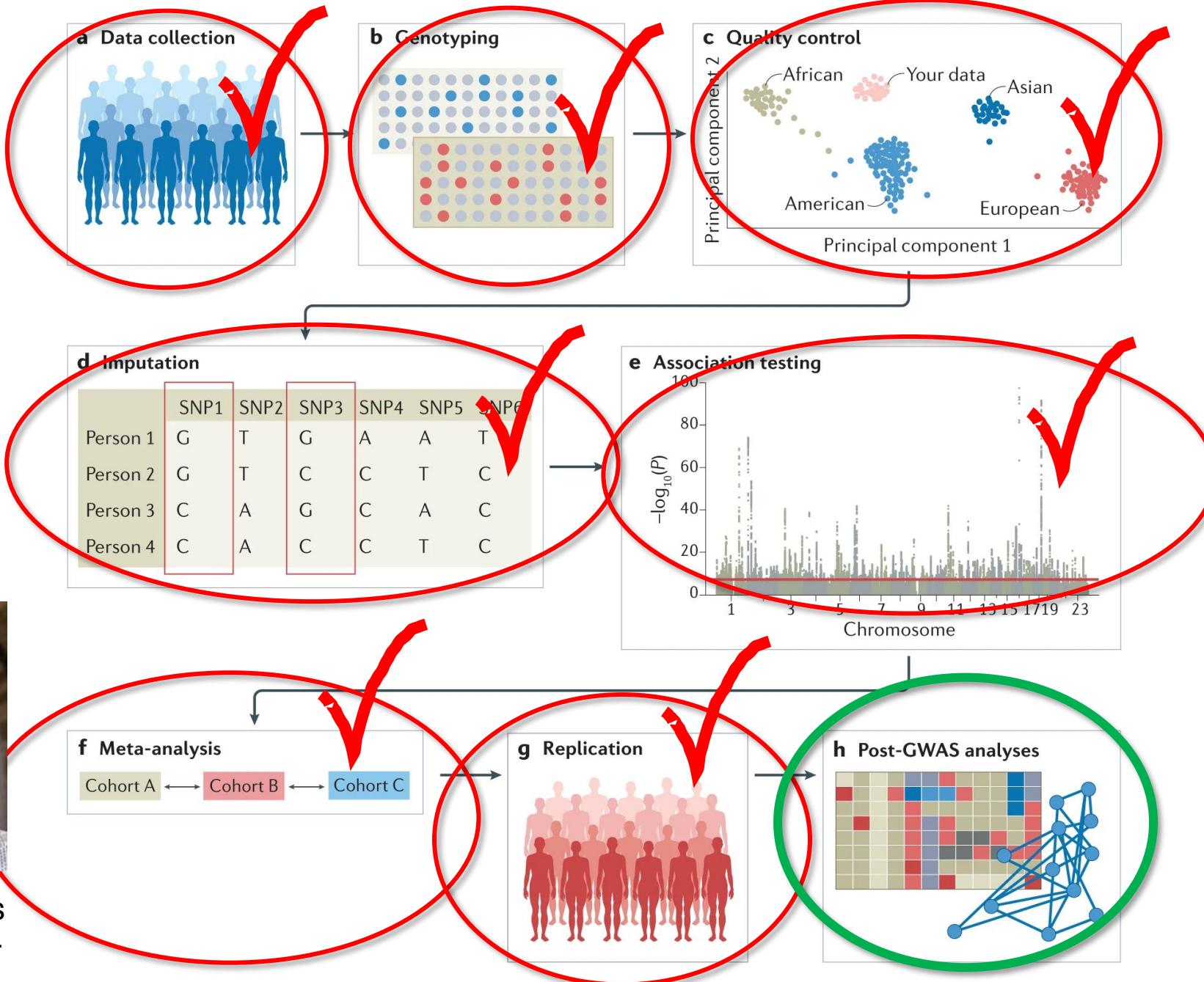
Cristian Pattaro

Eurac Research, Institute for Biomedicine, Bolzano, Italy

Johannesburg, 28 January 2026



Andrew Morris  
U Manchester



# **Examples of prioritized genes for treatment**

## **In population samples of African Ancestry**

- APOL1, GATM, PCSK9

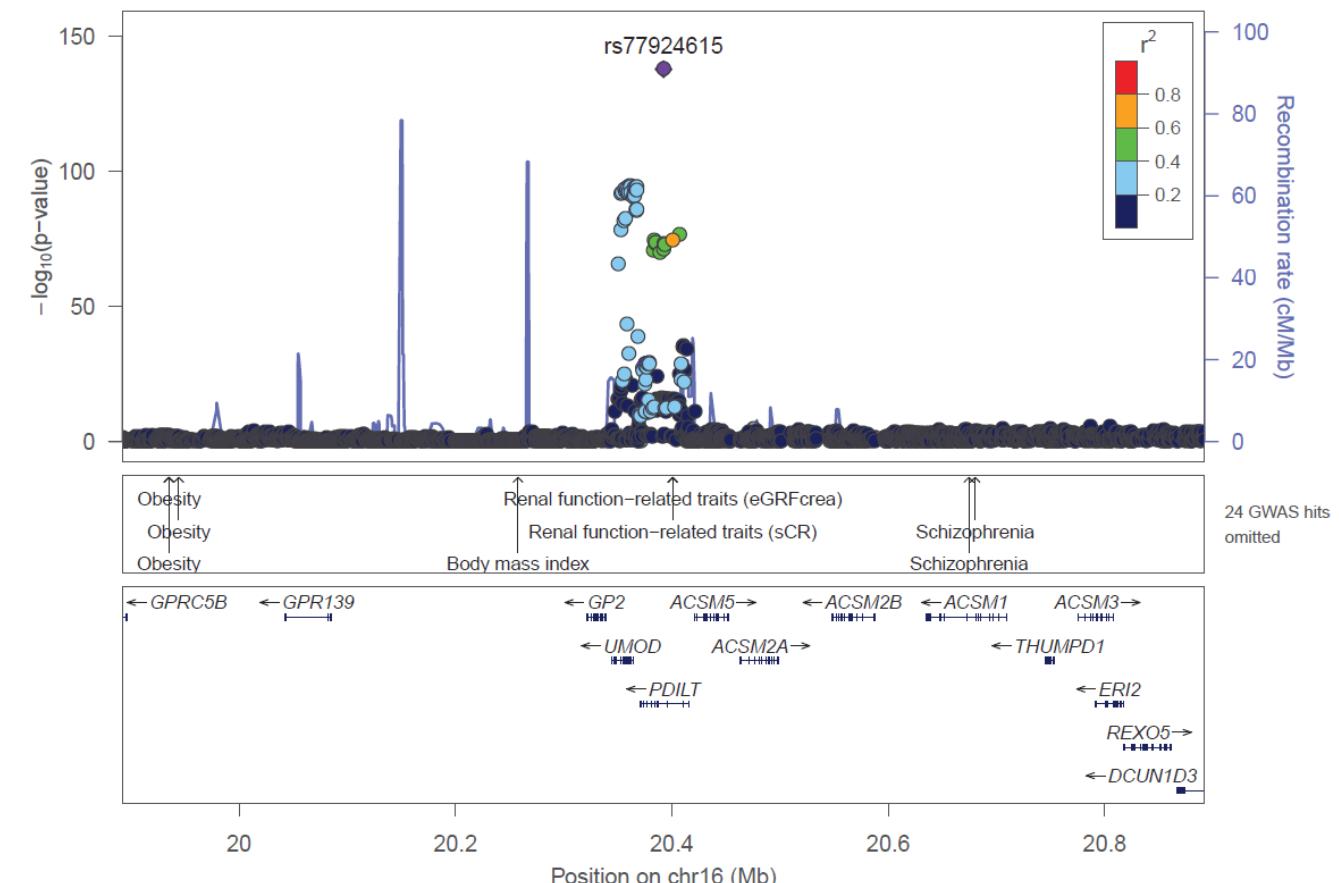
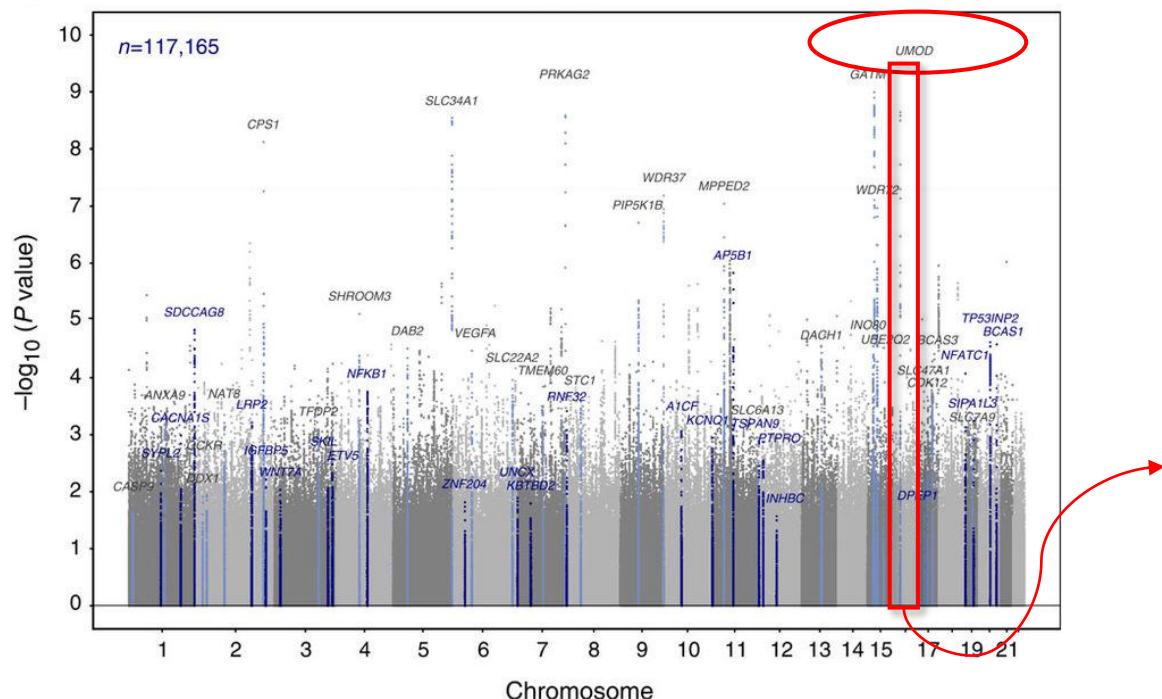
## **In population samples of other ancestries**

- UMOD, SHROOM3, OAF, DSP
- Proteomics

**UMOD**

# *UMOD*, eGFR, CKD

strongest association with  
kidney function & CKD



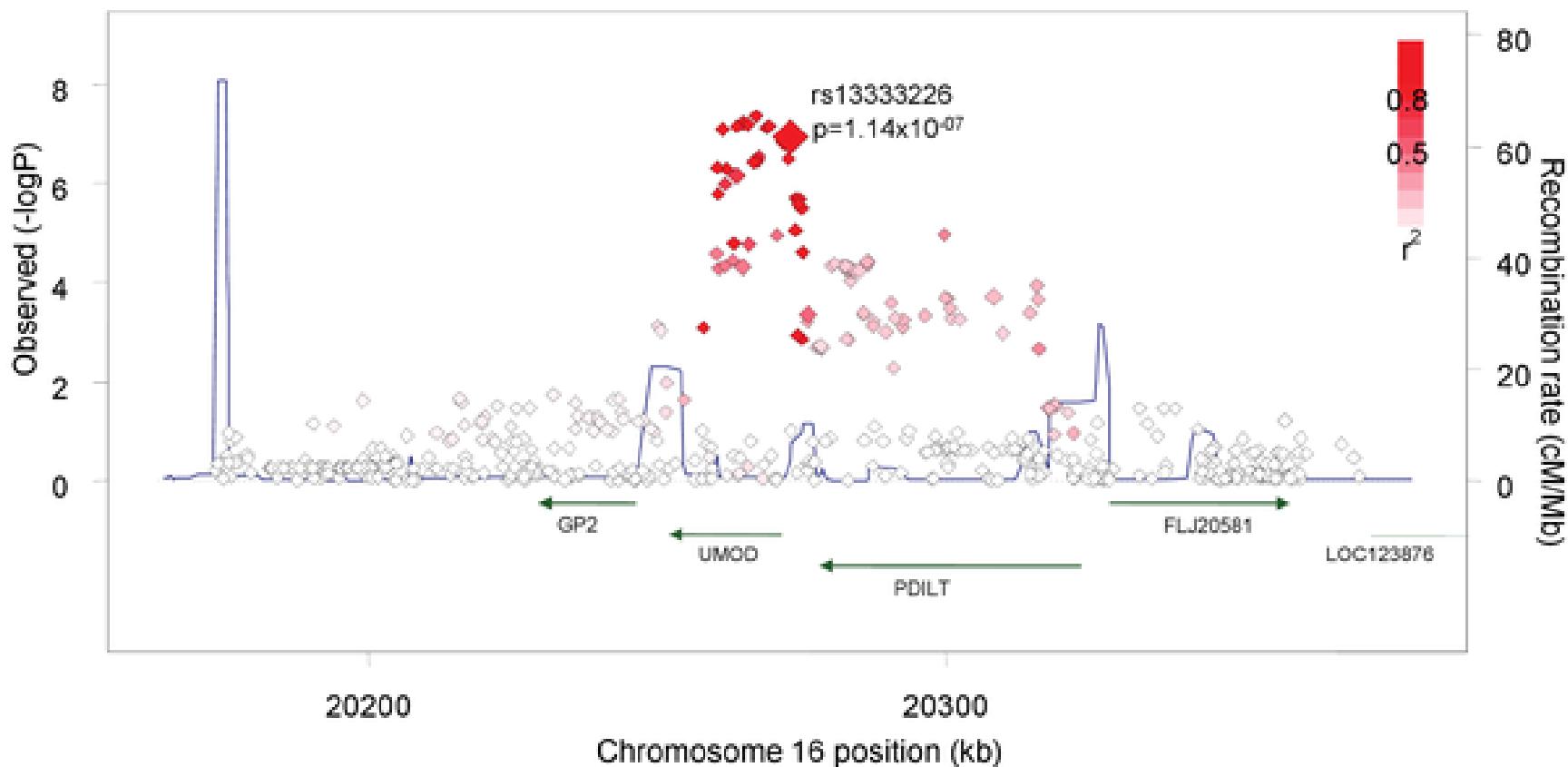
Köttgen Nat Genet 2009; Pattaro BMC Med Genet 2010;  
Gudbjartsson PLoS Genet 2010; Köttgen Nat Genet 2010;  
Pattaro PLoS Genet 2012; ...

Wuttke Nat Genet 2019

# ***UMOD*** and hypertension

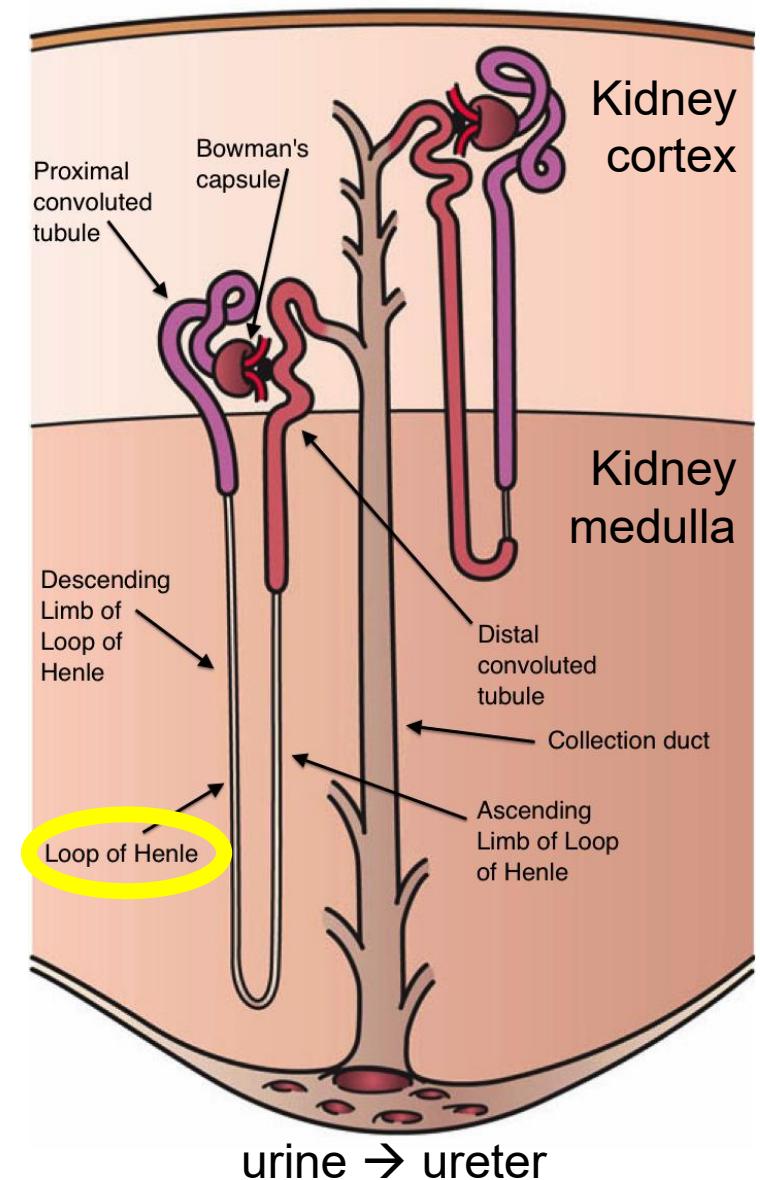
The same or variants in strong LD, associated with

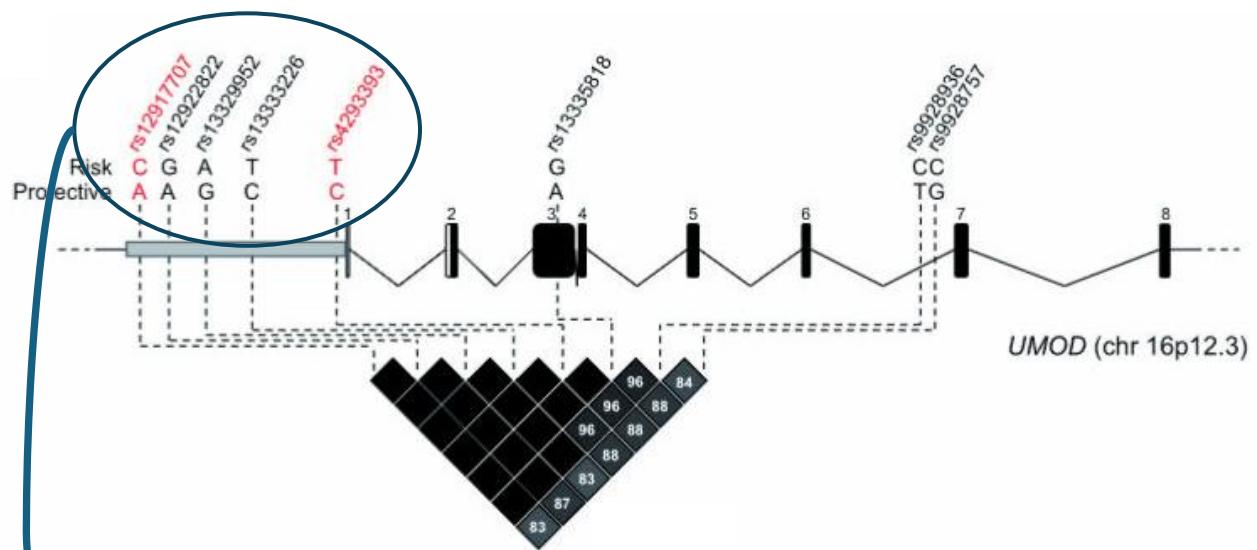
- **hypertension** ( $p=3.6\text{e-}11$ ), Padmanabhan PLoS Genet 2010
- **DBP** ( $p=2\text{e-}9$ ), Hoffman, Nat Genet 2016



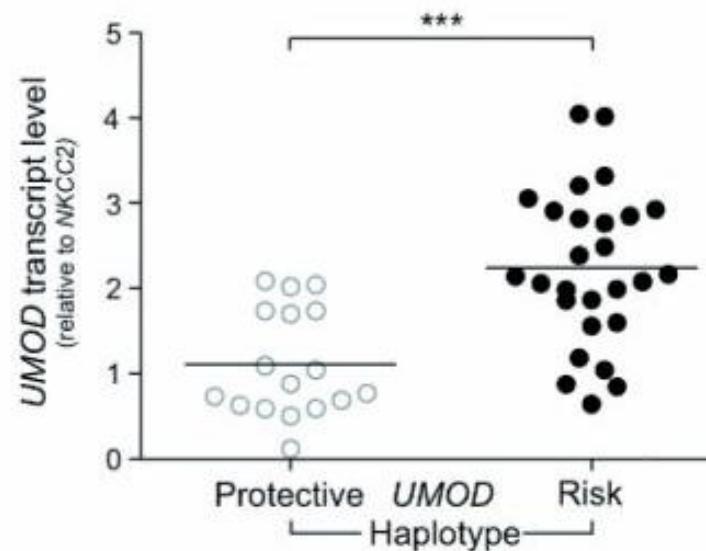
# Uromodulin

- exclusively produced in the **Henle loop**
- thought to regulate activity of NKCC2  
and *ROMK*, ie the two main ion transporters involved in the NaCl (sodium chloride) reabsorption by the thick ascending limb segment
- **Furosemide** is a common drug inhibiting NKCC2





