

# Modifiers of genetic risk and subtypes of obesity

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*University  
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*Swiss Institute  
of Bioinformatics*



Swiss Institute of  
Bioinformatics

# Outline

- **Introduction to Genetic association studies**
- **Revealing genetic subtypes of obesity**
- **Parent-of-origin modifies genetic effects**

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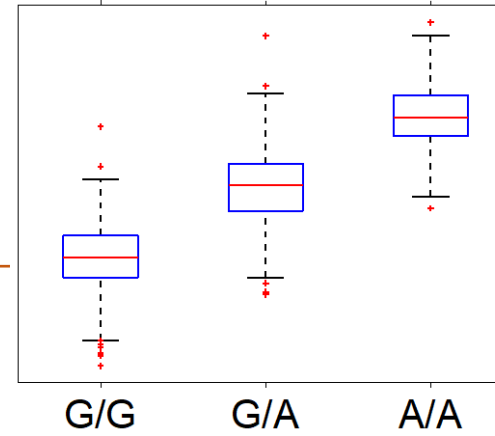
# Genetic associations



...

...

T	C	T	A	C	T	G	C	...	G	A	T	C	G	...	C	G	C	G	A
T	C	T	A	C	T	G	C	...	G	A	T	C	G	...	C	G	T	G	A
T	C	T	A	C	A	G	C	...	G	G	T	C	G	...	C	G	T	G	A
T	C	T	A	C	A	G	C	...	G	A	T	C	G	...	C	G	T	G	A
T	C	T	A	C	T	G	C	...	G	G	T	C	G	...	C	G	C	G	A
T	C	T	A	C	T	G	C	...	G	G	T	C	G	...	C	G	C	G	A



GWAS

**BMI**

24.5

24.8

25.1

# Genome-Wide Association Studies

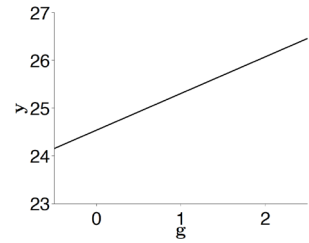
## Model

BMI                      SNP

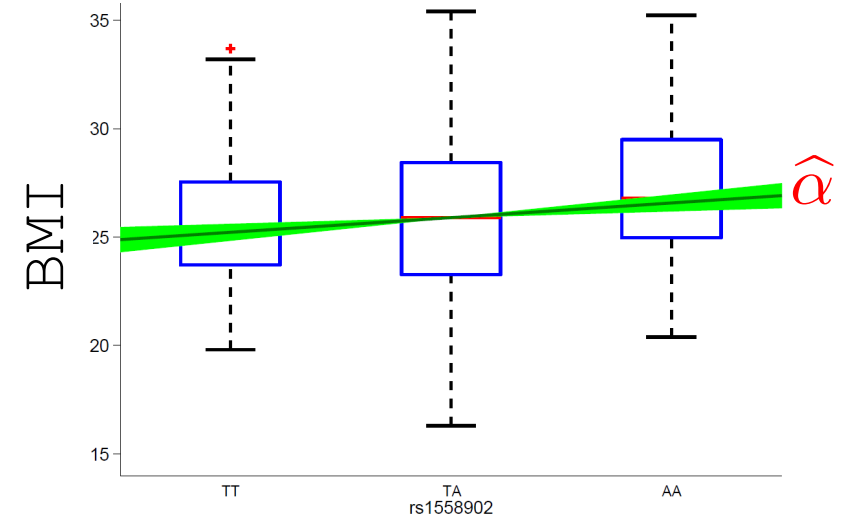
$$\mathbf{y} = \mu + \alpha \cdot \mathbf{g} + \varepsilon$$

with  $\varepsilon \sim \mathcal{N}(0, \sigma^2)$

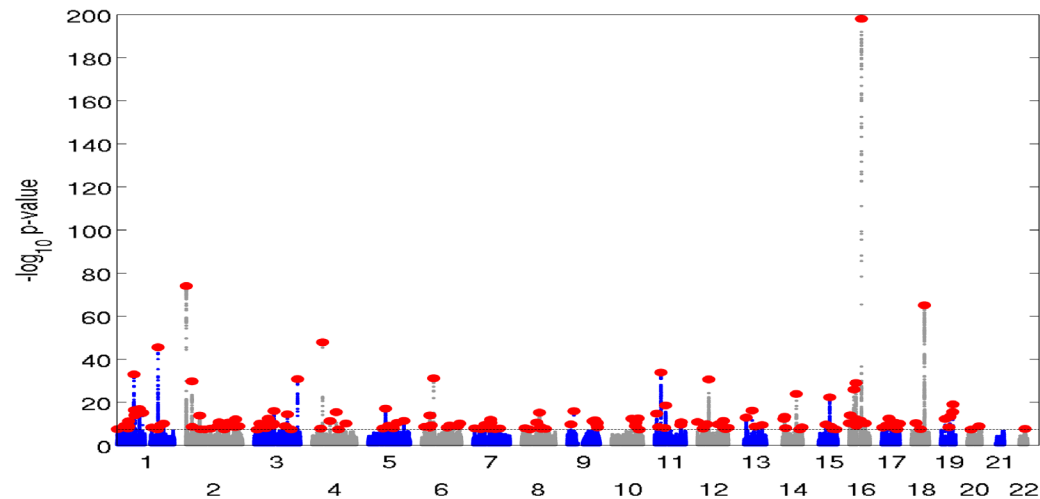
$$\theta = \{\mu, \alpha, \sigma^2\}$$



## Model fit

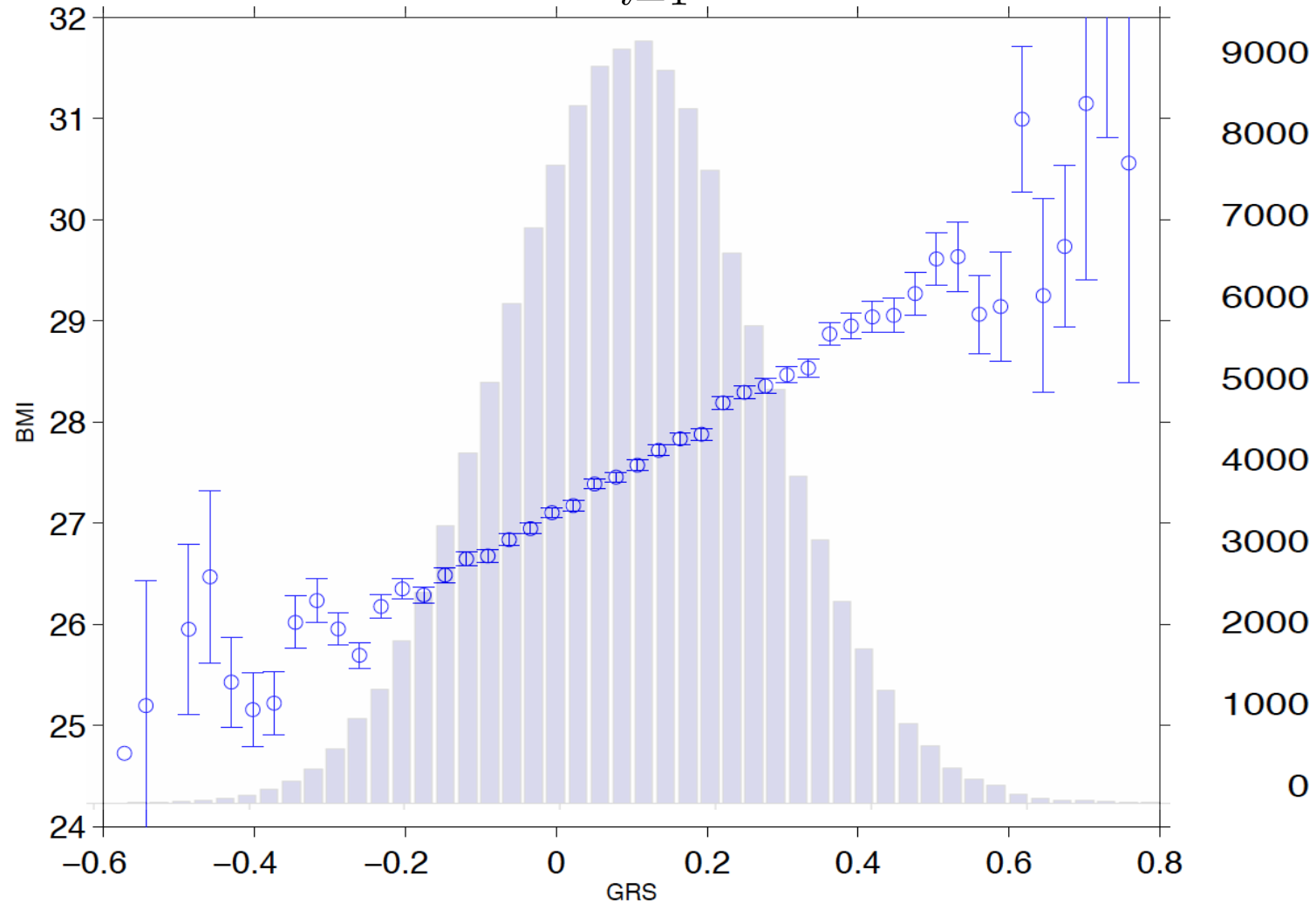


BMI



# Polygenic prediction

$$GRS = \sum_{i=1}^m \hat{\beta}_i \cdot \mathbf{g}(i)$$



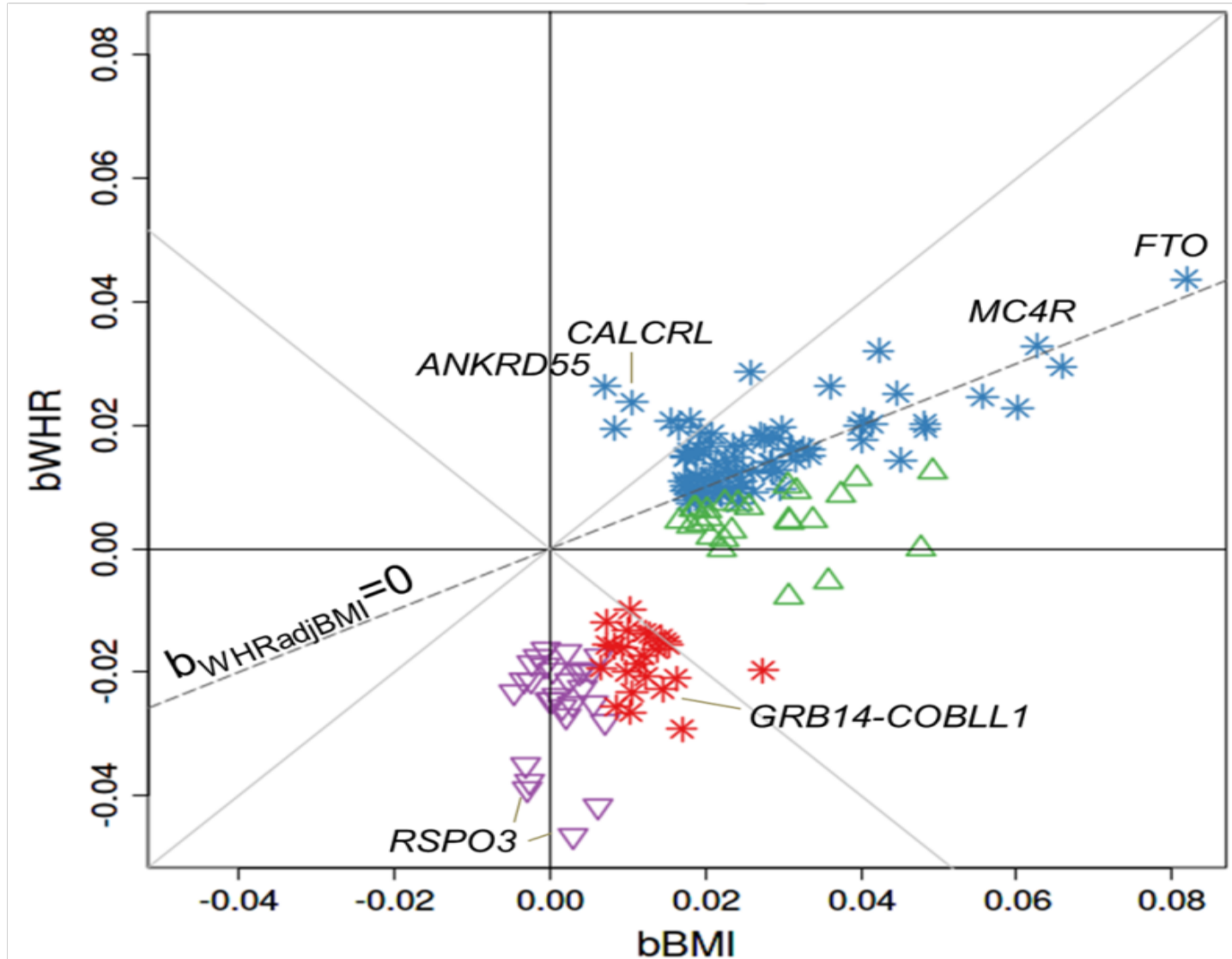
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- Parent-of-origin modifies genetic effects