Nefrectomy samples



UMOD risk haplotypes: a) ↑ *UMOD* expression



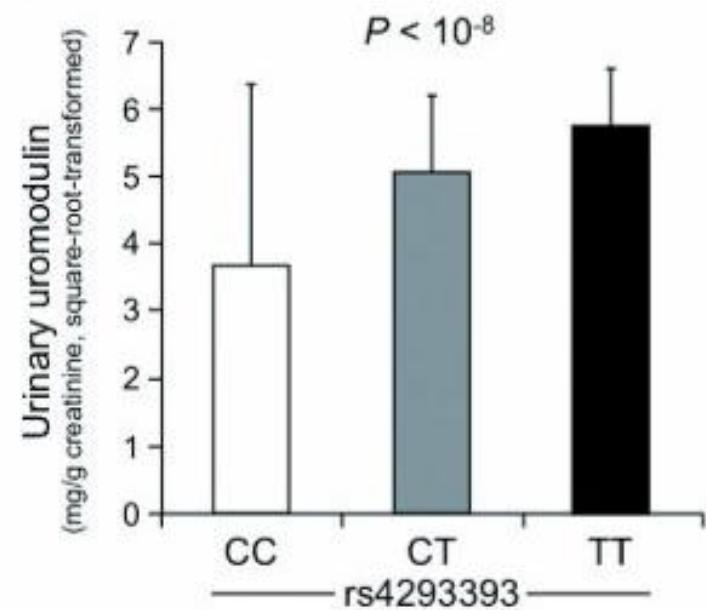
L. Rampoldi  
San Raffaele Uni



O. Devuyst  
Zurich Uni

Trudu et al. Nat Med 2013

Human urine samples

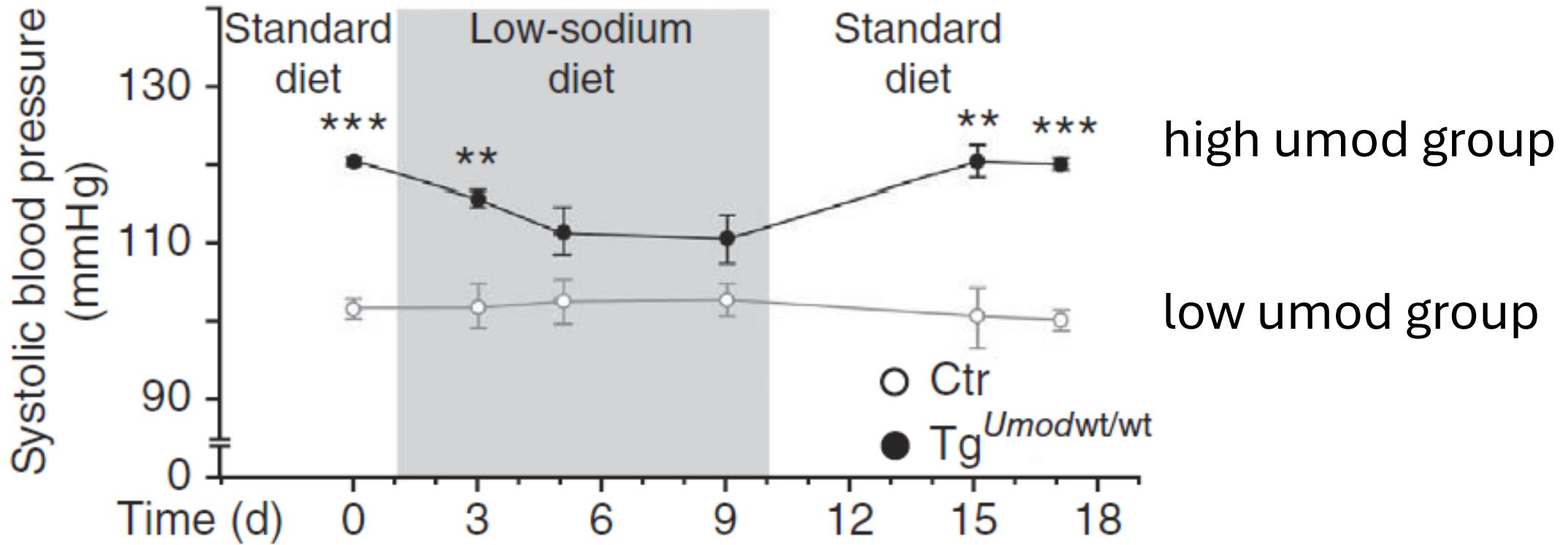


b) ↑ uromodulin production

# Transgenic mouse

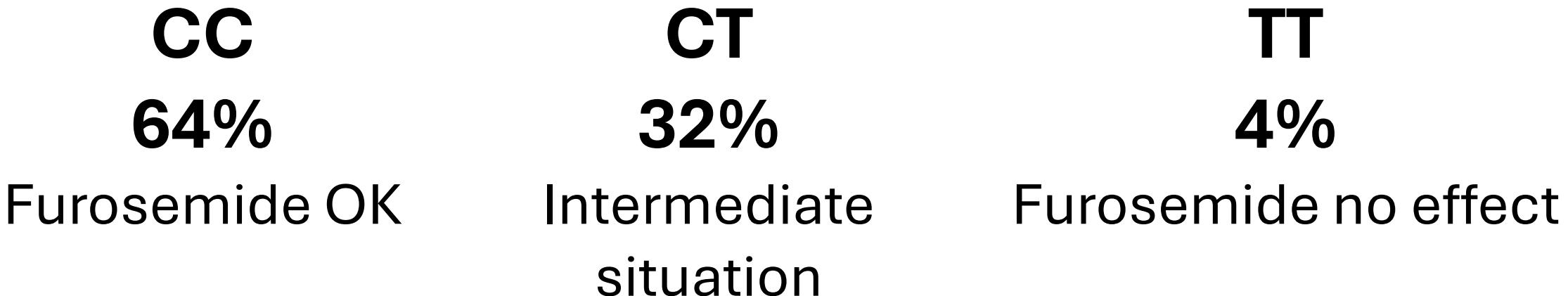


- ↑ uromodulin → ↑BP → BP may be controlled with diet
- ↓ uromodulin → ↓ BP and BP insensitive to diet



# Furosemide in hypertensive patients

**rs4293393**



Higher risk of CKD

Lower risk of CKD

Phase 4 trial

# Clinical Study of UMOD NKCC2 Interaction on Salt-sensitivity in Hypertension (UMOD)

Identifier: NCT03354897  
Status: **completed**

- **Hypothesis:** individuals with uncontrolled hypertension possessing the **common, homozygous genotype** of rs13333226 **respond better to loop diuretics [TORAZEMIDE]** compared to those carrying the other genotypes
- **Result:** hypothesis confirmed

## ORIGINAL ARTICLE

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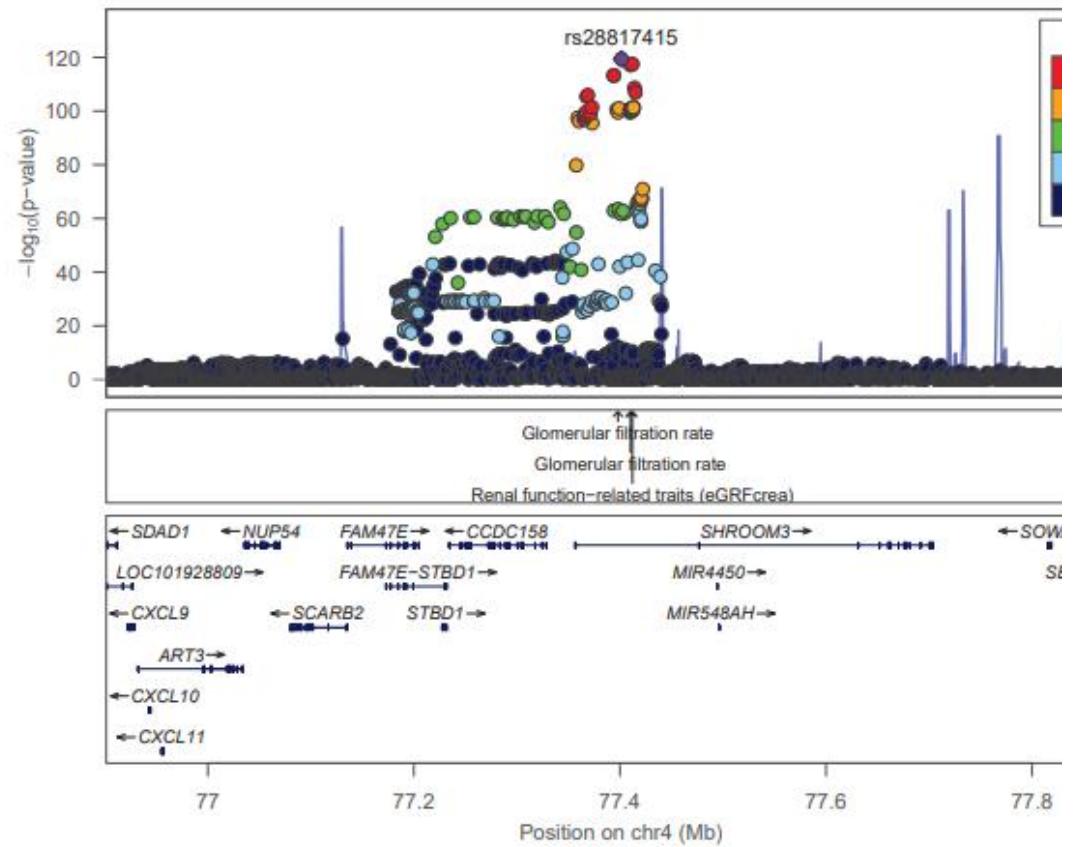
### ***UMOD Genotype-Blinded Trial of Ambulatory Blood Pressure Response to Torasemide***

Lindsay McCallum  , Stefanie Lip  , Alex McConnachie  , Katriona Brooksbank, Iain M. MacIntyre  , Alexander Doney  , Andrea Llano, Alisha Aman  , Thomas M. Caparrotta  , Gareth Ingram, Isla S. Mackenzie  , Anna F. Dominiczak  , Thomas M. MacDonald  , David J. Webb  , and Sandosh Padmanabhan 

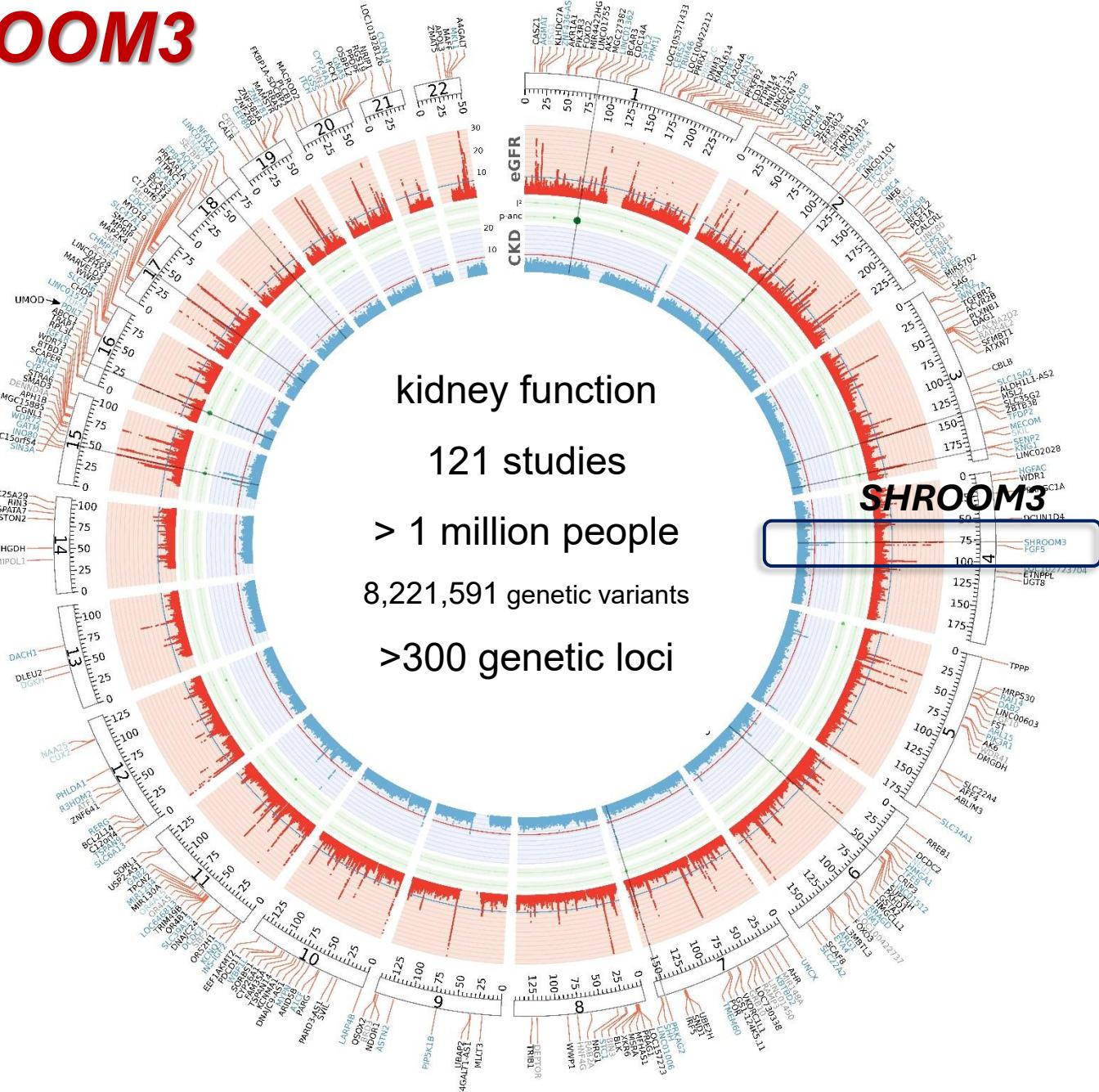
findings underscore the potential for **genotype-guided use of loop diuretics in hypertension management**

**SHROOM3**

# From GWAS to function: ***SHROOM3***



actin-binding protein involved in cell shape, neural tube formation, and epithelial morphogenesis

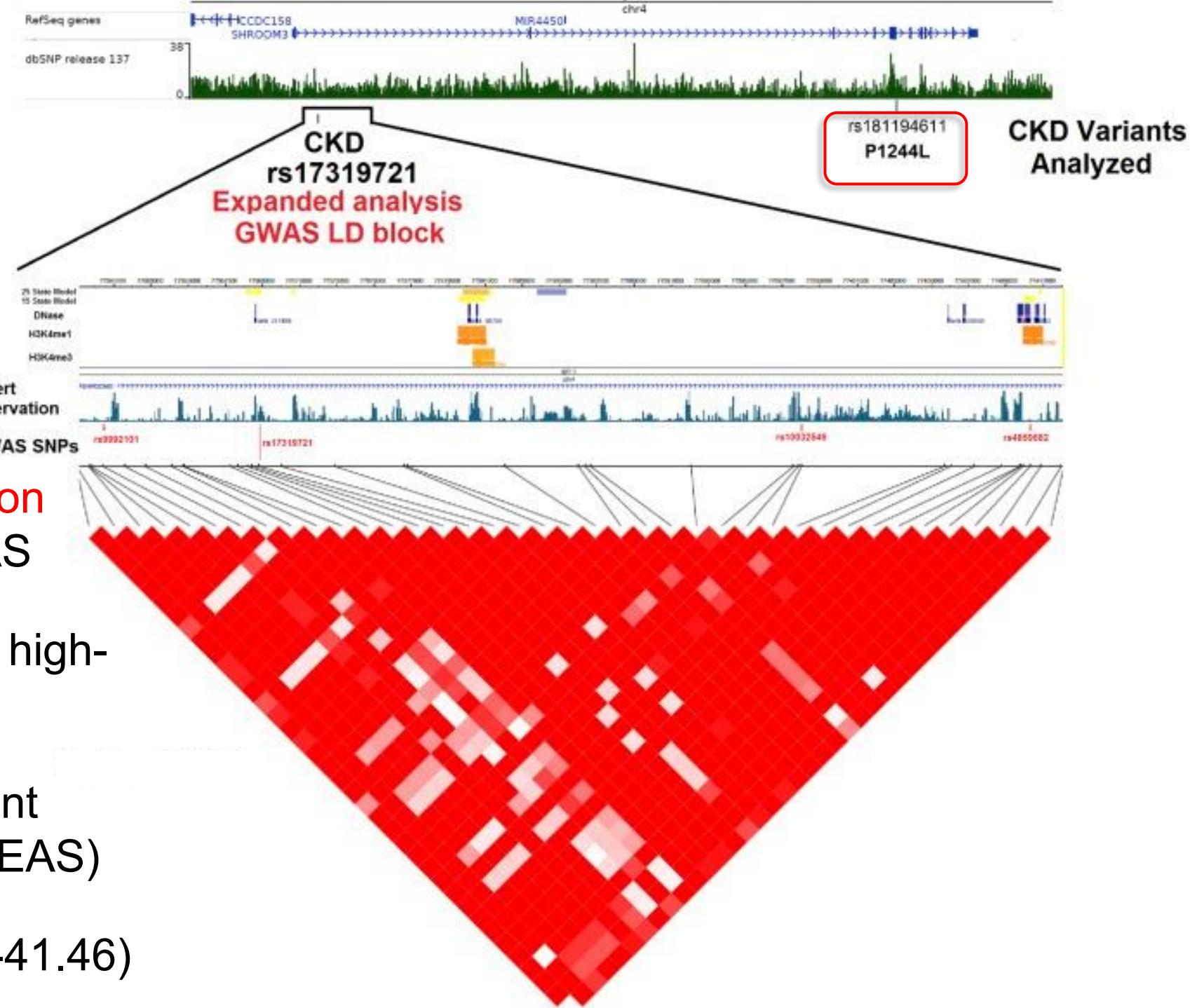


## Characterization of Coding/Noncoding Variants for SHROOM3 in Patients with CKD.

Prokop JW<sup>1</sup>✉, Yeo NC<sup>2</sup>, Ottmann C<sup>3</sup>, Chhetri SB<sup>4</sup>, Florus KL<sup>4</sup>, Ross EJ<sup>4</sup>, Sosonkina N<sup>4</sup>, Link BA<sup>5</sup>, Freedman BI<sup>6</sup>, Coppola CJ<sup>7</sup>, McDermott-Roe C<sup>8</sup>, Leysen S<sup>3</sup>, Milroy LG<sup>3</sup>, Meijer FA<sup>3</sup>, Geurts AM<sup>8</sup>, Rauscher FJ 3rd<sup>9</sup>, Ramaker R<sup>4</sup>, Flister MJ<sup>8</sup>, Jacob HJ<sup>4</sup>, Mendenhall EM<sup>4</sup> ... [Show all 21] ... Lazar J<sup>1</sup>✉

Author information ▾

Journal of the American Society of Nephrology : JASN, 23 Feb 2018, 29(5):1525-1535



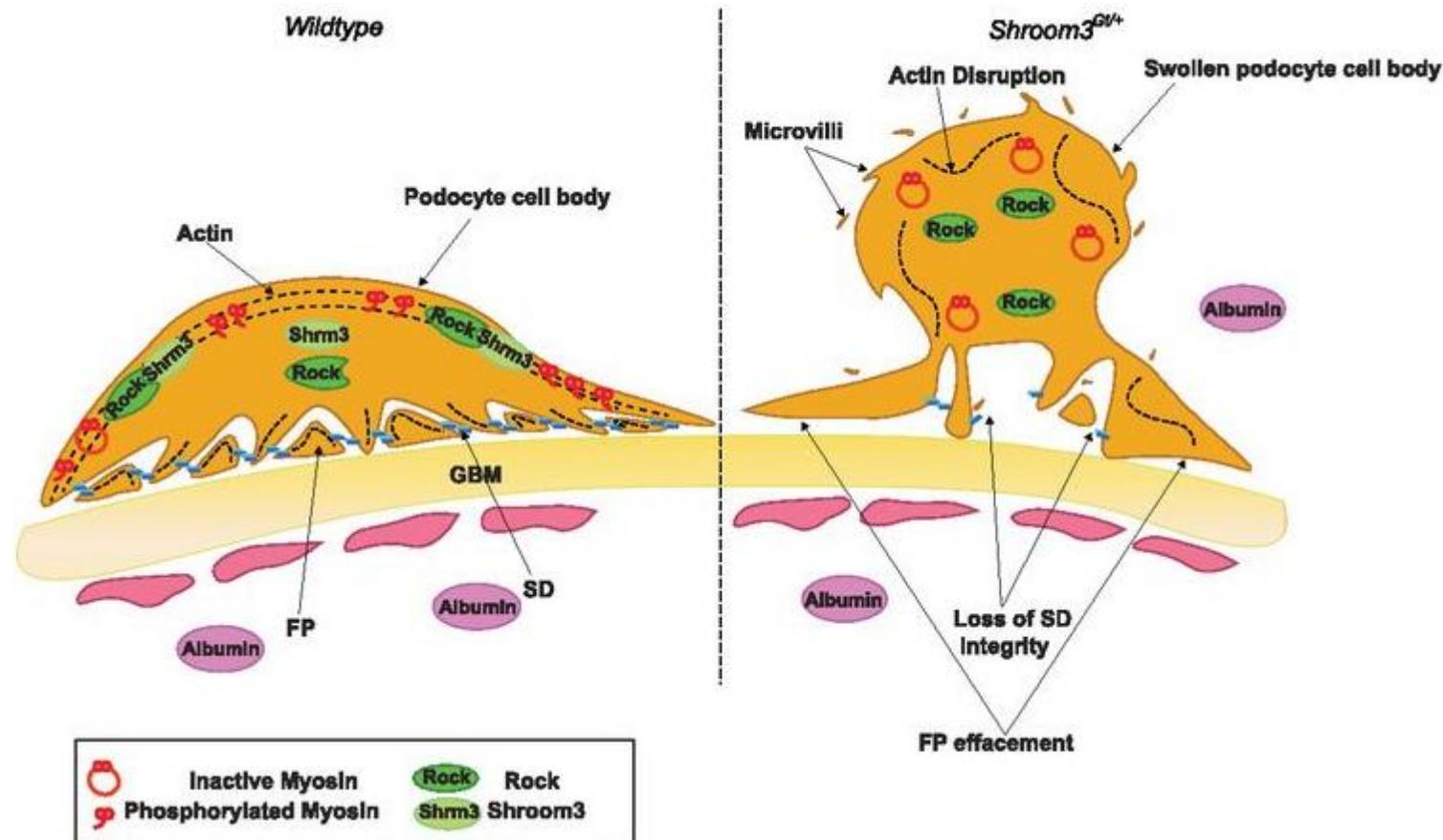
- In *SHROOM3*, the **common variant** identified by GWAS
- ...is in **LD** with 35 nearby high-effects variants
- ...and a rare coding variant **P1244L** (MAF=0.0027 in EAS)
- OR for CKD = 7.95 (1.53-41.46)

# In Fawn Hooded Hypertensive rats, missense variants within Shroom3 affects normal maintenance of kidney glomerular filtration

Yeo NC et al (2015). *Genome Res* 25: 57–65

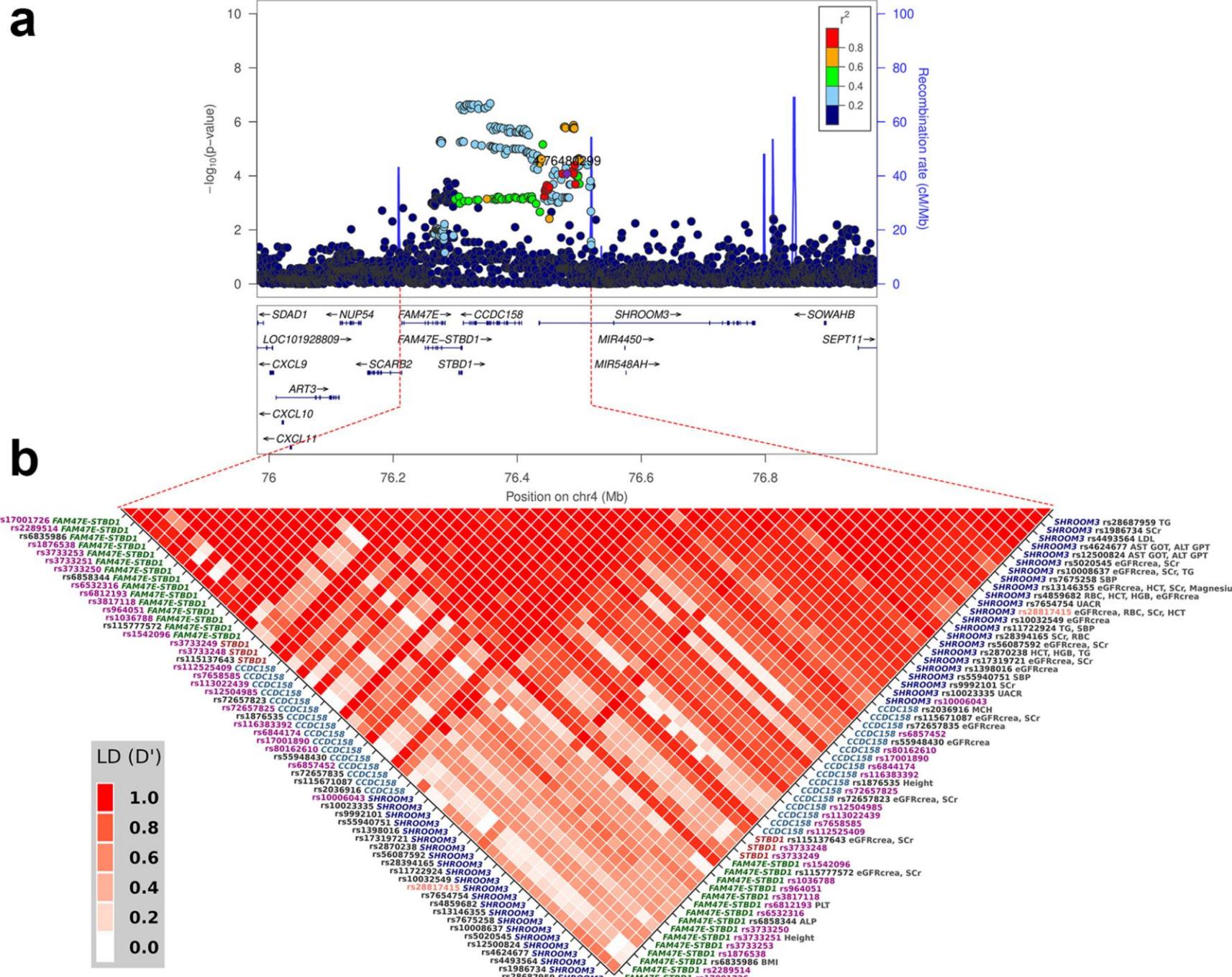
In mice, genetic deletion of Shroom3 affects **glomerular function** and **maintenance of proper podocyte morphology**, with alterations of apically distributed actin.