# Clustering obesity-associated genetic variants



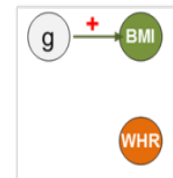
Thomas



BMI+WHR+  
82 signals



BMIonly+  
25 signals



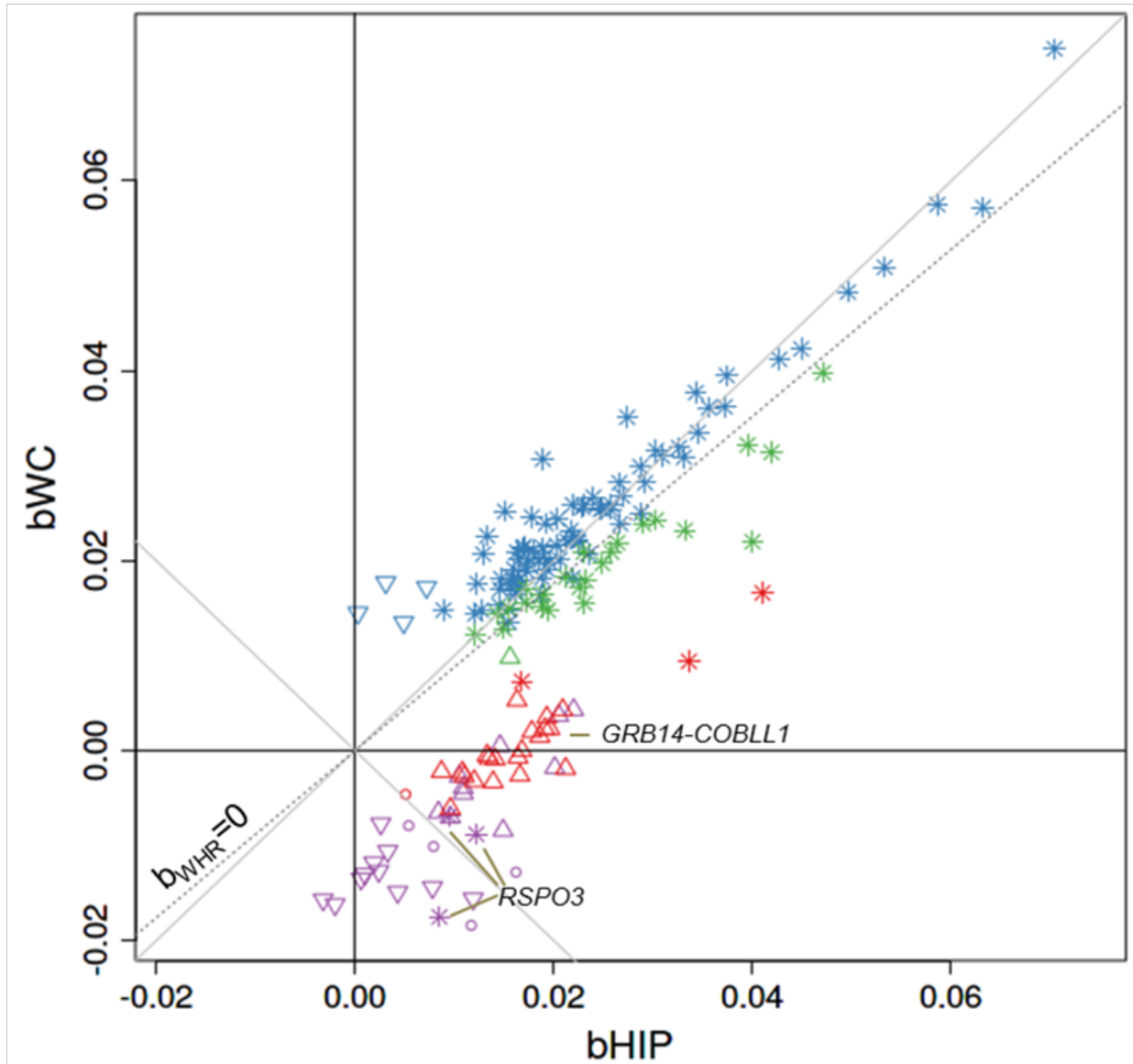
WHRonly-  
28 signals



BMI+WHR-  
24 signals:



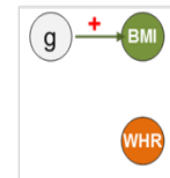
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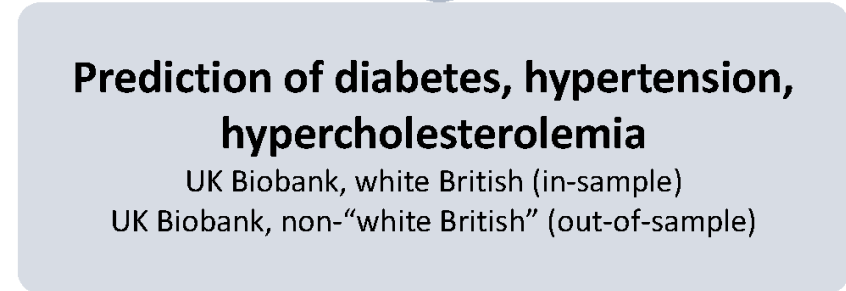
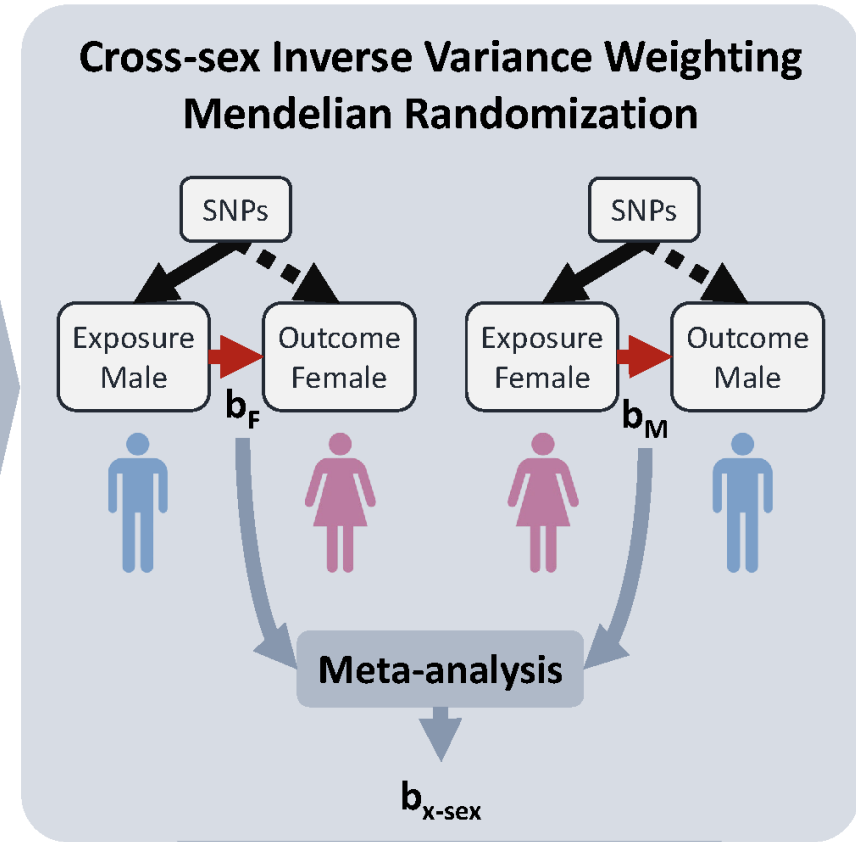
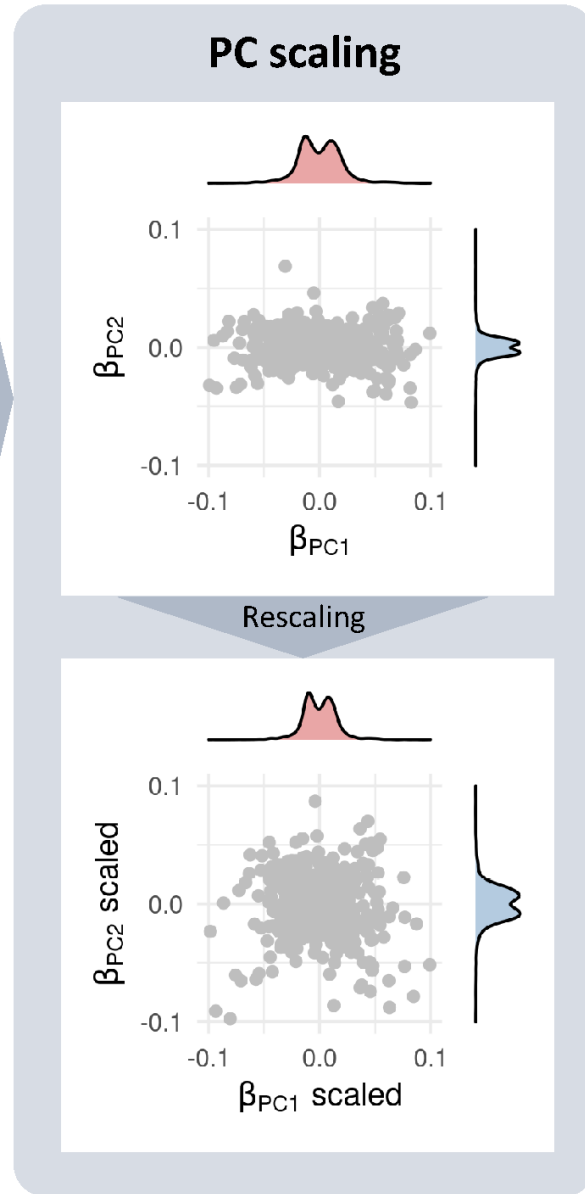
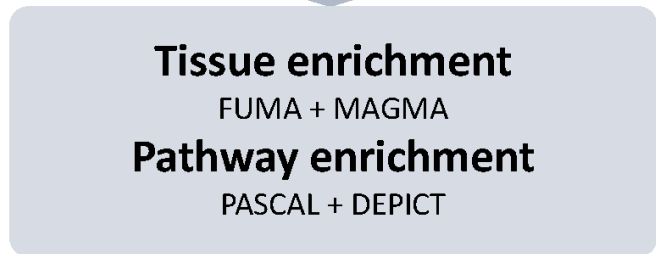
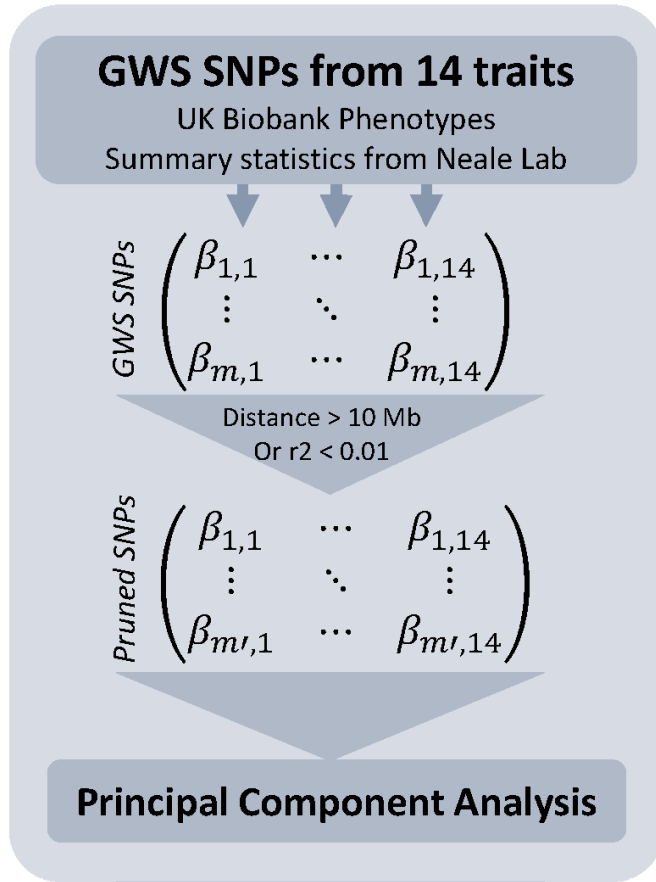
BMI+WHR-  
24 signals:



# Composite trait MR strategy



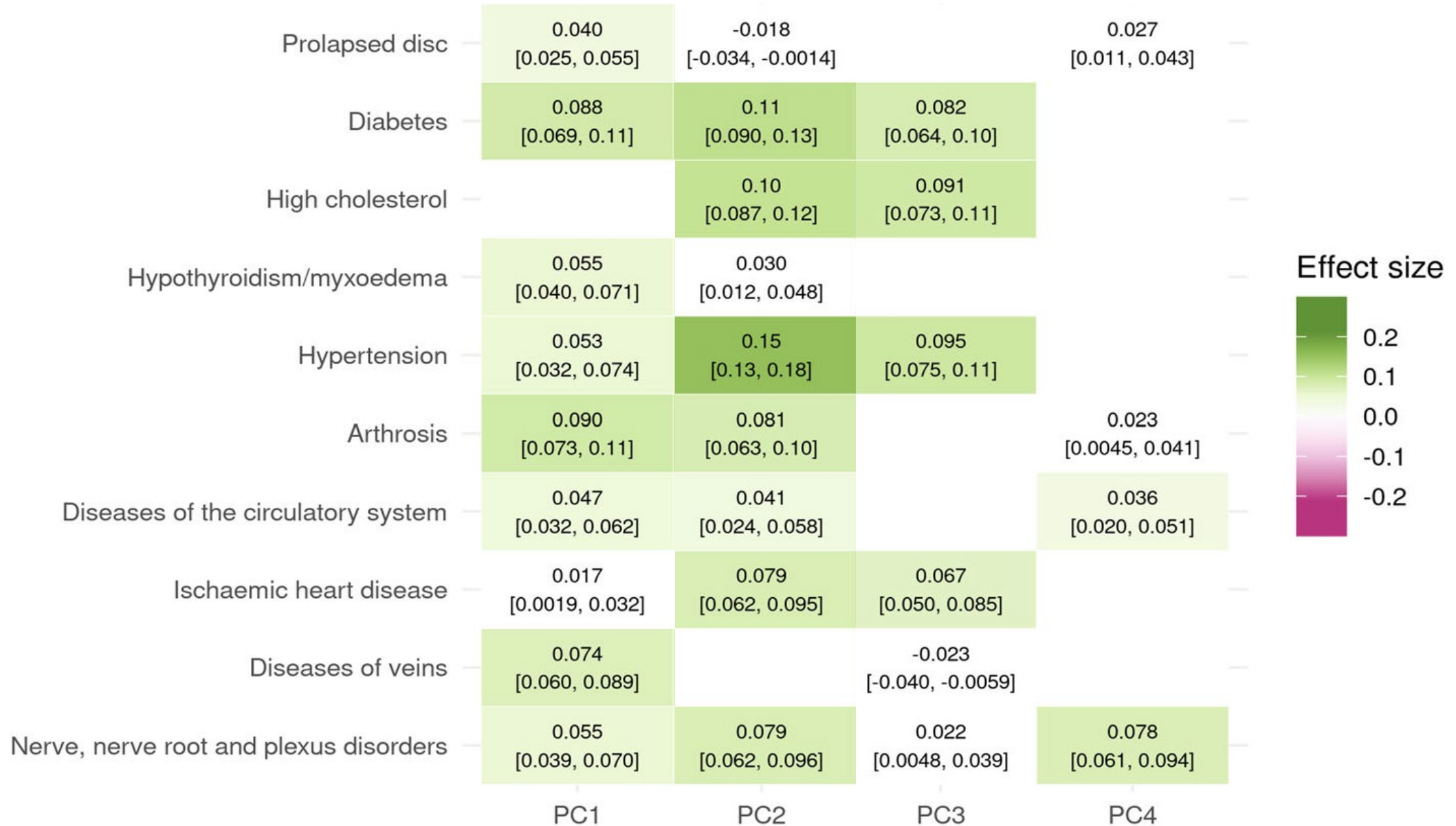
Jonathan



# Composite exposures

Leg fat-free mass	0.28	-0.099	0.26	-0.05	0.26
Leg fat mass	0.21	0.22	-0.084	0.11	0.023
Arm fat mass	0.27	0.27	-0.063	0.0078	0.28
Hip circumference	0.32	0.13	-0.021	-0.79	-0.5
Waist circumference	0.23	0.2	-0.062	0.58	-0.7
Basal metabolic rate	0.3	-0.13	0.26	0.045	0.091
Body fat percentage	0.15	0.28	-0.41	0.032	0.13
Standing height	0.35	-0.65	-0.41	0.042	-0.019
Weight	0.35	0.016	0.044	0.025	0.081
Body mass index (BMI)	0.19	0.44	0.32	0.017	0.13
Trunk fat mass	0.32	0.17	-0.45	0.034	0.26
Arm fat-free mass	0.27	-0.13	0.3	0.12	-0.022
Trunk fat-free mass	0.28	-0.22	0.34	0.094	-0.015
	PC 1 (73%)	PC 2 (23%)	PC 3 (2.6%)	PC 4 (0.56%)	PC 5 (0.27%)