Khalili H, et al (2016) *JASN* 27: 2965–73

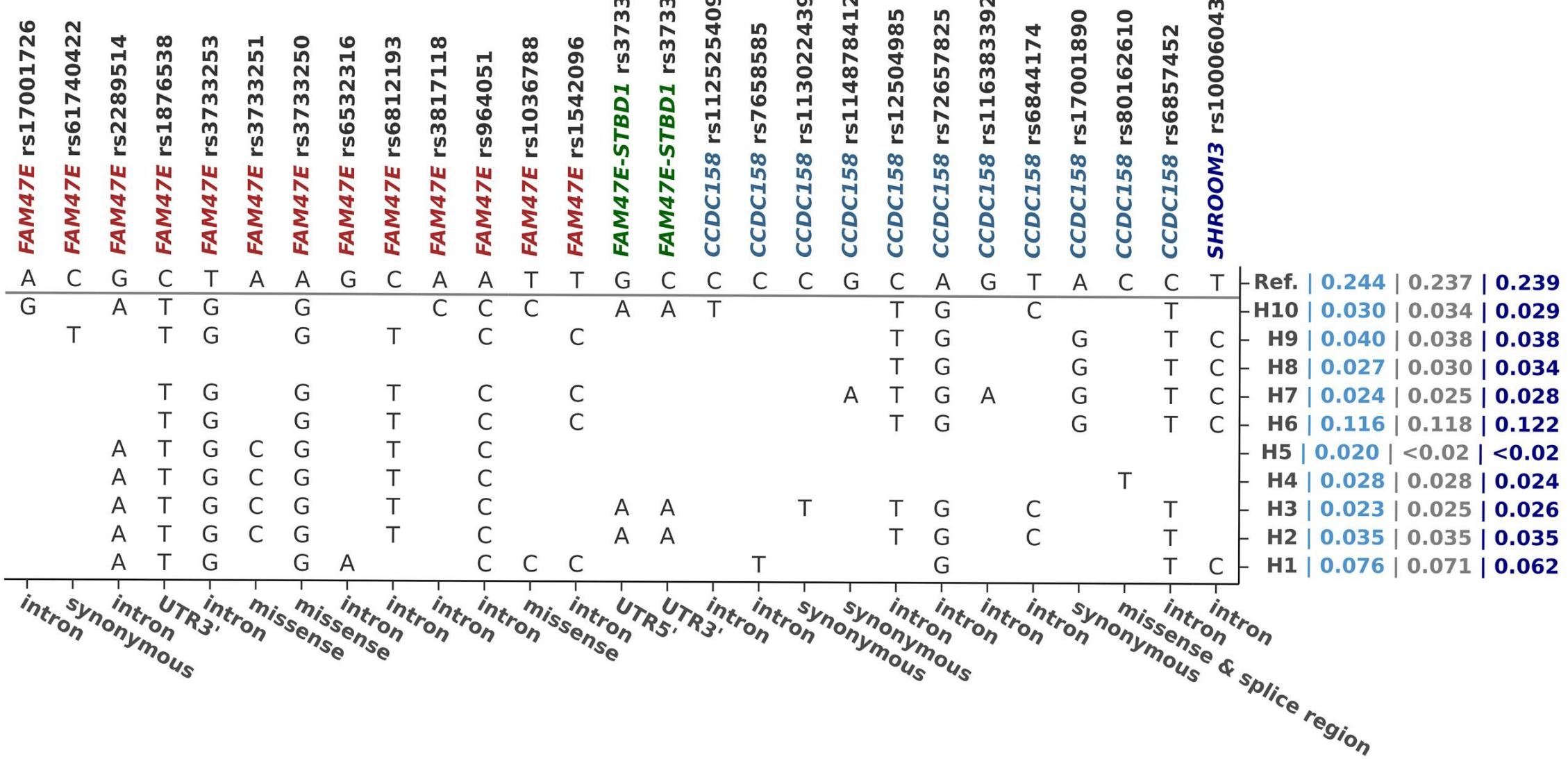


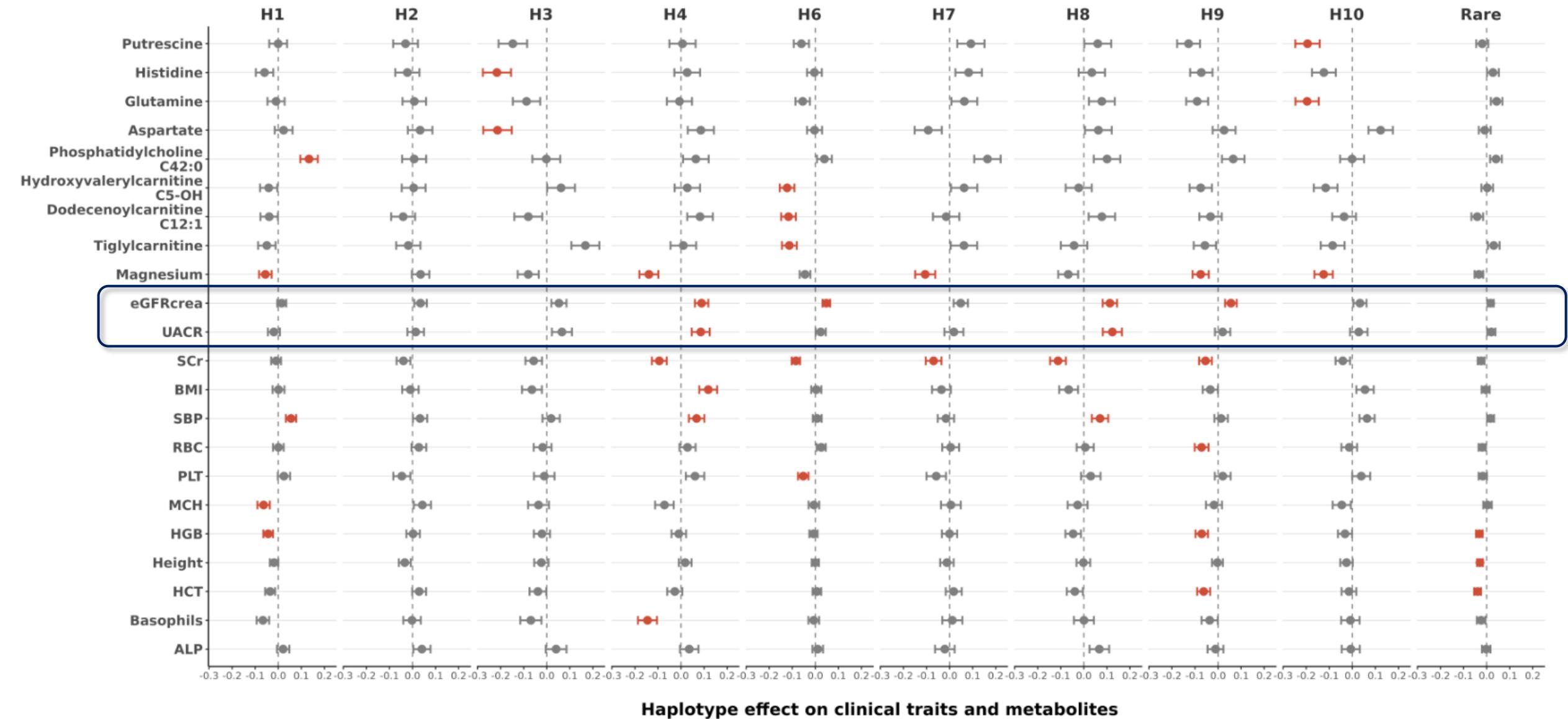


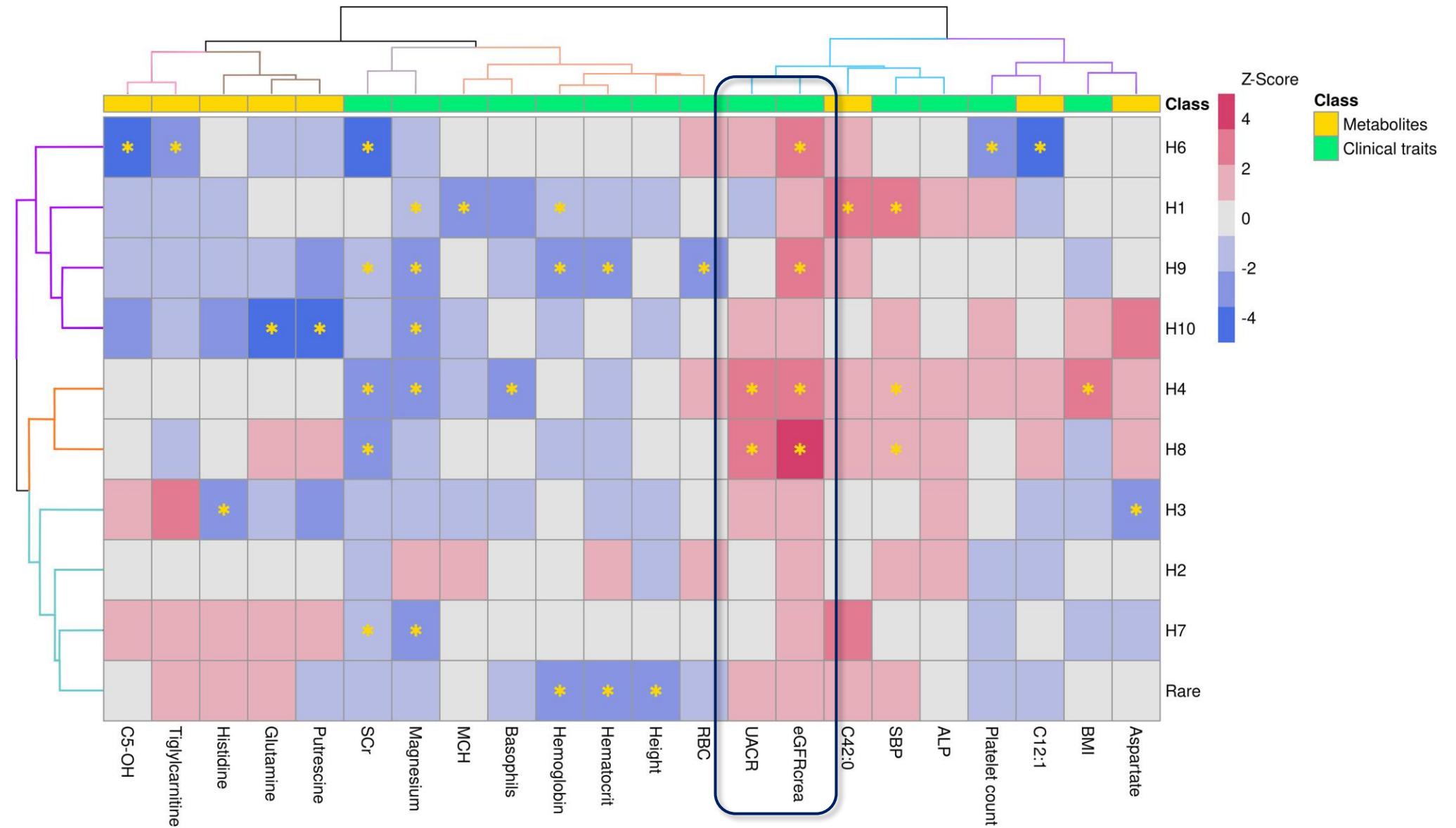
Ghasemi-Semeskandeh,  
Dariush et al.  
**Clinical and Metabolic  
Signatures of *FAM47E*–  
*SHROOM3* Haplotypes in  
a General Population  
Sample**  
Kidney International  
Reports, 2025



# Haplotypes of 71 exonic variants on N=4000 individuals with WES data





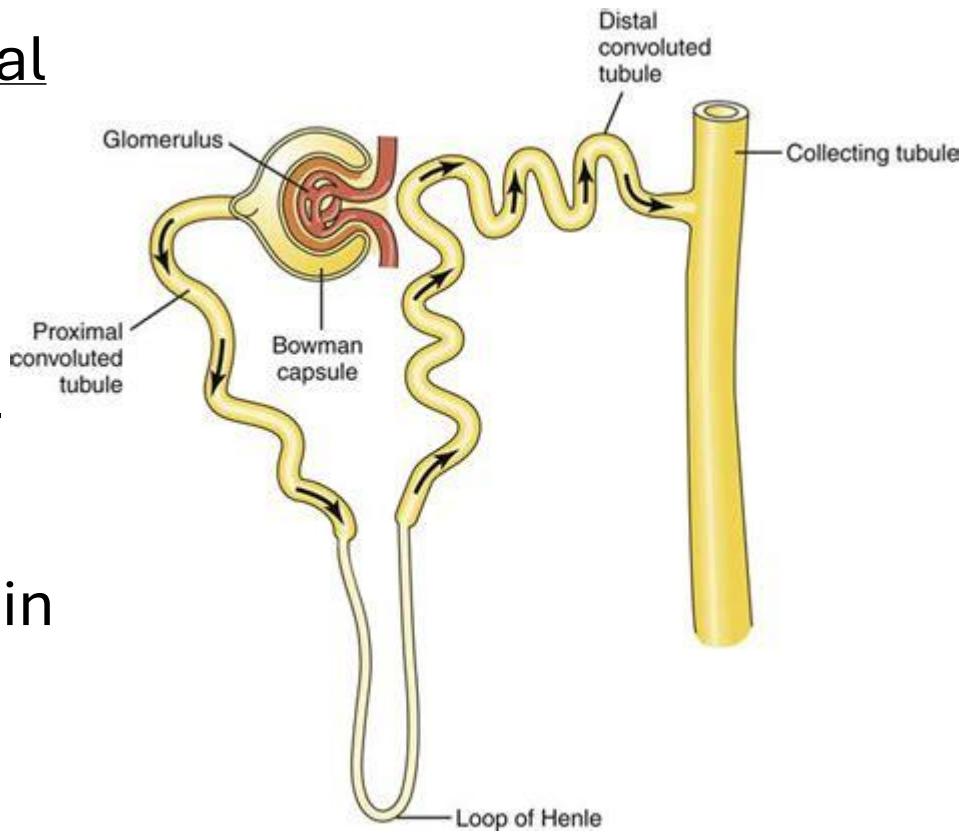


› Nat Commun. 2025 Dec 30. doi: 10.1038/s41467-025-67854-7. Online ahead of print.

# Design of precision therapeutics for a CKD risk allele by targeting Shroom3–Rock interaction

Anand Reghuvaran <sup># 1</sup>, Ashwani Kumar <sup># 1</sup>, Qisheng Lin <sup>2</sup>, Nallakandi Rajeevan <sup>3</sup>, Khadija Banu <sup>1</sup>, Zeguo Sun <sup>4</sup>, Hongmei Shi <sup>1</sup>, Gabriel Barsotti <sup>1</sup>, E M Tanvir <sup>1</sup>, John Pell <sup>1</sup>, Sudhir Perincheri <sup>5</sup>, Chengguo Wei <sup>4</sup>, Bhavya Bharathan <sup>1</sup>, Marina Planoutene <sup>4</sup>, Anne Eichmann <sup>6</sup>, Valeria Mas <sup>7</sup>, Weijia Zhang <sup>4</sup>, Lloyd G Cantley <sup>1</sup>, Leyuan Xu <sup>1</sup>, Bhaskar Das <sup>8</sup>, John Cijiang He <sup>4</sup>, Madhav C Menon <sup>9</sup>

- Enhancer variants in Shroom3 associate with renal fibrosis (tubular interstitial fibrosis, TIF), but with reduced albuminuria
- **Focus** → to (1) identify the specific profibrotic Shroom3 motif and (2) to separate it from its anti-proteinuric function.
- **Intuition** → given the role for Rho-kinases (Rock) in TIF, and the interaction of Rock with Shroom3 ASD2-domain, we hypothesized that Shroom3-mediated Rock-activation may be crucial for profibrotic function
- **What** → To test this, we developed transgenic tools that overexpress wild-type- (WT-Sh3) or ASD2-domain deletion- Shroom3 (ASD2 $\Delta$ -Sh3).



## Findings

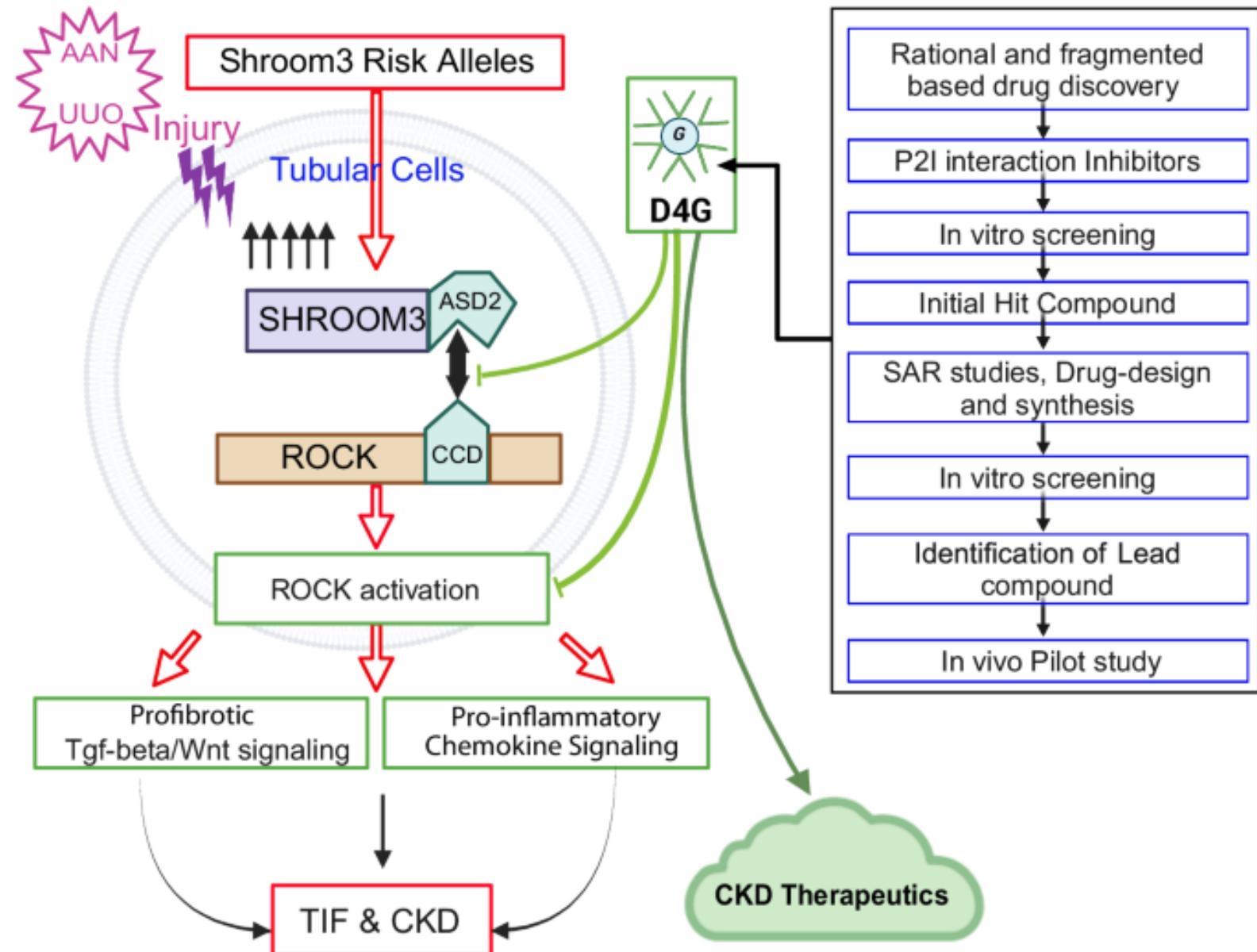
1. During TIF, Shroom3 and Rock co-expression occur in injured tubular cells and fibroblasts.
2. In tubular- & fibroblast- lines, **ASD2Δ-Sh3 overexpression reduces Rock activation, and pro-fibrotic/pro-inflammatory transcripts** downstream of TGFβ1/Wnt/Ctnnb1-signaling vs WT-Sh3.
3. In vivo, inducible global-, or tubular-specific-, but not fibroblast-specific-, **ASD2Δ-Sh3 overexpression mitigate TIF**, vs WT-Sh3 overexpression.
4. **Importantly, ASD2Δ-Sh3 mice do not develop albuminuria**, while overexpression of a distinct Fyn-binding deficient mutant Shroom3 (FBDM-Sh3) induces albuminuria.
5. **We developed small molecule inhibitors of Shroom3-Rock interaction (P2Is)** and confirm Rock inhibition with these agents in WT-Sh3 cell lines.
6. The lead among these molecules **mitigates Rock-activation, profibrotic signaling and TIF** in WT-Sh3 mice.

## Design of precision therapeutics for a CKD risk allele by targeting Shroom3-Rock interaction

Anand Reghuvaran # 1, Ashwani Kumar # 1, Qisheng Lin 2, Nallakandi Rajeevan 3, Khadija Banu 1,  
Zeguo Sun 4, Hongmei Shi 1, Gabriel Barsotti 1, E M Tanvir 1, John Pell 1, Sudhir Perinchery 5,  
Chengguo Wei 4, Bhavya Bharathan 1, Marina Planoutene 4, Anne Eichmann 6, Valeria Mas 7,  
Weijia Zhang 4, Lloyd G Cantley 1, Leyuan Xu 1, Bhaskar Das 8, John Cijiang He 4,  
Madhav C Menon 9

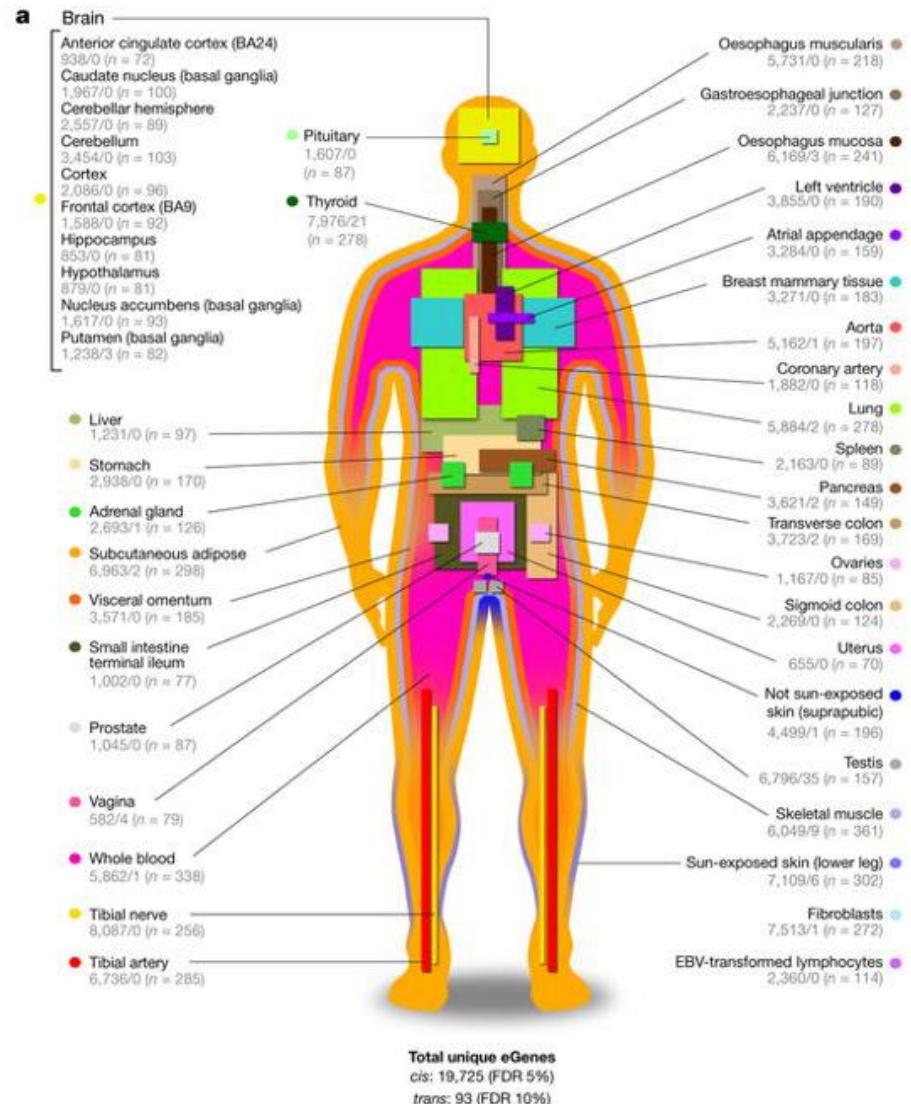
## Summary

Hence, we delineate the profibrotic Shroom3 motif and develop therapeutics for kidney disease from Shroom3 excess.



**OAF1**

# Trascriptomics (gene expression)



 GTEx Portal

<https://www.gtexportal.org/home/documentationPage>

**GTEx is a database of genotype ↔ gene expression associations**

- Measured expression of >30,000 genes
- in 53 human tissues
- Sample size: 70 to ~500 samples per tissue

Identification of SNVs associated with gene expression

- within each tissue/organ
- within each cell type within organ

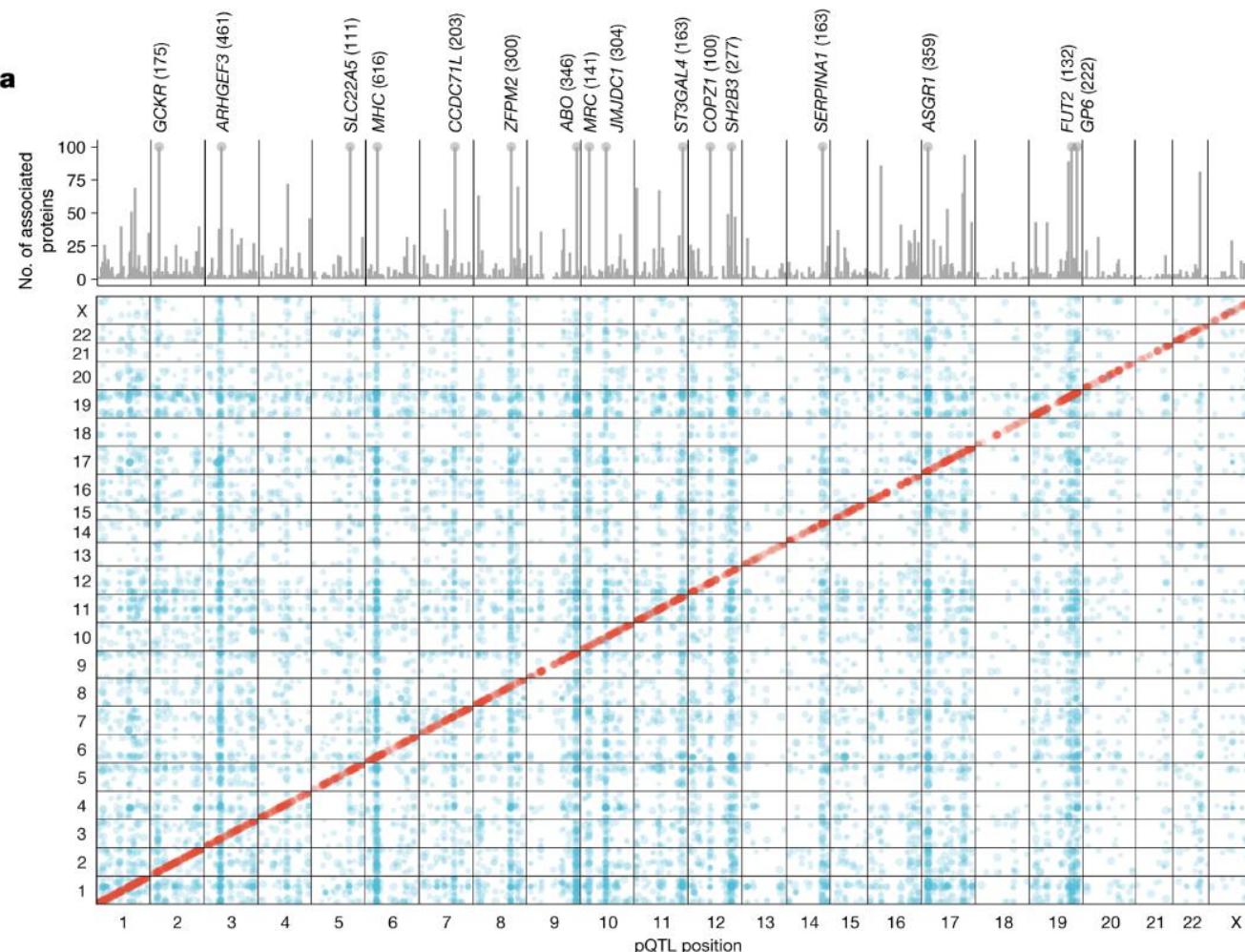
Article | Open access | Published: 04 October 2023

**Plasma proteomic associations with genetics and health in the UK Biobank**Benjamin B. Sun  Joshua Chiou, Matthew Taylor, Christian Benner, Yi-Hsiang Hsu, Tom G. Richardson, *Nature* 622, 329–338 (2023) | [Cite this article](#)

1

**Proteomics**

2

**GWAS of 2922 protein targets measured in plasma from 54,219 individuals**

3

Article | Published: 02 December 2021

**Large-scale integration of the plasma proteome with genetics and disease**Egil Ferkingstad, Patrick Sulem , Bjarni A. Atlason, Gardar Sveinbjörnsson, Magnus I. Magnusson, Edda L. *Nature Genetics* 53, 1712–1721 (2021) | [Cite this article](#)

**GWAS of 4907 protein targets measured in plasma from 35,559 Icelandic individuals tested plasma protein levels for association with 373 diseases and other traits and identified 257,490 associations, identifying 938 genes encoding potential drug targets**

**Science**

HOME &gt; SCIENCE &gt; VOL. 374, NO. 6569 &gt; MAPPING THE PROTEO-GENOMIC CONVERGENCE OF HUMAN DISEASES

RESEARCH ARTICLE | DISEASE GENOMICS

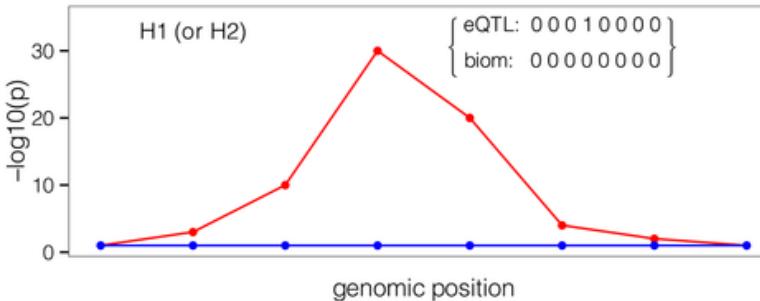
**Mapping the proteo-genomic convergence of human diseases**MAIK PIETZNER , ELEANOR WHEELER , JULIA CARRASCO-ZANINI , ADRIAN CORTES , MINE KOPRULU , MARIA A. WÖRHEIDE , ERIN OERTON , JAMES COOK , SOBELO D. STEWART, CLAUDIA LANGENBERG , +12 authors | [Authors Info & Affiliations](#)

SCIENCE • 14 Oct 2021 • Vol 374, Issue 6569 • DOI: 10.1126/science.abj541

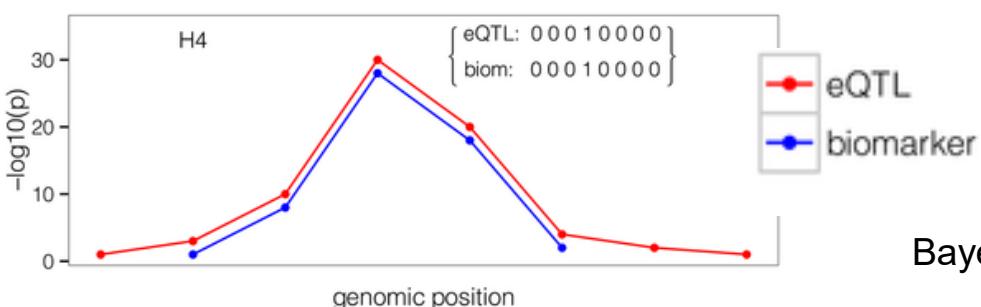
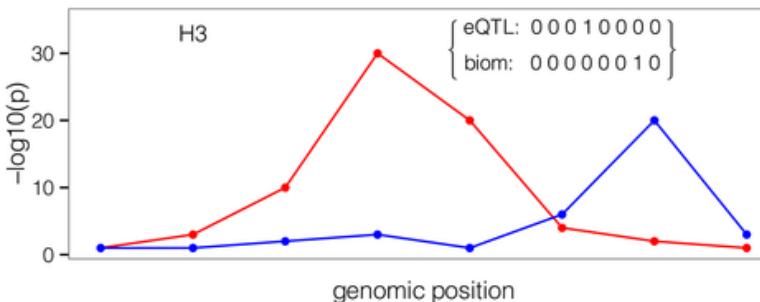
**GWAS of 4775 protein targets measured in plasma from 10,708 individuals**

# Statistical colocalization

Bayesian method to assess the presence of a common causal variant



- $H_0$ : No association with either trait
- $H_1$ : Association with trait 1, not with trait 2
- $H_2$ : Association with trait 2, not with trait 1
- $H_3$ : Association with trait 1 and trait 2, two independent SNPs
- $H_4$ : Association with trait 1 and trait 2, one shared SNP

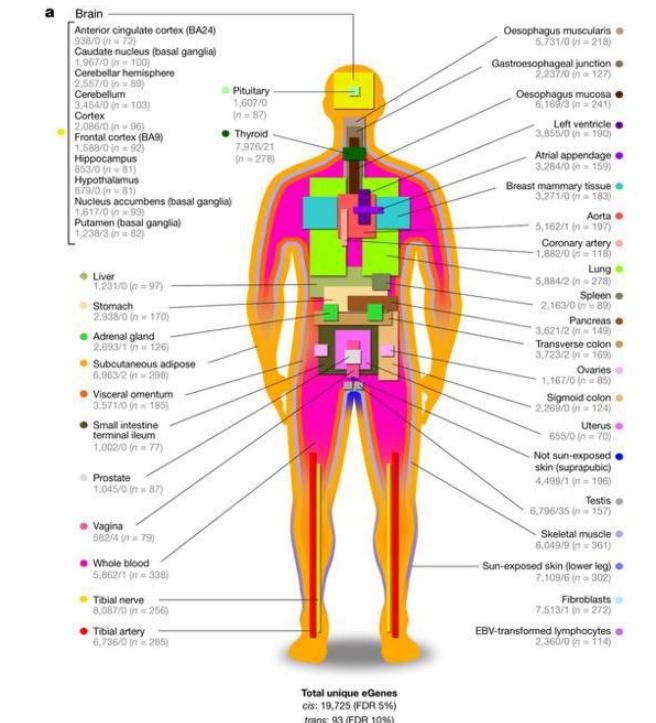
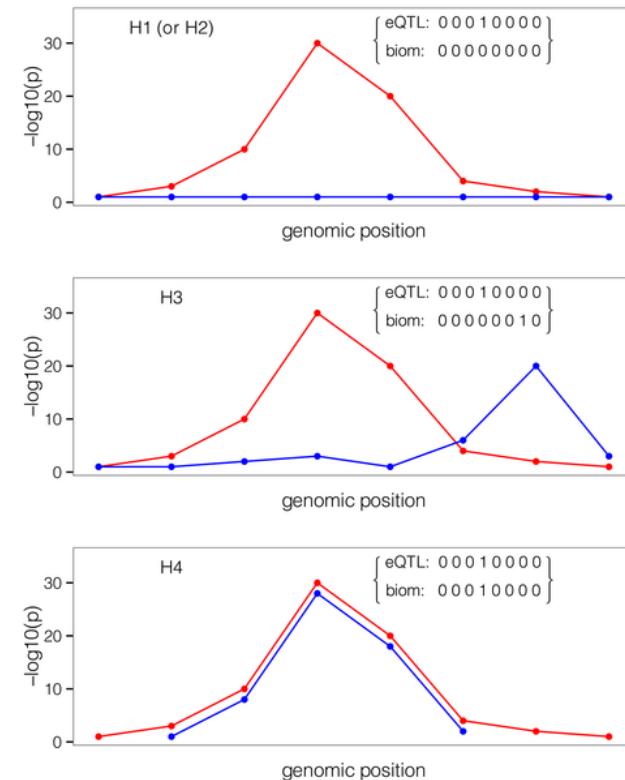
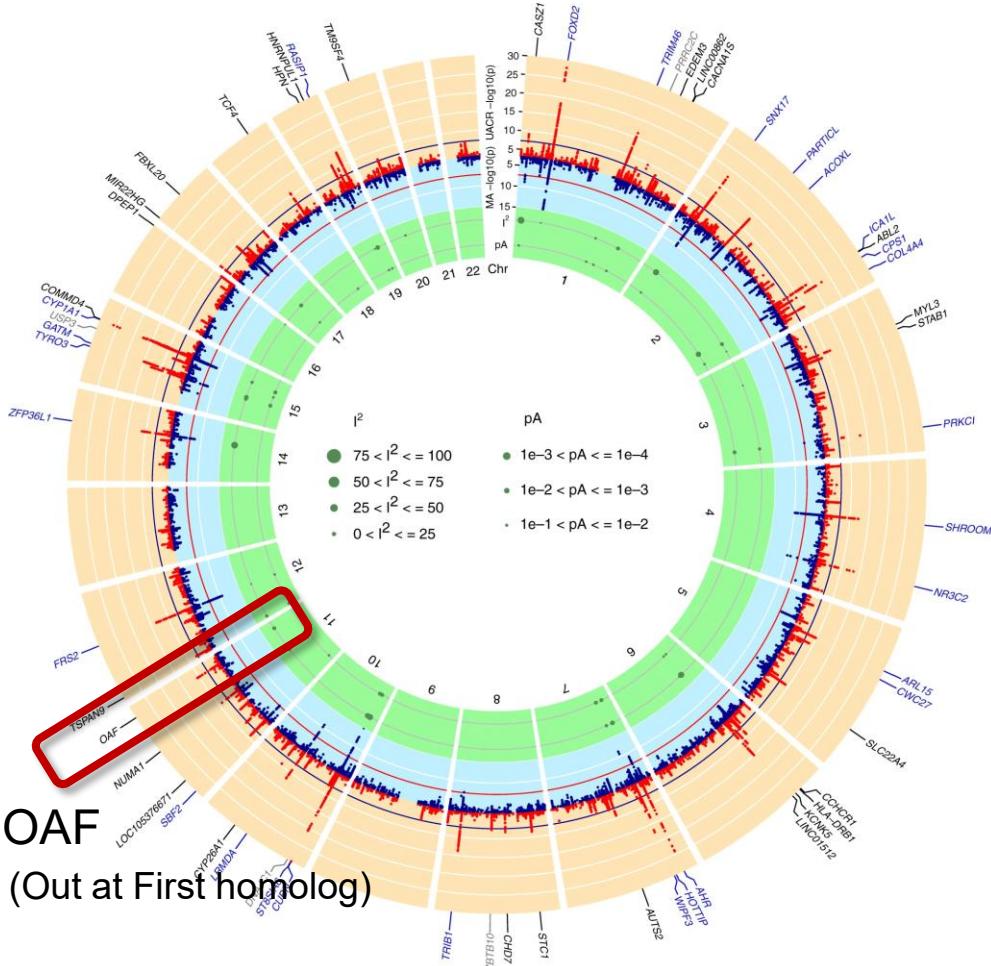


Giambartolomei C, et al. (2014)  
Bayesian Test for Colocalisation between Pairs of Genetic Association Studies Using Summary Statistics. PLOS Genetics 10(5): e1004383.

<https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1004383>

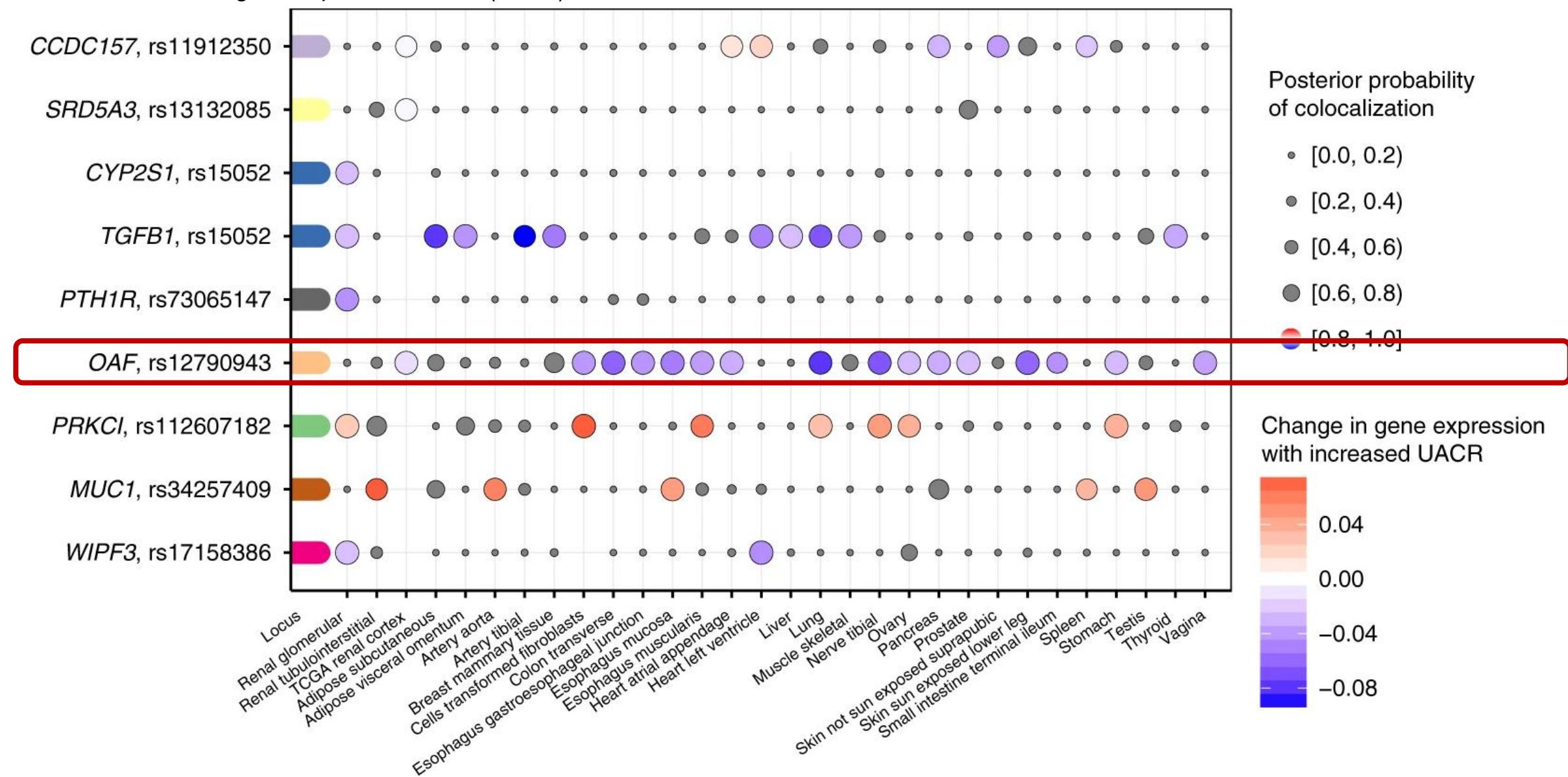
# Tested colocalization vs. 30,000 genes by 50 tissues (incl. kidney) × 700 participants

(= 1,500,000 GWAS, each one on ~7,000,000 genomic variants)