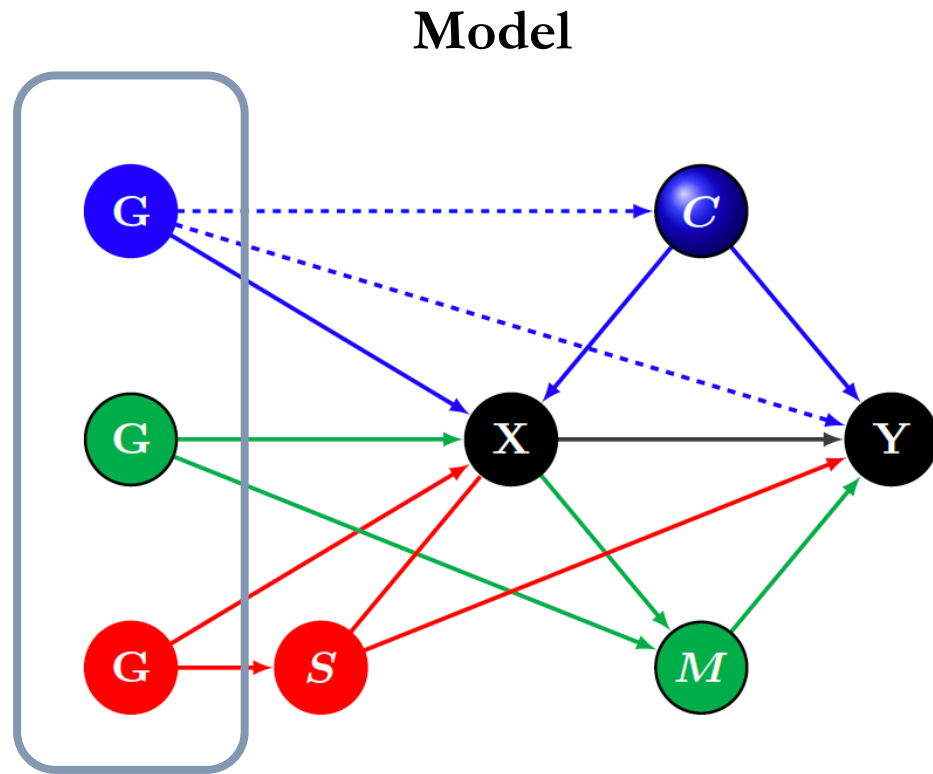
# Downstream consequences of subtypes



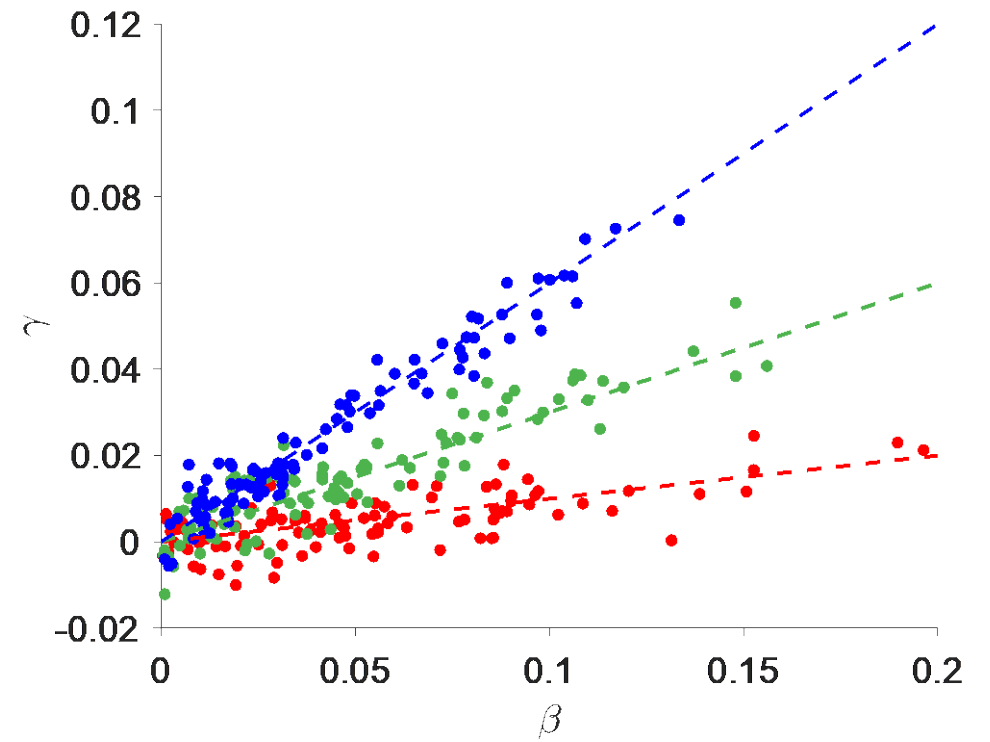
# Heterogeneous effects: BMI on Education