# Gene prioritization supported by statistical colocalization

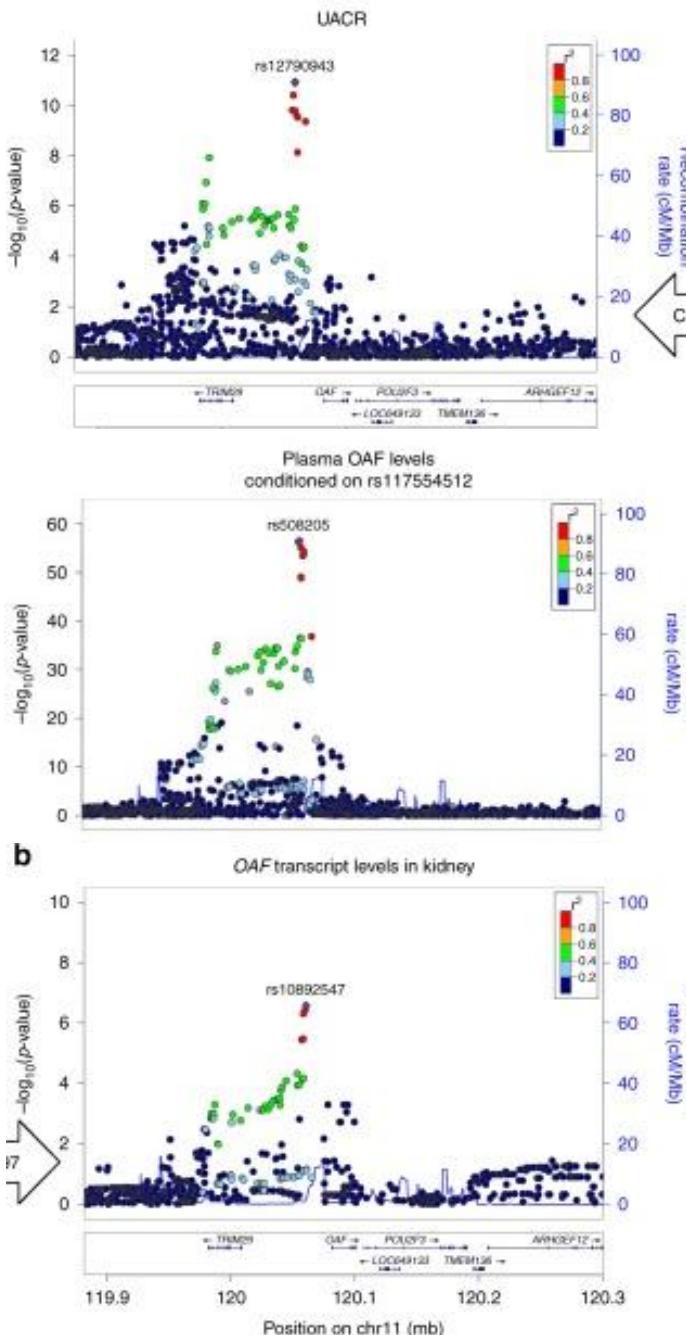
Colocalization with gene expression levels (GTEx)



# Gene prioritization supported by statistical colocalization

INTERVAL study, 3000 participants  
OAF was among the 3000 measured proteins

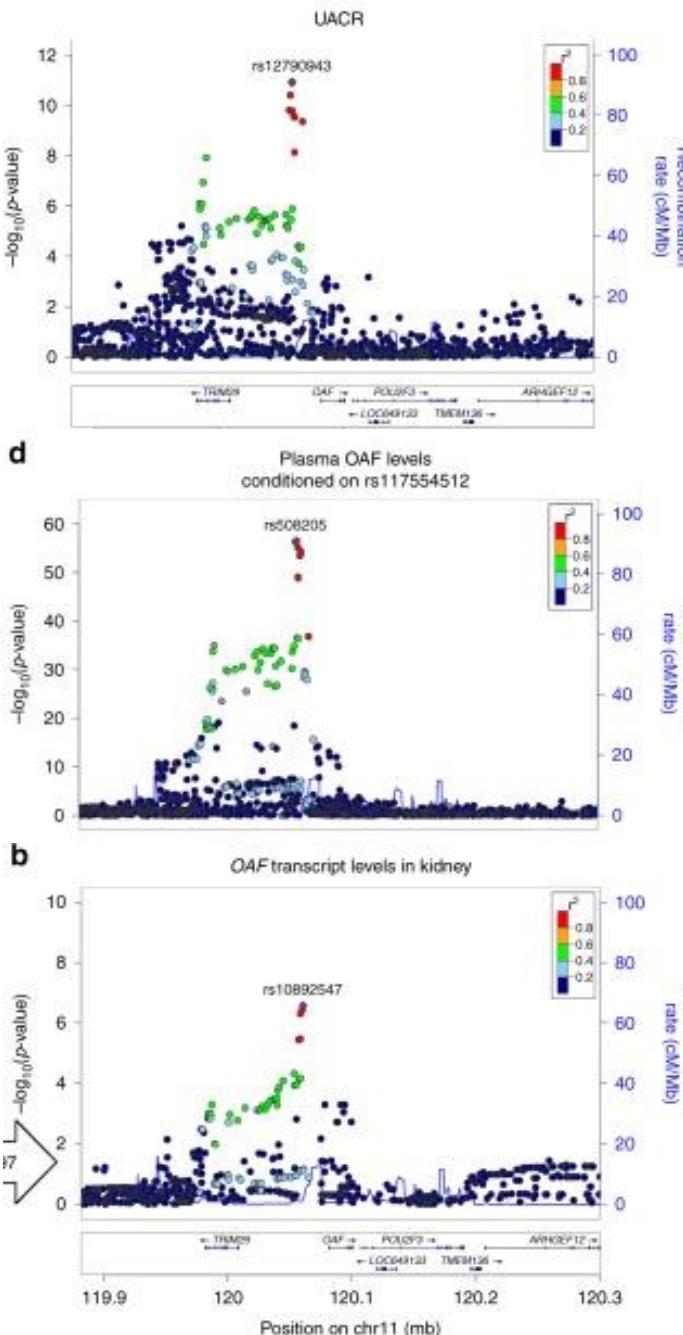
NEPTUNE study, 187 participants, microdissected glomerular & tubulointerstitial kidney portions



# Gene prioritization supported by statistical colocalization

INTERVAL study, 3000 participants  
OAF was among the 3000 measured proteins

NEPTUNE study, 187 participants,  
microdissected glomerular & tubulointerstitial kidney portions

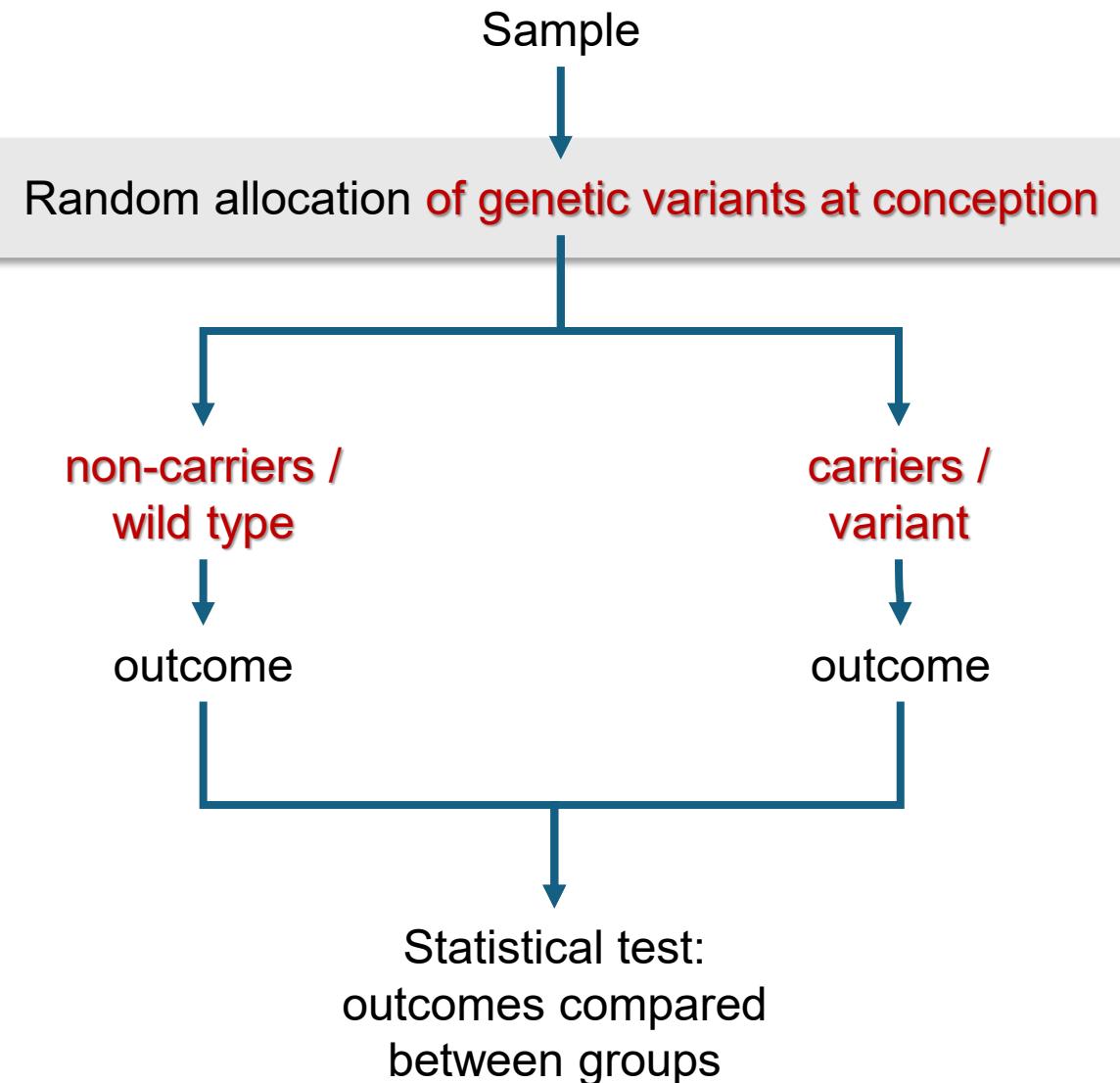
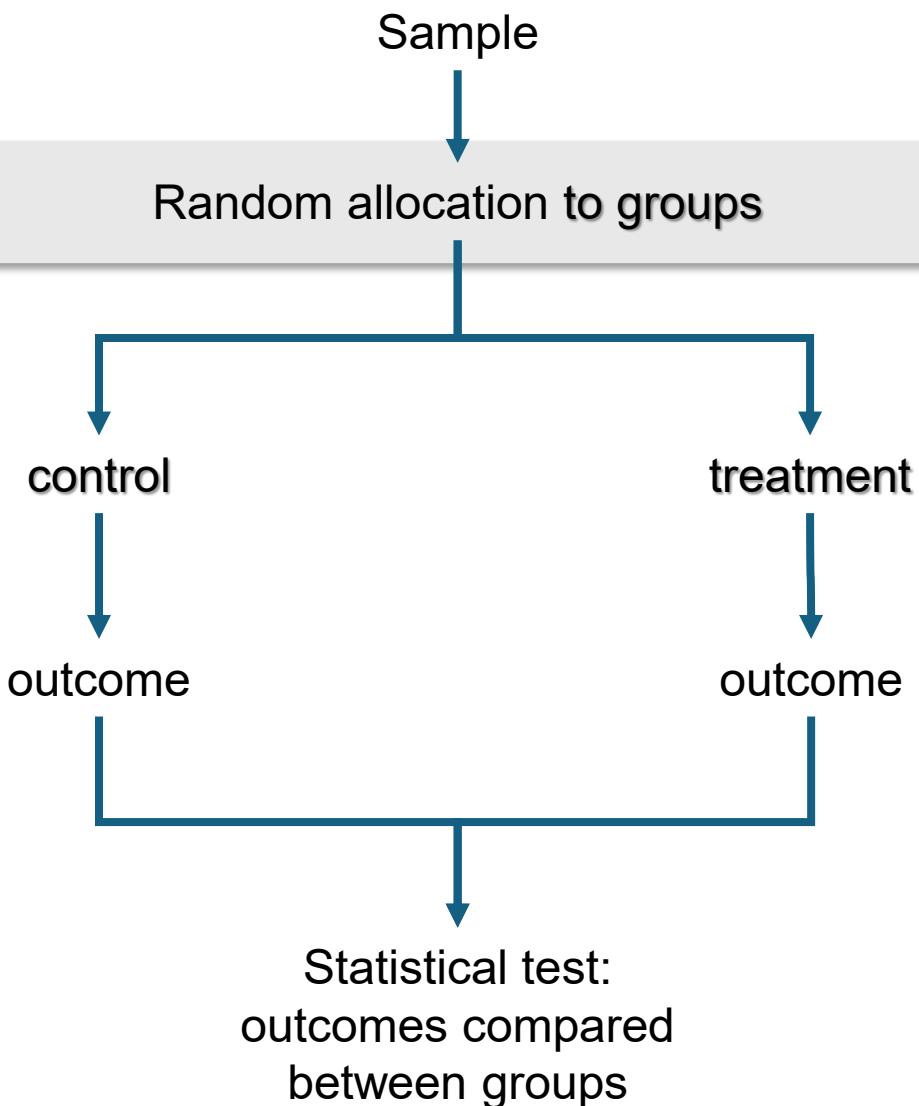


 Knockdown of *OAF* orthologs in *Drosophila* nephrocytes reduced albumin endocytosis.

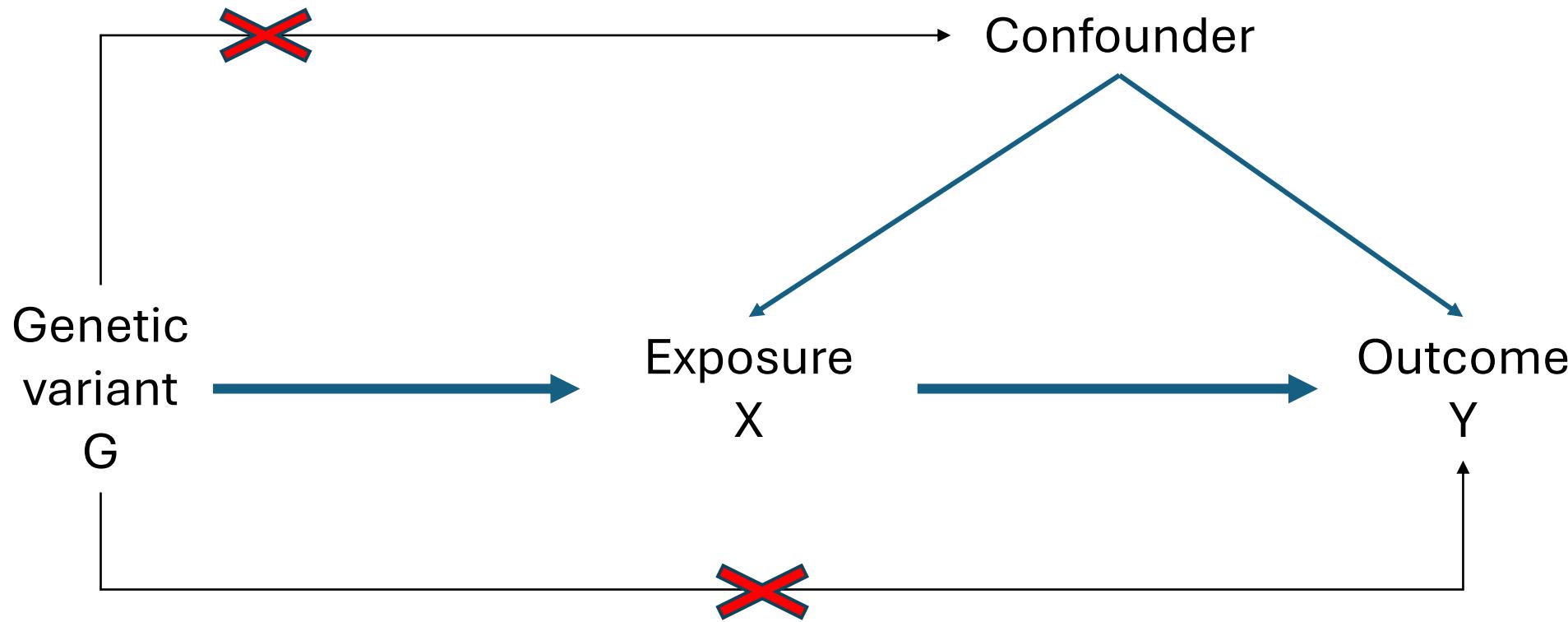
# Causality

## **Randomized controlled trial**

## **Mendelian randomization**



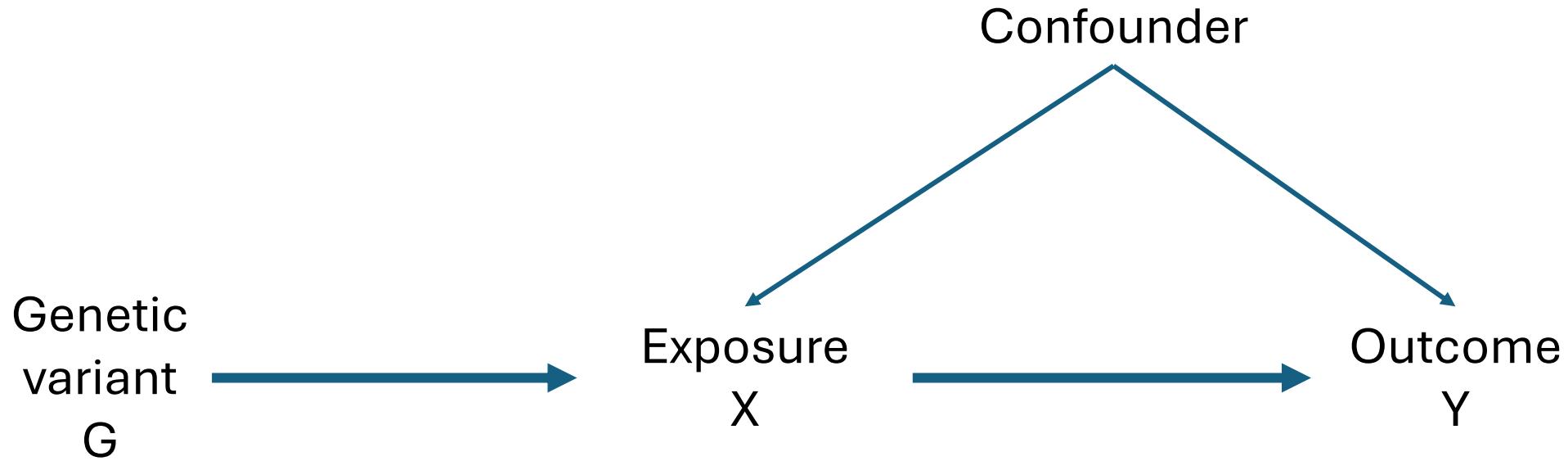
## Mendelian Randomization = instrumental variable analysis



### Core assumptions

- 1) Instrumental Variable G is associated with the Exposure X
- 2) The association between G and X is not confounded by hidden factors (eg: population stratification)
- 3) There is no independent pathway from G to the Outcome Y other than through X

# Mendelian Randomization = instrumental variable analysis



Examples:

1. Does expression of **gene X** influence the levels of **protein Y** ?
2. Does **protein X** affect the **risk of disease Y**?
3. Does **changes of a biomarker** (eg: BMI) affect the **risk of a disease** (eg: atrial fibrillation)?

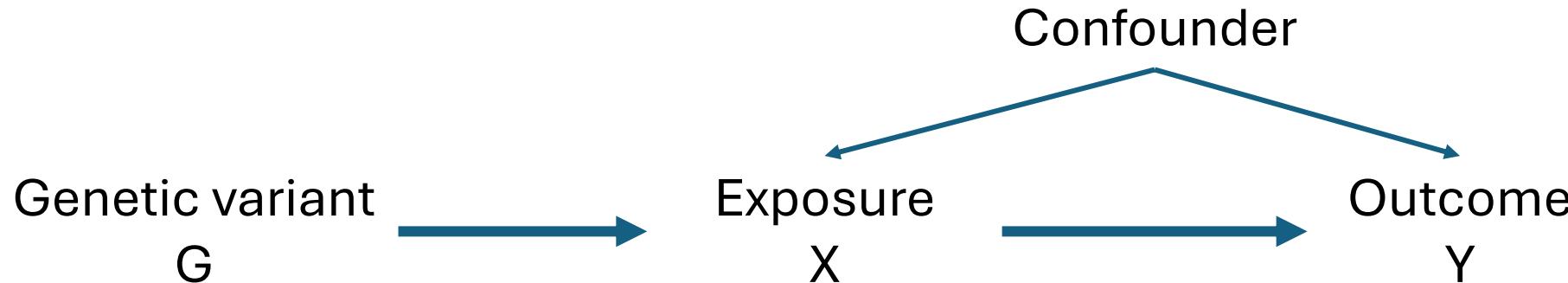
➤ Int J Epidemiol. 2023 Dec 25;52(6):1878-1886. doi: 10.1093/ije/dyad104.