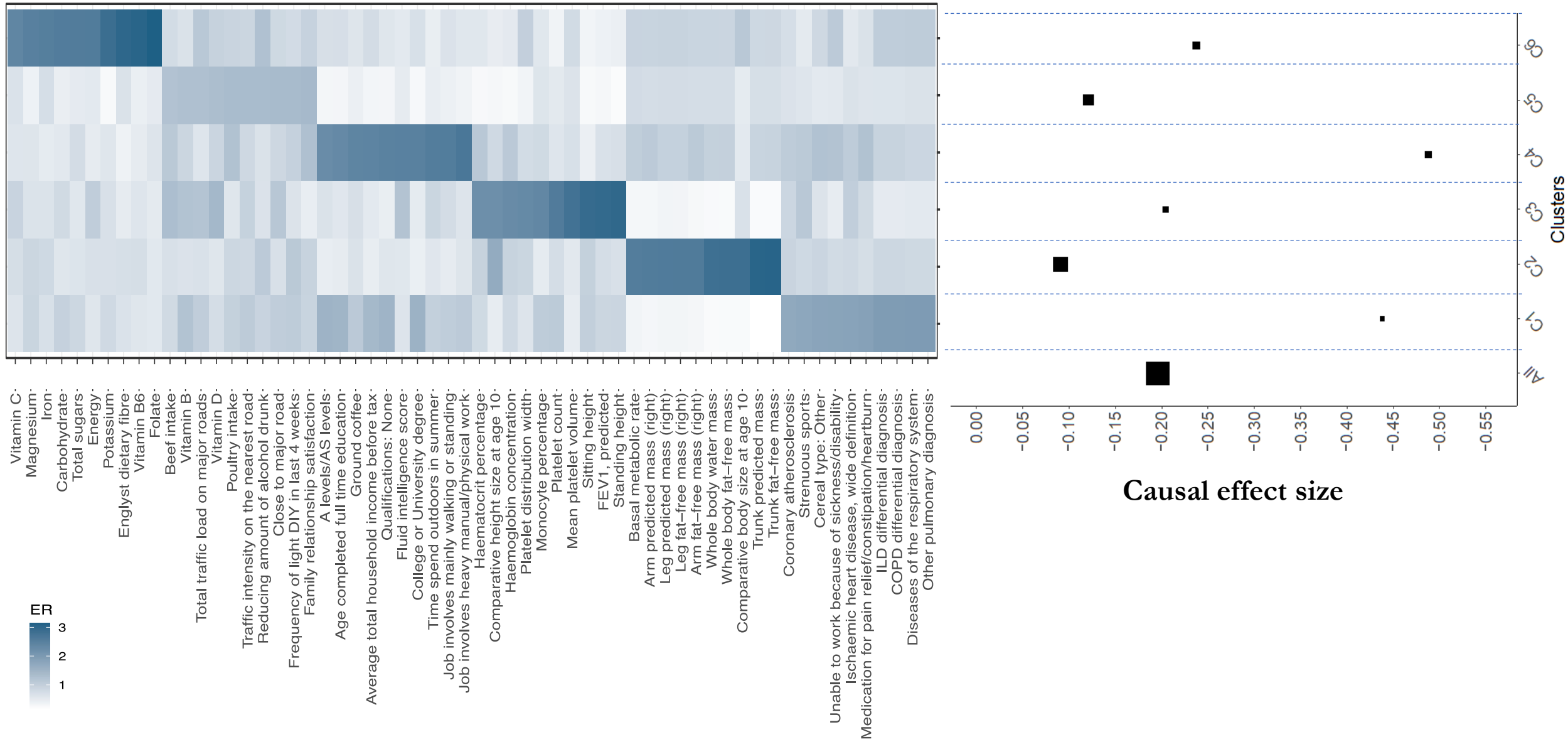
Liza



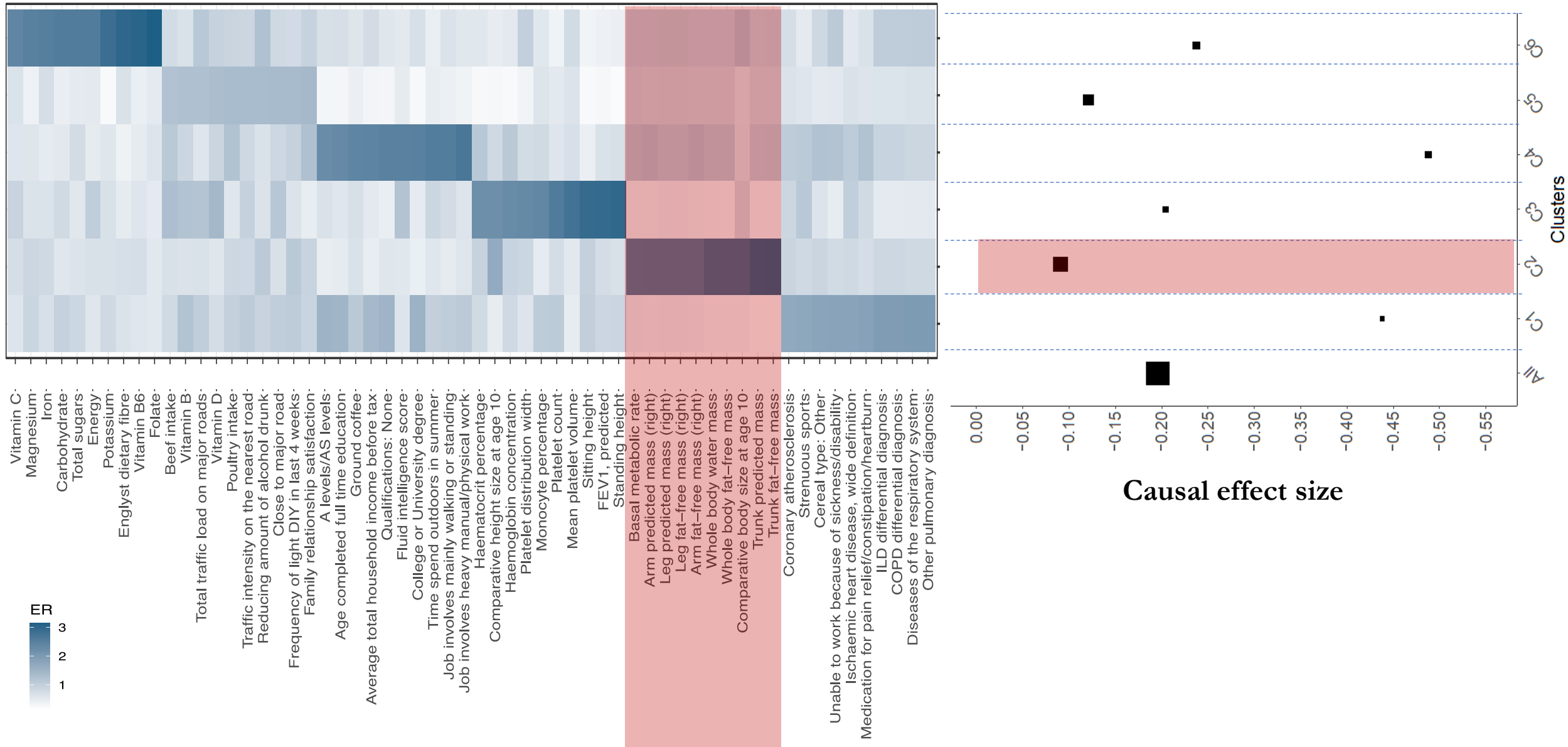
Resulting association effects



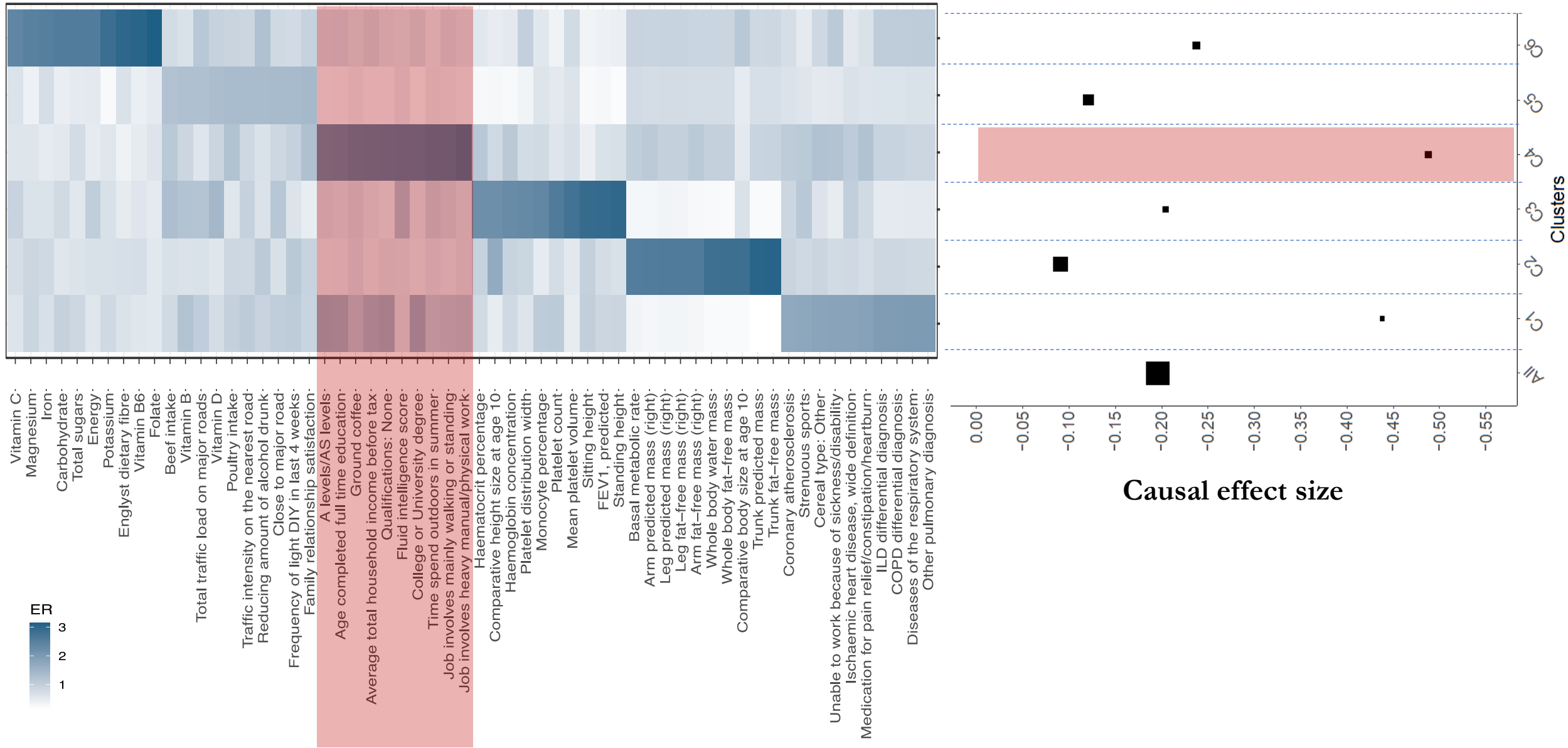
# Obesity – Education?



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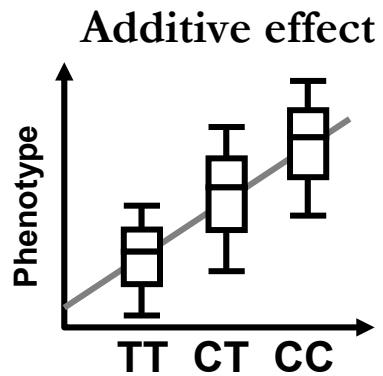