The causal effects of education on adult health, mortality and income: evidence from Mendelian randomization and the raising of the school leaving age

Neil M Davies [1](#) [2](#) [3](#) [4](#), Matt Dickson [5](#), George Davey Smith [4](#) [6](#), Frank Windmeijer [4](#) [7](#), Gerard J van den Berg [8](#) [9](#)

# Instrumental variable analysis

## the 2-stage least square approach



$$Y = \alpha + \beta X + \varepsilon$$

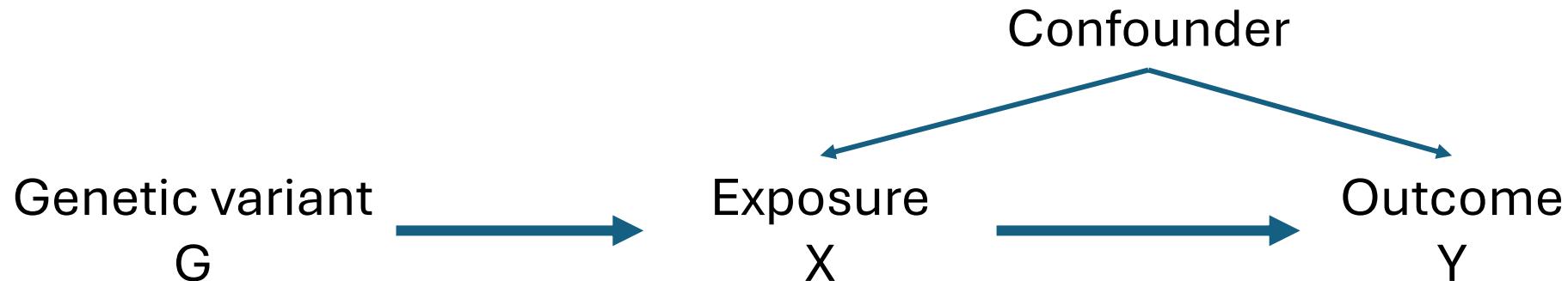
**STAGE 1:**  $X = \delta + \gamma G + u$

$$\hat{X} = \hat{\delta} + \hat{\gamma} G$$

**STAGE 2:**  $Y = \alpha' + \beta' \hat{X} + \varepsilon$

# Instrumental variable analysis

## the Wald-ratio estimator for summary data



$$Y = \alpha + \beta X + \varepsilon$$

- $X = \delta + \gamma G + \varepsilon$  (*Stage 1*)
- $Y = \eta + \theta G + u$
- $\hat{\beta} = W = \frac{E[Y|G]}{E[X|G]} = \frac{\hat{\theta}}{\hat{\gamma}}$

The variance can be estimated via delta method, using a Taylor series expansion:

$$\text{var}(\hat{W}) \approx \frac{\text{var}(\hat{\theta})}{\hat{\gamma}^2} + -2\frac{\hat{\theta}}{\hat{\gamma}^3}\text{cov}(\hat{\theta}, \hat{\gamma}) + \frac{\hat{\theta}^2}{\hat{\gamma}^4}\text{var}(\hat{\gamma})$$

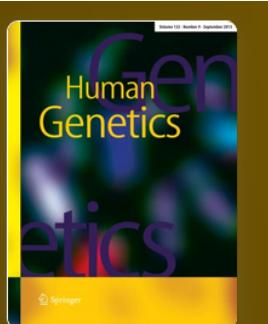
# DSP

[Home](#) > [Human Genetics](#) > Article

# Genomic and molecular evidence that the LncRNA *DSP-AS1* modulates desmoplakin expression

Original Investigation | Open access | Published: 30 July 2025

(2025) [Cite this article](#)



Human Genetics

Luisa Foco , Marzia De Bortoli, Fabiola Del Greco M, Laura S. Frommelt, Chiara Volani, Diana A. Riekschnitz, Benedetta M. Motta, Christian Fuchsberger, Thomas Delerue, Uwe Völker, Tianxiao Huan, Martin Gögele, Juliane Winkelmann, Marcus Dörr, Daniel Levy, Melanie Waldenberger, Alexander Teumer, Peter P. Pramstaller, Alessandra Rossini & Cristian Pattaro 



Luisa Foco



Marzia De Bortoli

# Arrhythmogenic Cardiomyopathy (ACM)

Rare inherited **cardiac disease**

- Progressive loss of cardiomyocytes
- fibrofatty replacement of the myocardium
- severe ventricular arrhythmias
- sudden cardiac death



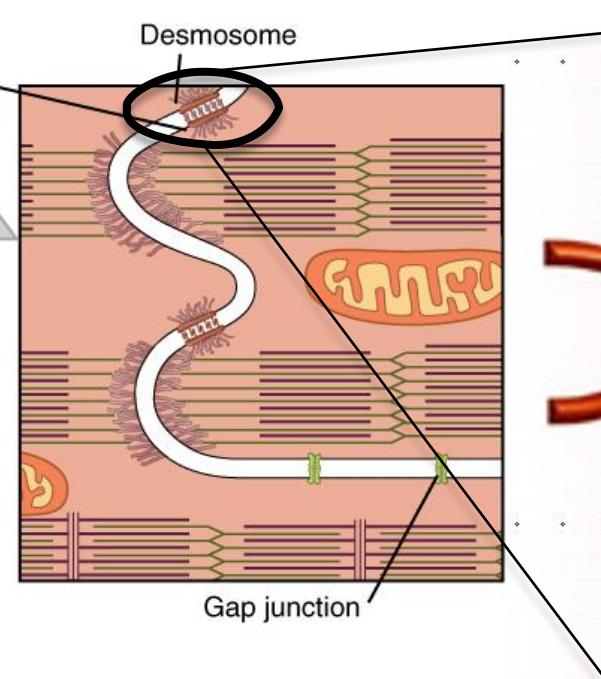
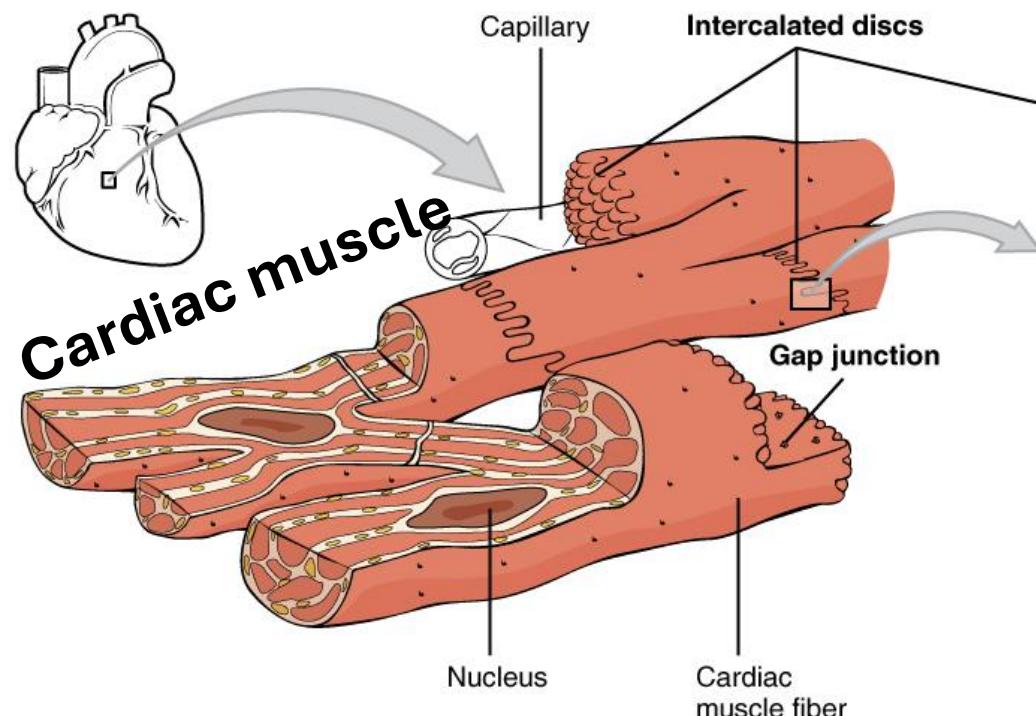
Marzia De Bortoli  
Senior Researcher, Eurac  
Research



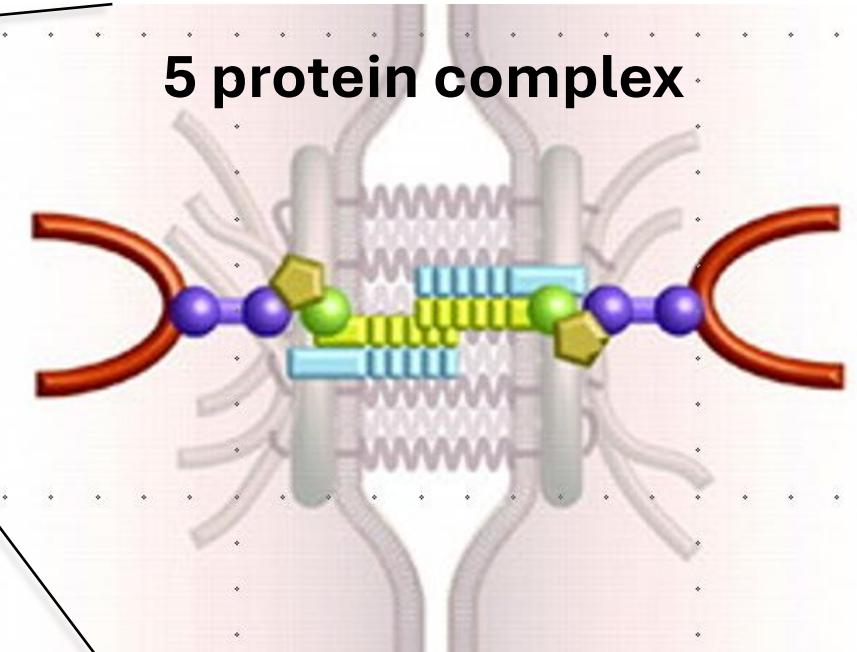
Rare pathogenic variants most frequently located in **desmosomal genes**

# Cardiac desmosome

cell-cell adhesion structure between cardiomyocytes



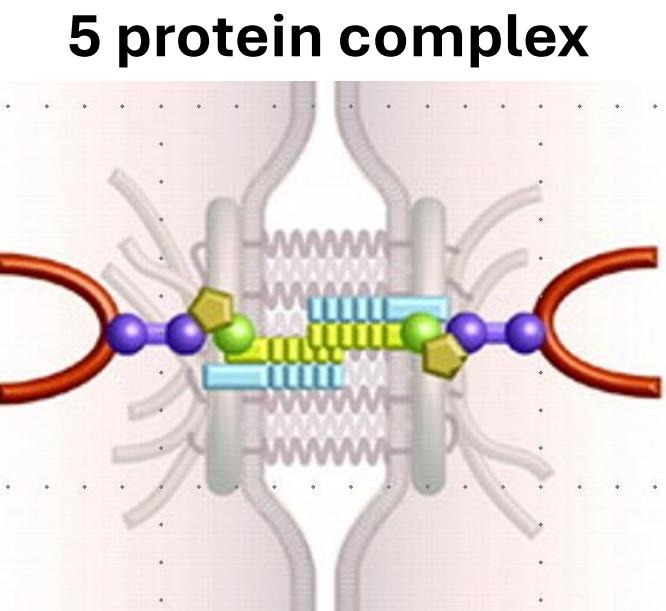
**Desmosome**  
**5 protein complex**



Delmar, McKenna, Circ Res 2010

# Cardiac desmosome

cell-cell adhesion structure between cardiomyocytes

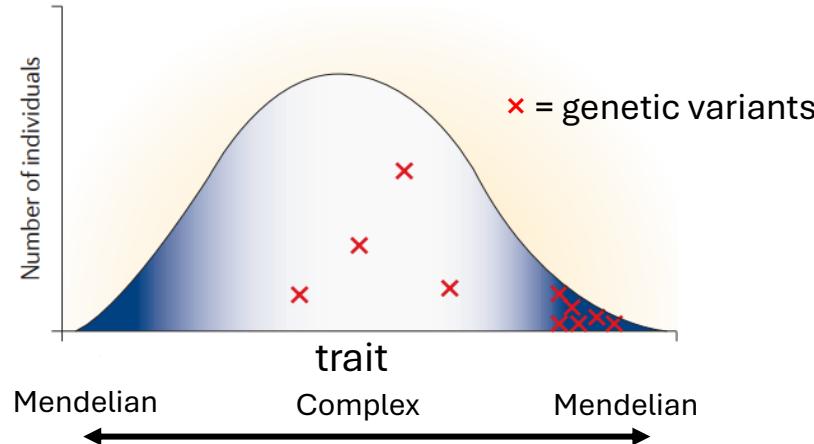


Delmar, McKenna, *Circ Res* 2010

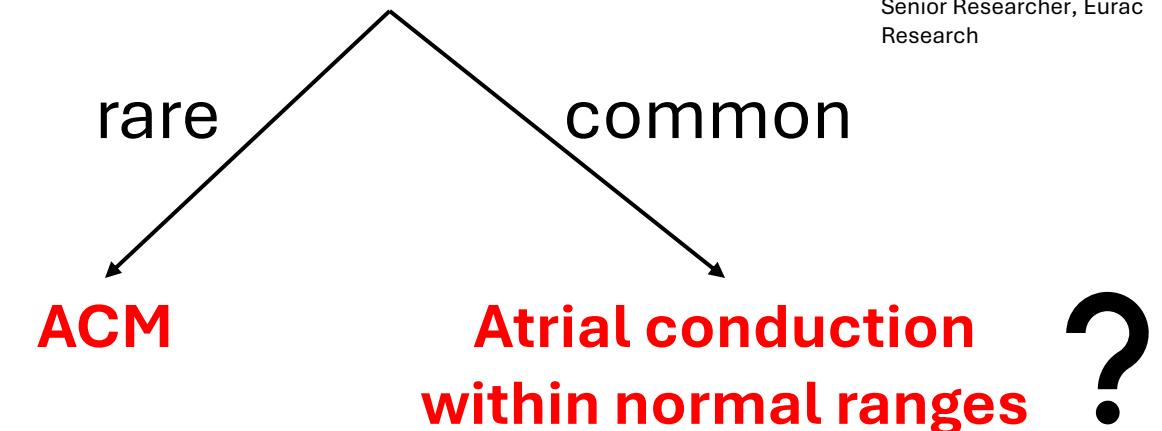
- **Plakoglobin** *JUP*
- **Desmoplakin** *DSP*
- **Plakophilin-2** *PKP2*
- **Desmocollin-2** *DSC2*
- **Desmoglein-2** *DSG2*

# Scientific question #1

Mendelian and complex traits share genetic architecture (*Blair 2013, Cell*)



## Variants in desmosomal genes



**Q1**

Are common variants at desmosomal genes associated with ECG trait variability in the general population?



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Research

# Cross-sectional studies

## DISCOVERY

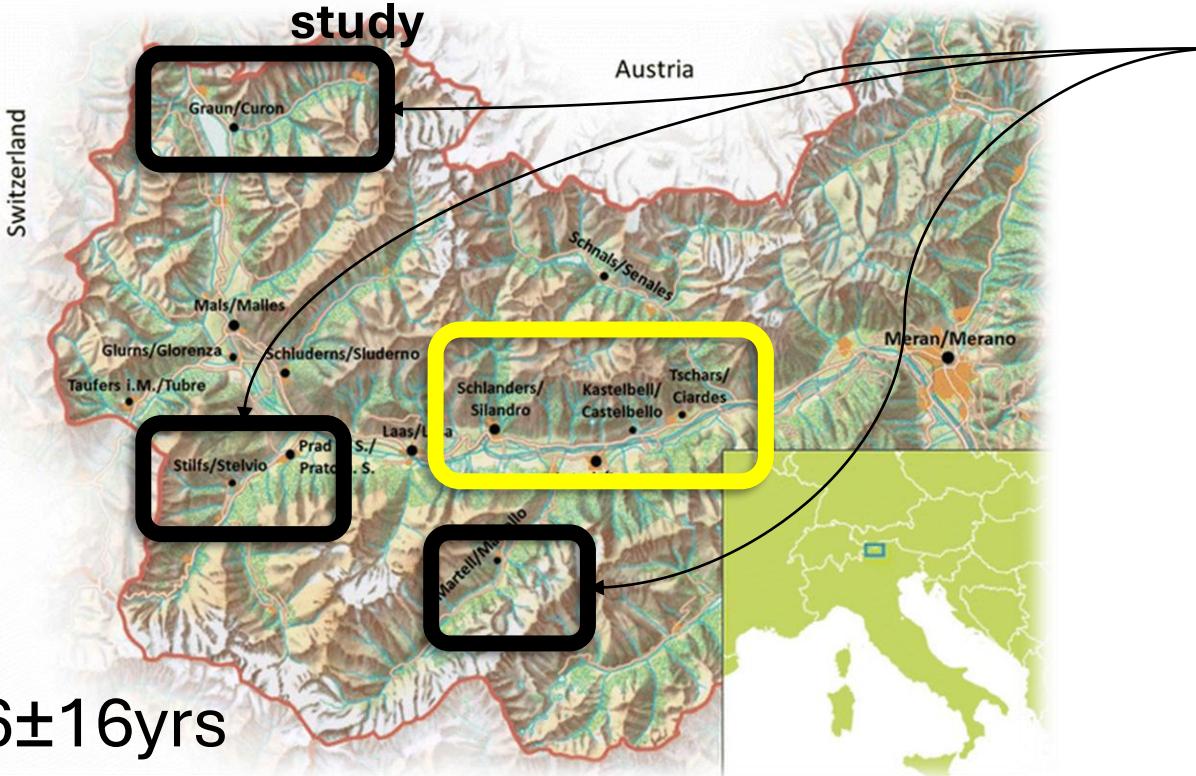
### Cooperative Health Research In South Tyrol (CHRIS) study

**CHRIS**  
eurac research



N=4338

56%F,  $46\pm16$ yrs



Pattaro et al, *J Transl Med* 2015; Lundin et al, *Int J Epidemiol* 2025

## REPLICATION

### MICROisolates In South Tyrol (MICROS) study

N=636, 51%F,  $44\pm17$ yrs

Pattaro et al, *BMC Med Genet* 2008

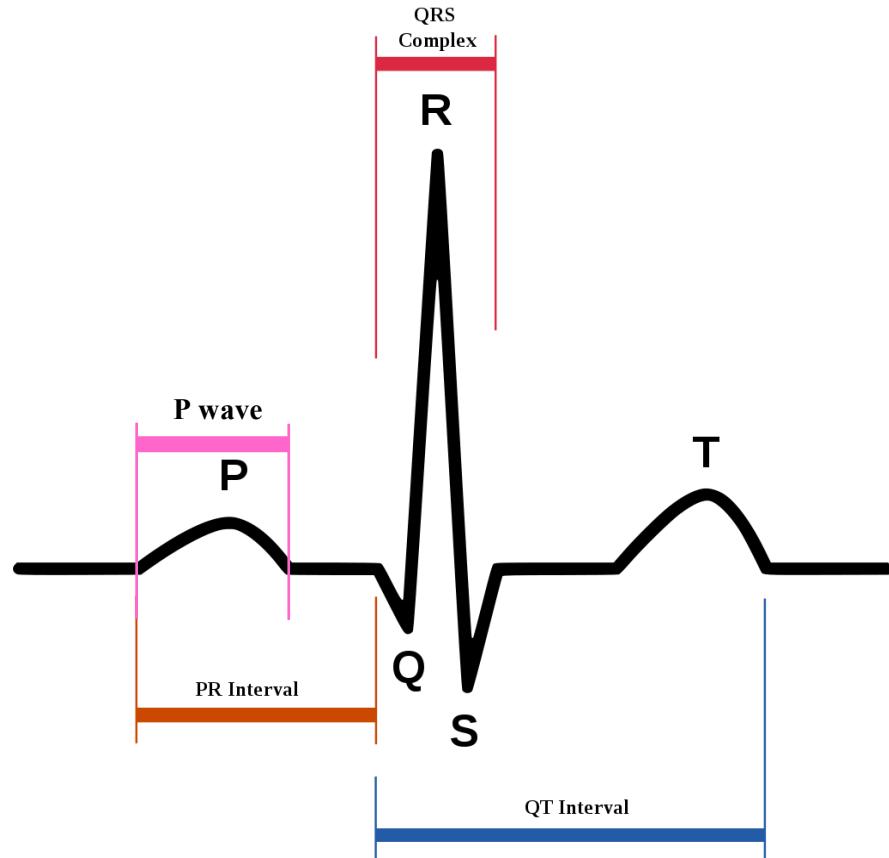
### SHIP and SHIP-TREND

N=3779, 52%F,  $48\pm16$ yrs

Völzke et al, *Int J Epidemiol* 2022



# Outcomes



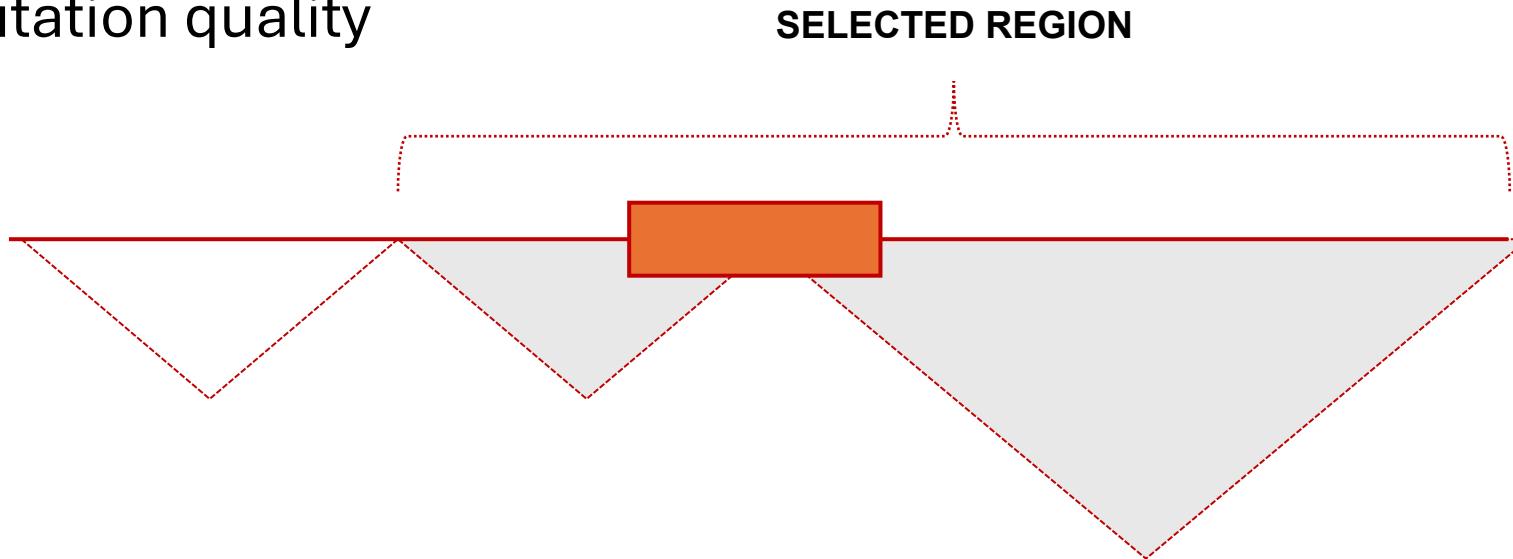
## P-wave, PR, QRS, QT intervals

- from standard 10" 12-lead ECGs
- excl. history of atrial fibrillation, myocardial infarction, heart failure, Wolff-Parkinson-White syndrome, assuming class I and III antiarrhythmics and/or digoxin, pacemaker carriers, and pregnant women
- excl. outliers  $> | \text{IQR} \pm 3 \times \text{IQR} |$
- ~normally distributed

# Exposures

## Imputed, single nucleotide polymorphism (SNP) dosage levels

- Illumina Human OmniExpress Exome array imputed on 1000 Genome Phase 1
- Selected at DSP, PKP2, JUP, DSC2, DSG2
- Total: **2742 SNPs, spanning 570 kb**
- with high imputation quality



# Association testing

## Linear mixed models

$$ECG\ trait \sim SNP_i + Fixed\ Effects + Random\ Intercepts + \varepsilon$$

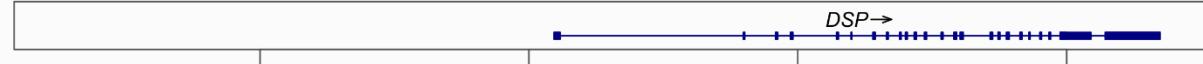
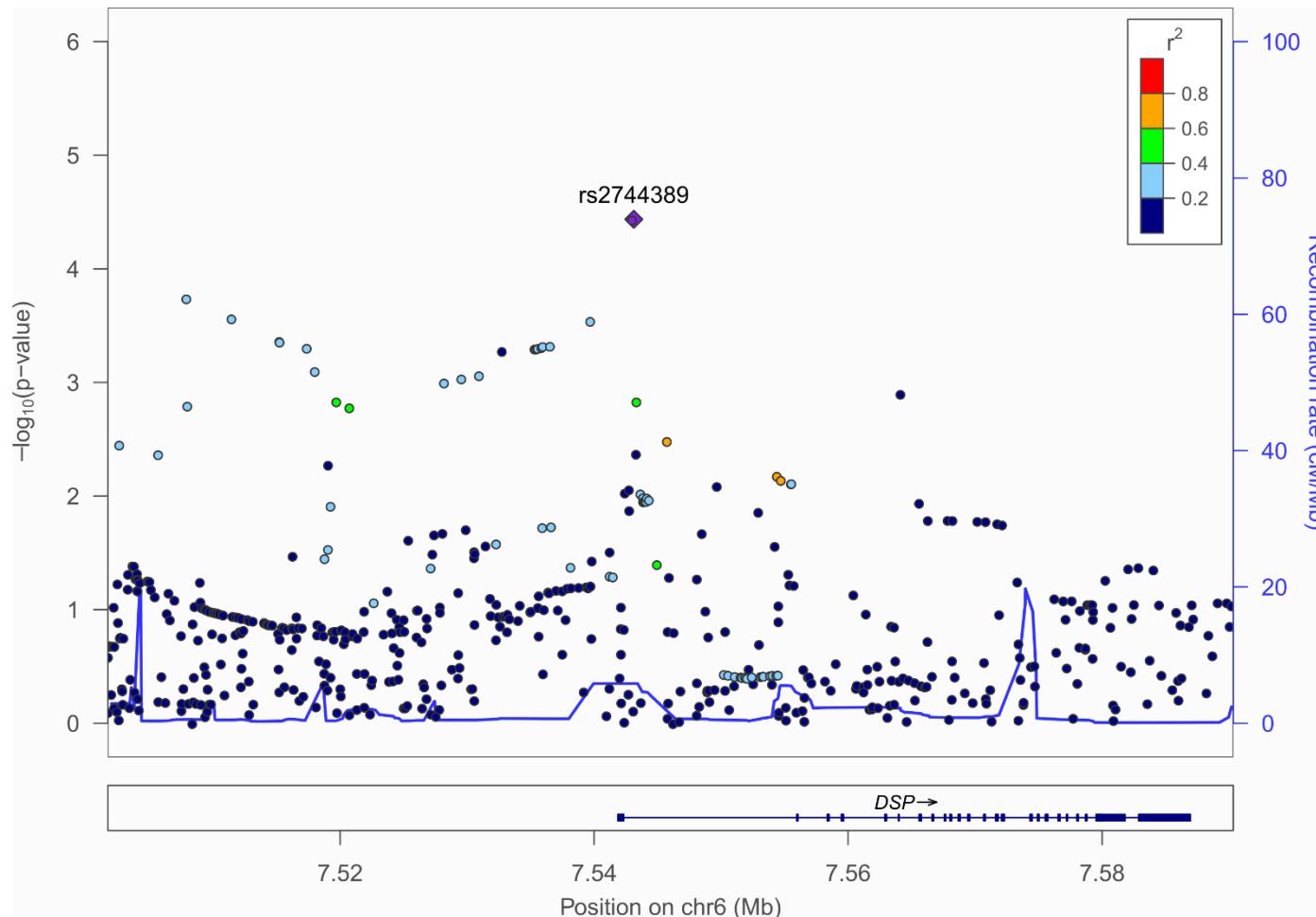
$$i = 1..2742; \quad \varepsilon \sim N(0, \sigma_K^2 K + \sigma^2 I)$$

- **Fixed effect covariates:** age, sex
- **Random intercept:** day of participation
- **Variance component:** kinship matrix
- **Significance level:**  $\alpha_{\text{discovery}} = 2 \times 10^{-4}$ ;  $\alpha_{\text{replication}} = 0.017$  (1-sided test / 3)
- **Software:** EMMA and coxme in R

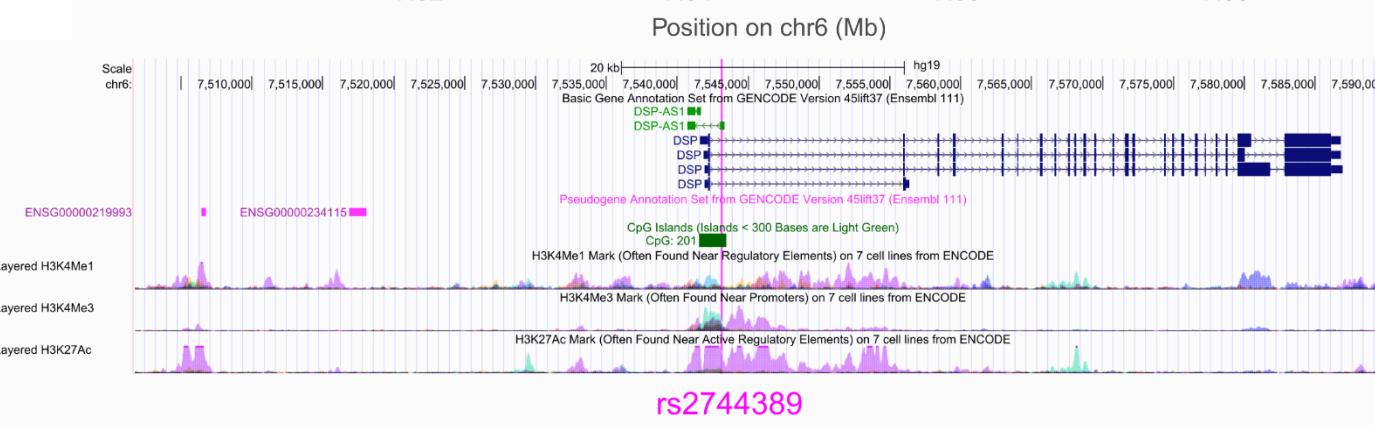
# Results

			CHRIS, n=4338			MICROS, n=636			SHIP, n=3779		
Trait	SNP, gene	Alleles	EAF	Beta(SE)	P	EAF	Beta(SE)	P‡	EAF	Beta(SE)	P‡
P-wave	rs115171396, <i>JUP</i>	C/T	0.02	4.87(1.08)	$6.6 \times 10^{-6}$	0.02	-0.19(3.12)	0.525	0.01	1.59(1.45)	0.136
P-wave	rs72835665, <i>JUP</i>	G/A	0.51	-1.10(0.27)	$4.5 \times 10^{-5}$	0.56	0.18(0.87)	0.585	0.53	-0.06(0.29)	0.416
QRS, ms	rs2744389, <i>DSP</i>	A/C	0.18	-1.10(0.24)	$3.5 \times 10^{-6}$	0.18	-1.47(0.64)	0.010	0.16	0.21(0.32)	0.748

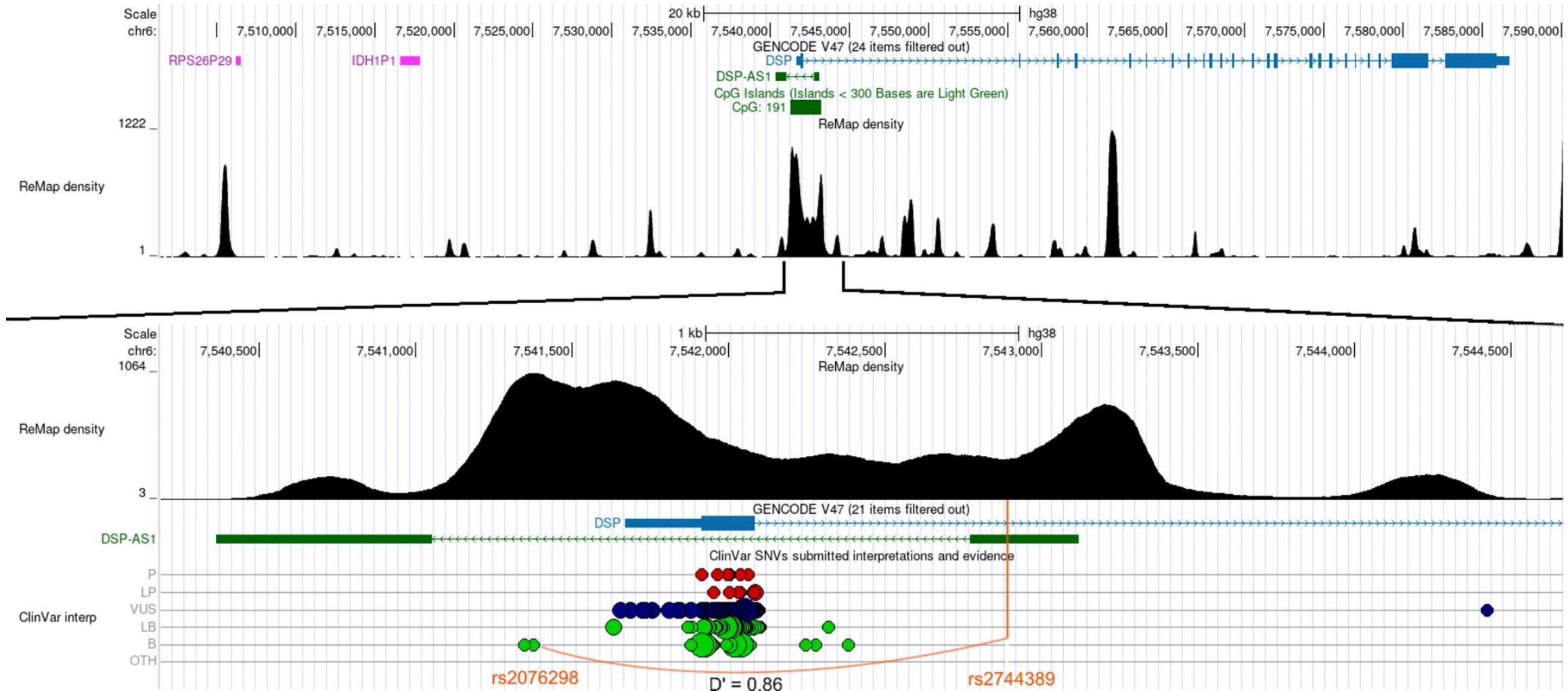
indep. replication



Position on chr6 (Mb)



# rs2744389 is an expression quantitative locus (eQTL) of the antisense RP3-512B11.3 (DSP-AS1) lncRNA



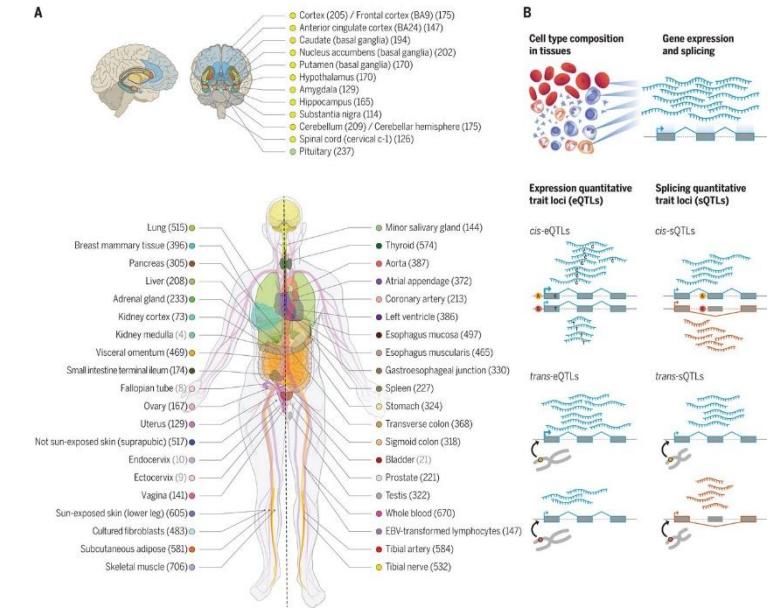
# Results

## GTEX Portal

<https://www.gtexportal.org/home/snp/rs2744389>

**rs2744389 is associated with**

- **expression of *DSP-AS1* lncRNA**  
( $p = 3.1e-14$  liver;  $2.3e-7$  heart atrial appendage)
- but not with expression of *DSP*



# Scientific question #2

$DSP\text{-}AS1 \longrightarrow DS \longrightarrow QRS\text{ interval}$

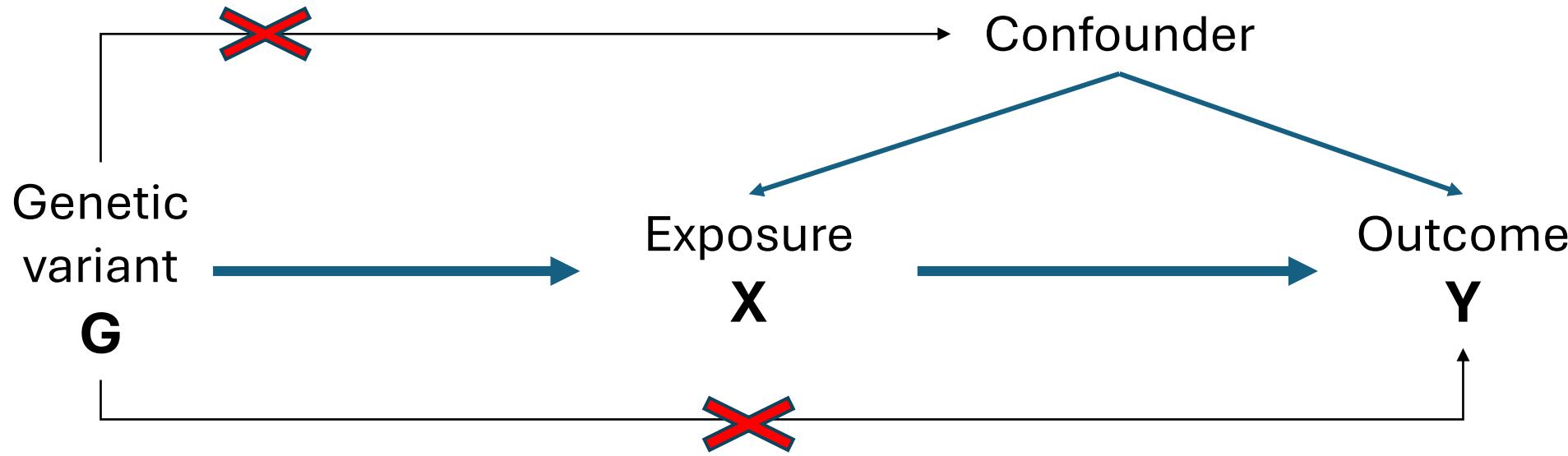
$P$

$DSP\text{-}AS1 \longrightarrow QRS\text{ interval}$

**Q2**

is  $DSP\text{-}AS1$  expression causally associated with  $DS$  expression and with the ECG QRS interval?

# 2-sample MR



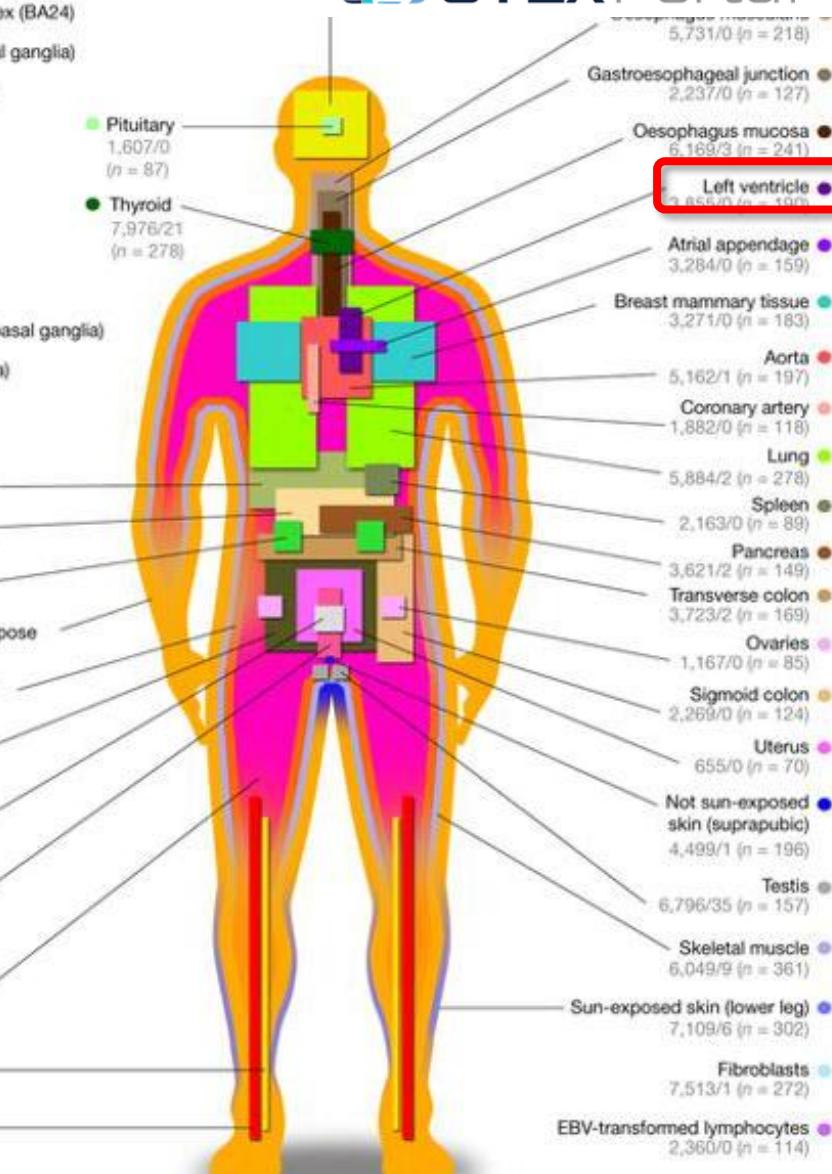
## Core assumptions

- 1)  $G$  is strongly associated with  $X$
- 2) The  $G$ - $X$  association is not confounded by hidden factors (eg: population stratification)
- 3) There is no other pathway from  $G$  to  $Y$  other than through  $X$

## Wald-ratio estimator

$$b = \frac{\text{effect of } G \text{ on } Y}{\text{effect of } G \text{ on } X}$$

if multiple variants:  
meta-analysis;  
regression  
techniques; polygenic  
score



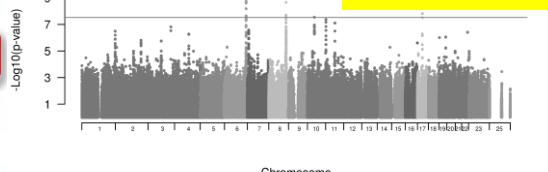
DSP-AS1  
RNA

DSP  
mRNA

QRS  
duration

Left ventricle

N=386  
STRONG IV



perfect tissue 😊

DSP-AS1 RNA  
GTEx  
left ventricle  
N=386

D cg02643433 methylation  
Framingham Heart study  
N=4170

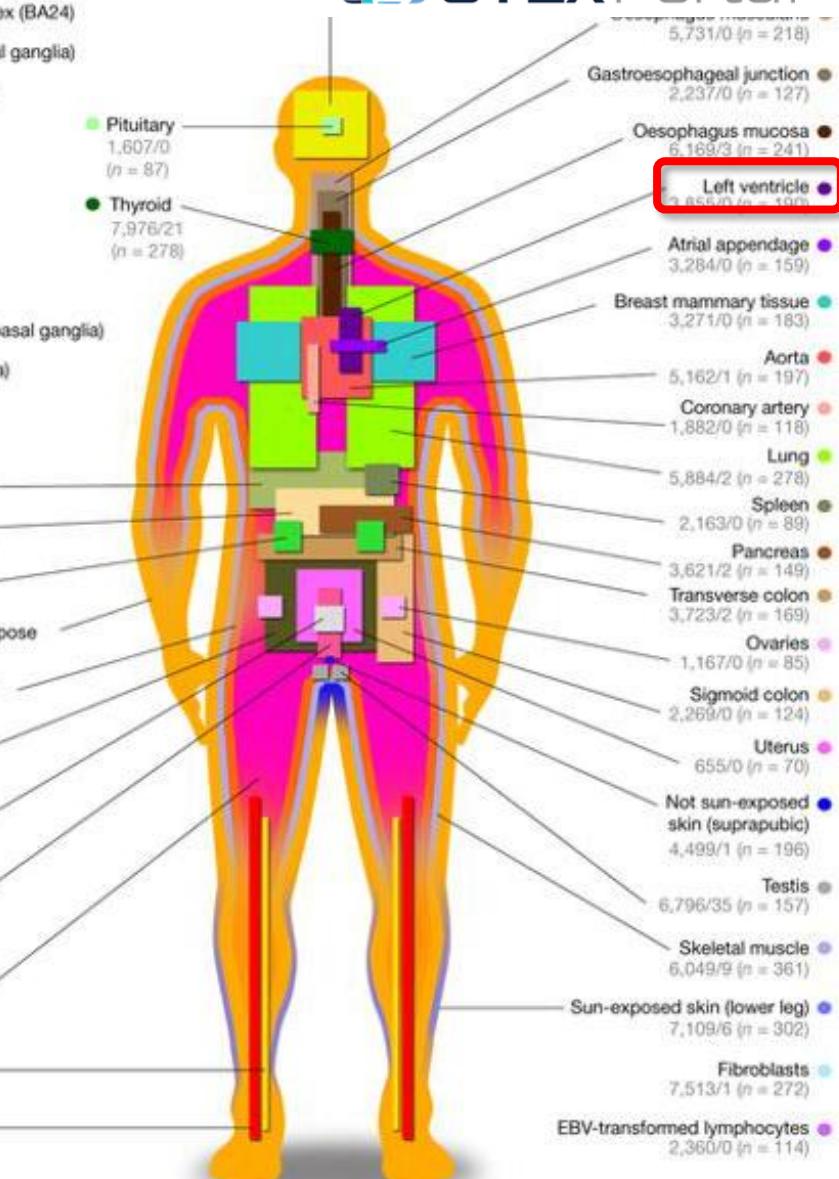
E\* DSP mRNA  
GTEx, left ventricle  
N=386

b=neg  
p= $6.33 \times 10^{-5}$

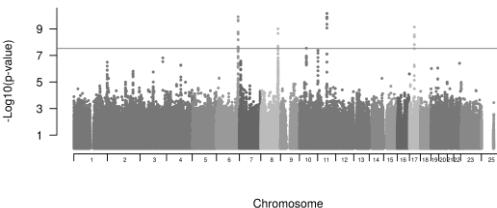
F\* QRS duration  
CHRIS study  
N=4259

b=neg  
p=0.015





## Left ventricle

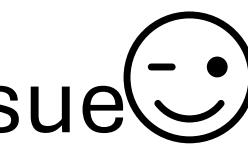


perfect tissue 😊

DS

GTEx, left ventricle

NO VALID IVs

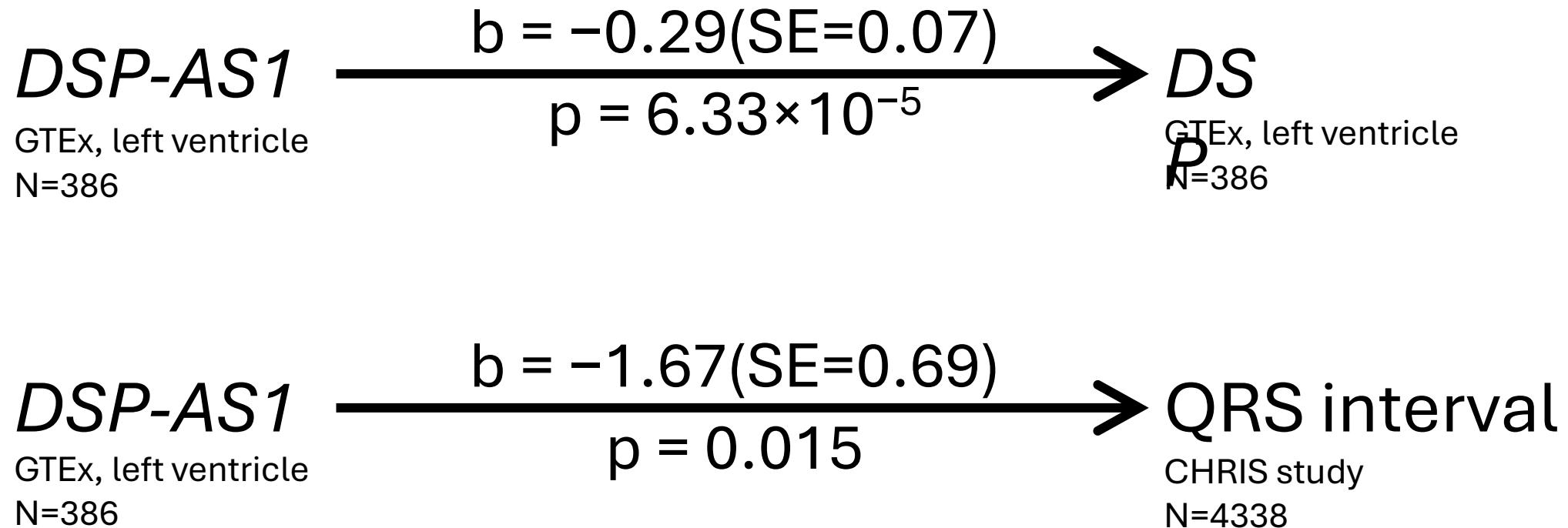


QRS interval

CHRIS study

N=4338

# Results



# Scientific question #3

**Q3**

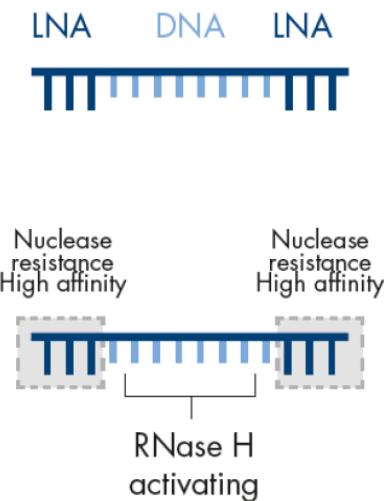
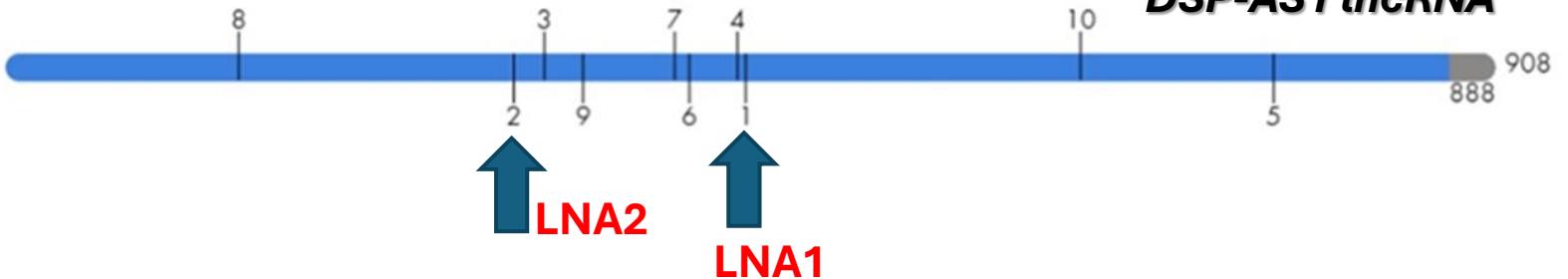
Can we confirm *in vitro* the causal, negative effect of  
DSP-AS1 on DSP?

# In vitro confirmation

## Antisense LNA GapmeRs design to downregulate DSP-AS1 lncRNA



16 nucleotide sequence enriched with locked nucleic acids (LNAs) in the flanking regions, to increase affinity to the specific target → hybrid DNA/RNA double-strand



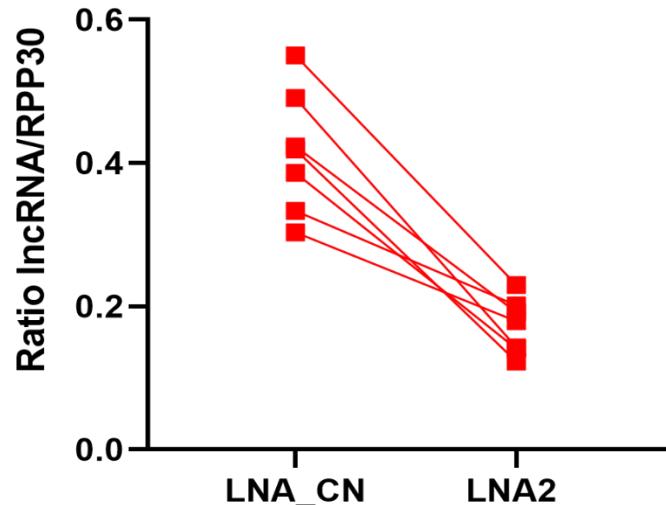
# In vitro confirmation

in iPSC-derived cardiomyocytes (CMs)

lncRNA downregulation by LNA2 ↑ DSP mRNA expression

## DSP-AS1 expression

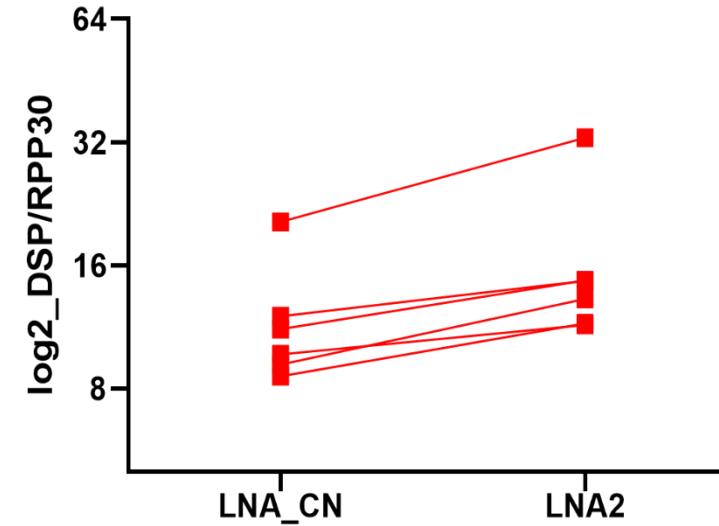
Treatment: 1000nM of Gapmers for 10days



*Wilcoxon matched-pairs signed rank  
test*

\*  $p=0.0156$

## DSP expression



*Wilcoxon matched-pairs signed rank  
test*

\*  $p=0.0313$

# Conclusions

- First time a mechanism for DSP regulation was identified in cardiomyocytes
  - LNA2 Gapmer induces ~60% *DSP-AS1* downregulation in hiPSC-CMs
  - *DSP-AS1* downregulation increases *DSP* mRNA expression in hiPSC-CMs
- Potential to develop therapeutic strategies targeting *DSP* through *DSP-AS1*
- Further investigations warranted to assess results in ACM patients carrying *DSP* mutations

**Causal screening  
of actionable  
targets**

# A novel multi-ancestry proteome-wide Mendelian randomization study implicates extracellular proteins, tubular cells, and fibroblasts in estimated glomerular filtration rate regulation



see commentary on page 1059

OPEN

Matthew B. Lanktree<sup>1,2,3,4,9</sup>, Nicolas Perrot<sup>1,9</sup>, Andrew Smyth<sup>1,5</sup>, Michael Chong<sup>1,6</sup>, Sukrit Narula<sup>1</sup>, Meera Shanmuganathan<sup>7</sup>, Zachary Kroezen<sup>7</sup>, Philip Britz-Mckibbin<sup>6,7</sup>, Mario Berger<sup>8</sup>, Joan C. Krepinsky<sup>2,4</sup>, Marie Pigeyre<sup>1,4</sup>, Salim Yusuf<sup>1,4</sup> and Guillaume Paré<sup>1,3,4,6</sup>

## **Causal Association testing between**

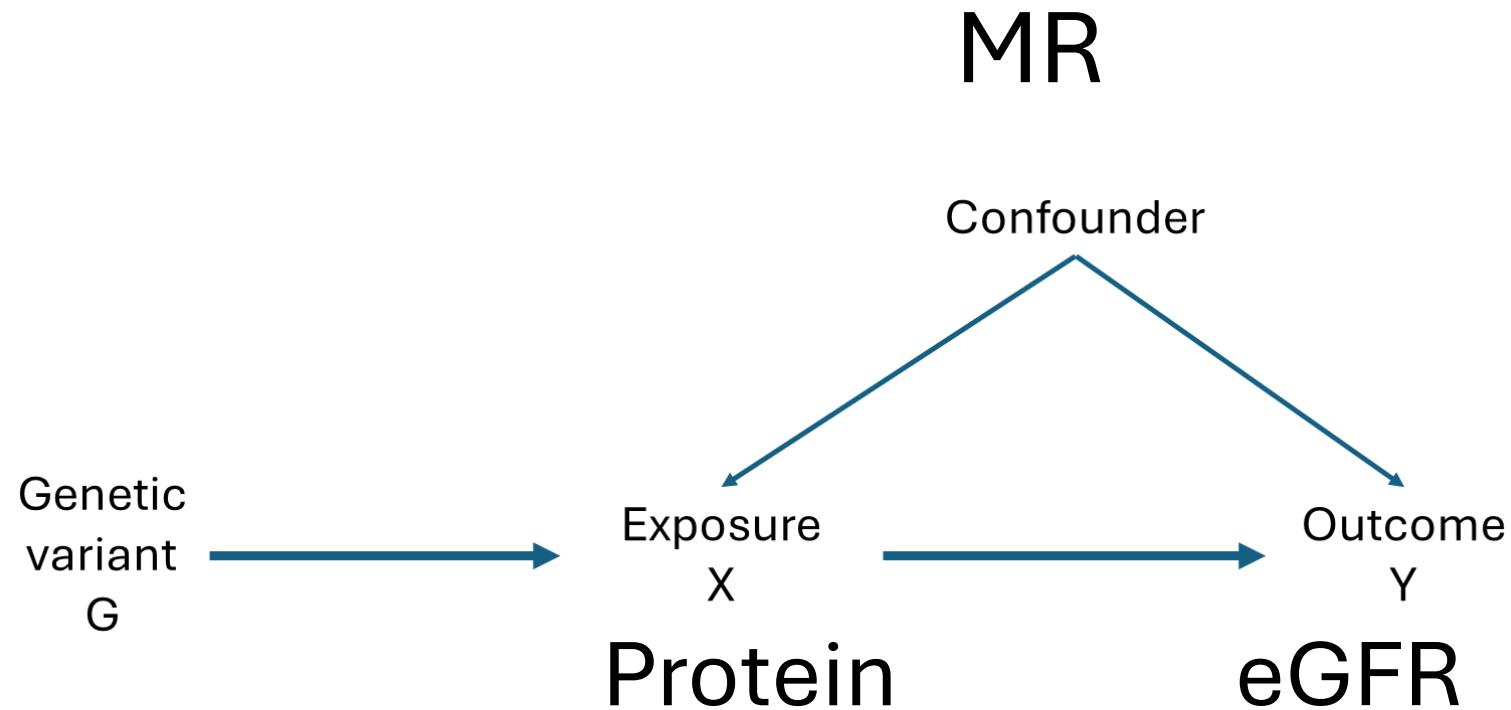
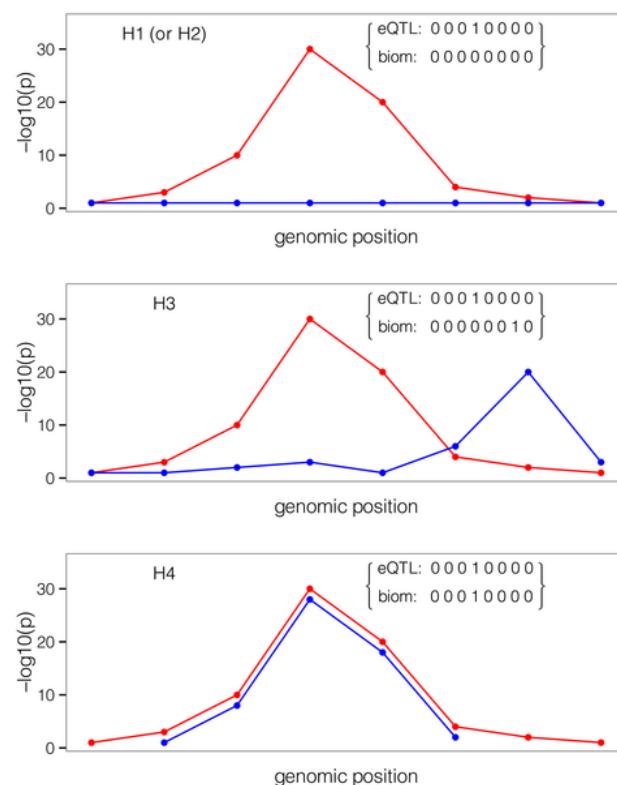
- 1161 biomarkers (protein levels)
- eGFR and other kidney traits

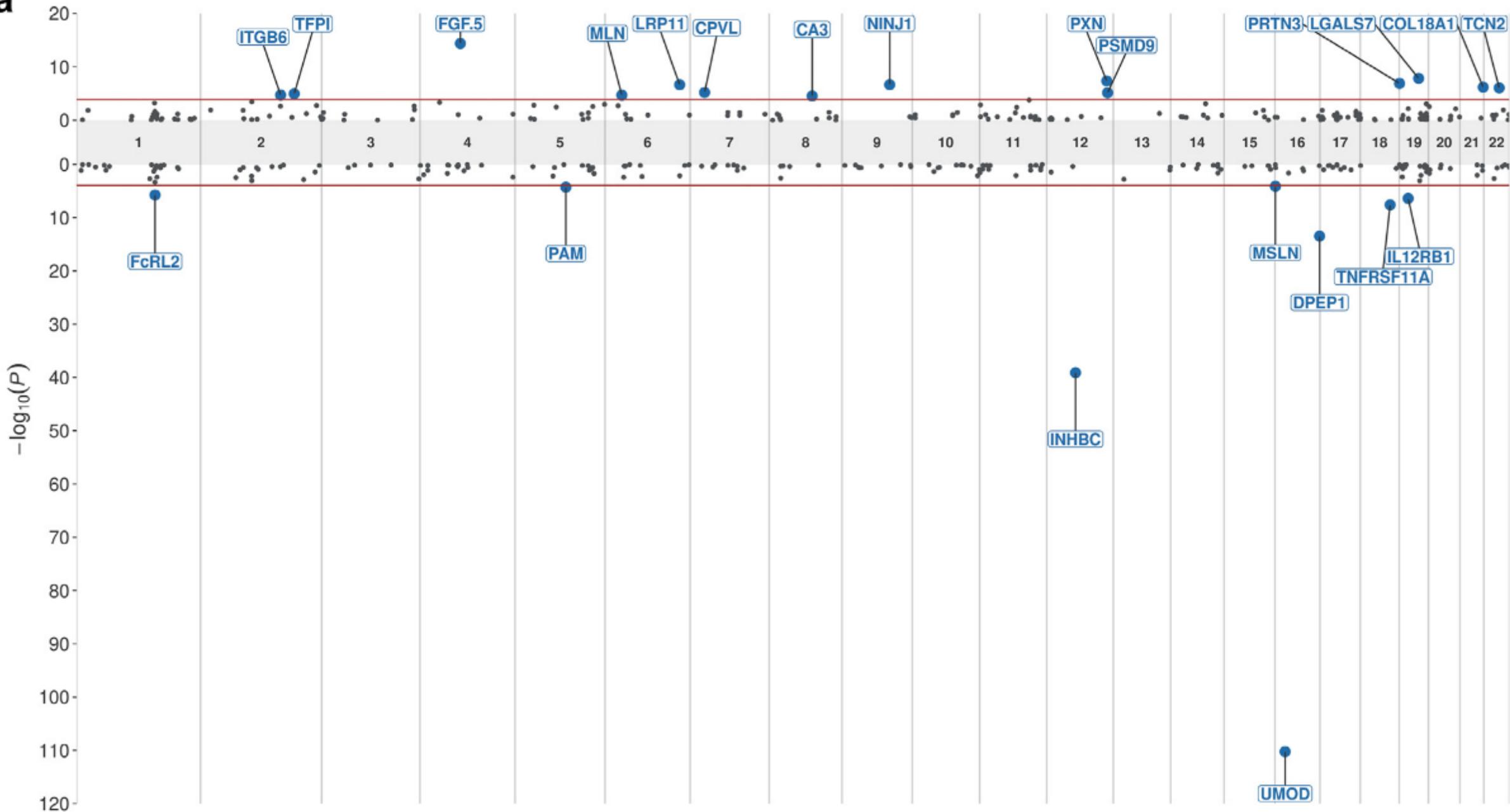
1st : 1161 GWAS in Prospective Urban and Rural

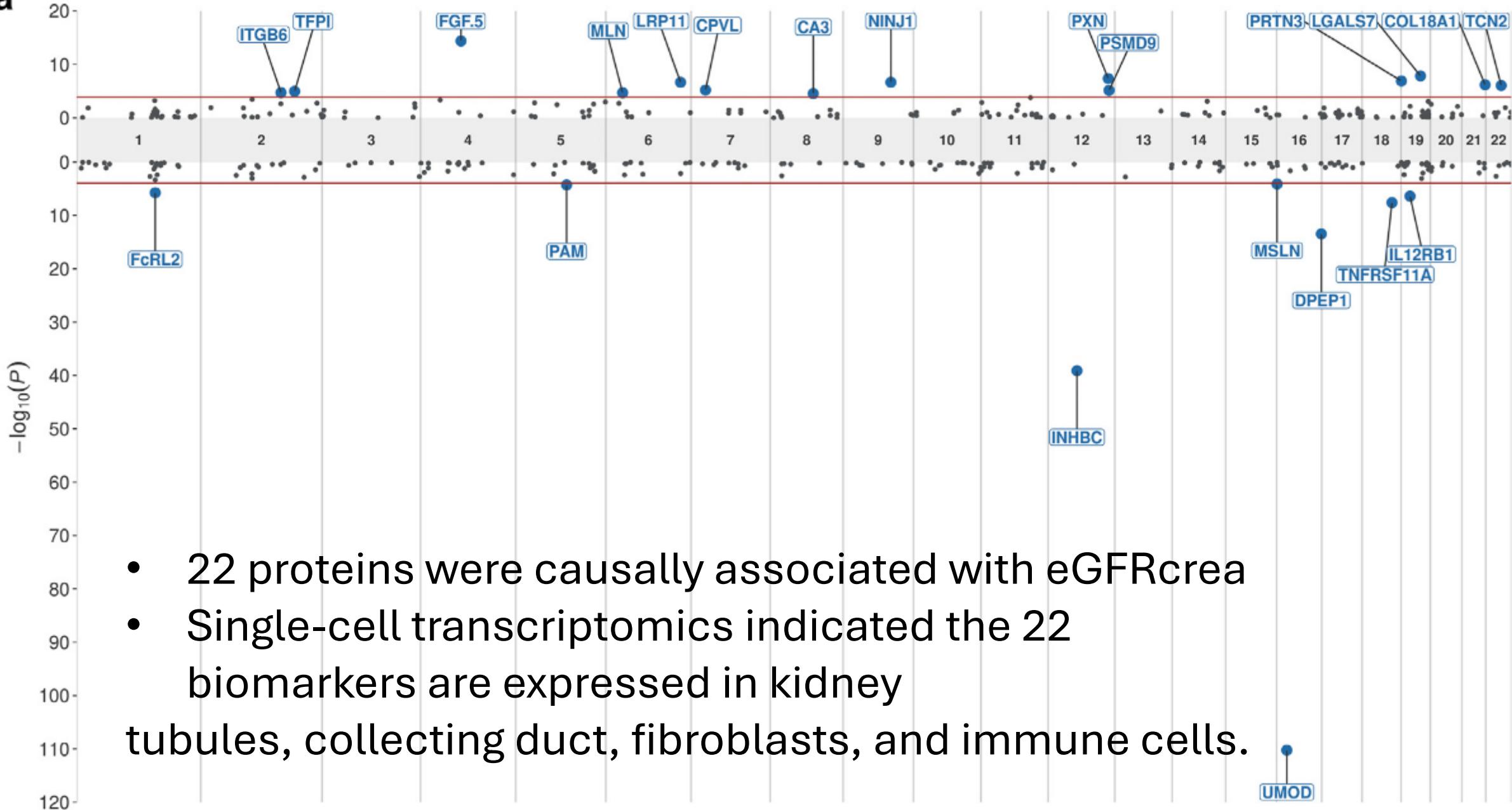
Epidemiological (PURE) study (N=12,066)

2<sup>nd</sup>: took GWAS results for kidney traits from CKDGen

# Colocalization Protein - eGFR



**a**

**a**

**Table 4 | Association of genetically predicted uromodulin with kidney phenotypes**

Outcome	Outcome source	Ancestry	N <sub>outcome</sub> (total or case/control)	Change or OR per SD genetically predicted uromodulin change	P value
eGFR <sub>Cr</sub>	Stanzick <i>et al.</i> 2021 <sup>2</sup>	European	1,004,040	-1.18% (-1.28 to -1.08)	$5.8 \times 10^{-111}$
eGFR <sub>Cr</sub>	Stanzick <i>et al.</i> 2021 <sup>2</sup>	Multi-ancestry	1,201,929	-1.31% (-1.48 to -1.14)	$3.6 \times 10^{-52}$
eGFR <sub>Cys</sub>	Stanzick <i>et al.</i> 2021 <sup>2</sup>	Multi-ancestry	460,826	-1.32% (-1.44 to -1.20)	$3.2 \times 10^{-102}$
eGFR <sub>Cr</sub>	Liu <i>et al.</i> 2022 <sup>4</sup>	Multi-ancestry	>1,500,000	-6.63% (-7.10 to -6.17)	$4.4 \times 10^{-161}$
Urea	Stanzick <i>et al.</i> 2021 <sup>2</sup>	Multi-ancestry	436,500	+0.99% (0.87 to 1.11)	$8.2 \times 10^{-77}$
CKD <sup>a</sup>	Wuttke <i>et al.</i> 2019 <sup>22</sup>	European	41,395/439,303	1.26 (1.23 to 1.29)	$1.1 \times 10^{-122}$
Rapid3 <sup>b</sup>	Gorski <i>et al.</i> 2021 <sup>20</sup>	European	34,874/107,090	1.11 (1.09 to 1.12)	$1.2 \times 10^{-37}$
CKDi25 <sup>c</sup>	Gorski <i>et al.</i> 2021 <sup>20</sup>	European	19,901/175,244	1.24 (1.19 to 1.29)	$1.7 \times 10^{-30}$
eGFR Decline <sup>d</sup>	Gorski <i>et al.</i> 2022 <sup>21</sup>	European	320,737	11.35% (9.96 to 12.76)	$3.9 \times 10^{-63}$
Systolic BP	Evangelou <i>et al.</i> 2018 <sup>23</sup>	Multi-ancestry	757,601	+0.51 mm Hg (0.41 to 0.63)	$1.4 \times 10^{-29}$
Diastolic BP	Evangelou <i>et al.</i> 2018 <sup>23</sup>	Multi-ancestry	757,601	+0.41 mm Hg (0.35 to 0.49)	$5.3 \times 10^{-40}$

BP, blood pressure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR<sub>Cr</sub>, estimated glomerular filtration rate estimated from serum creatinine using the CKD-EPI equation; eGFR<sub>Cys</sub>, estimated glomerular filtration rate estimated from serum cystatin using the eCKD-EPI equation; OR, odds ratio.

<sup>a</sup>CKD defined by eGFR <60 ml/min per 1.73 m<sup>2</sup>.

<sup>b</sup>Dichotomous "Rapid3" phenotype defined as greater than 3 ml/min per 1.73 m<sup>2</sup> per year by Gorski *et al.*<sup>20</sup>

<sup>c</sup>Dichotomous "CKDi25" phenotype defined as a greater than 25% eGFR drop and final eGFR below 60 ml/min per 1.73 m<sup>2</sup> by Gorski *et al.*<sup>20</sup>

<sup>d</sup>Baseline-adjusted eGFR decline phenotype as defined by Gorski *et al.*<sup>21</sup>

# Take home

- Multiomics resources help to make the discovery of treatment targets more systematic
- However, target identification requires experience, knowledge, intuition and luck
- There is no best or predefined way to identify a target