# Obesity – Education?



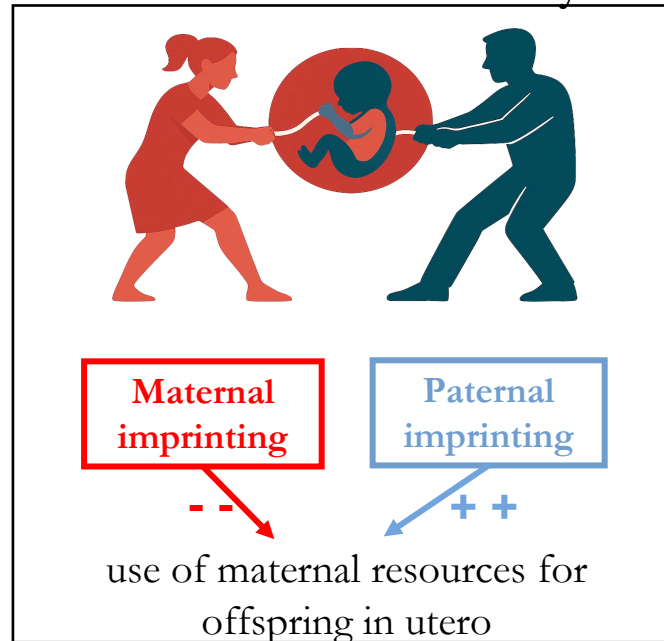
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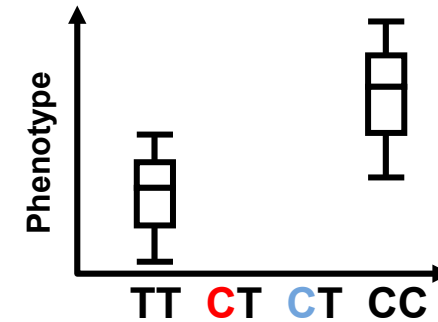
# The parental conflict hypothesis



## Parental conflict theory

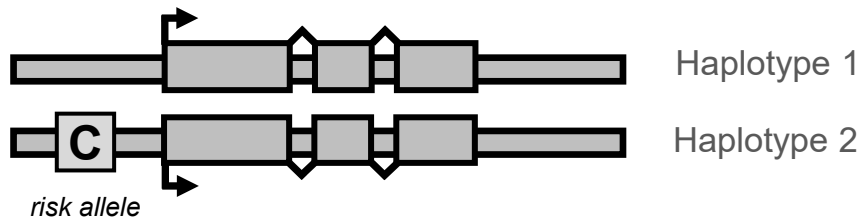


## Parent-of-Origin effect (POE)



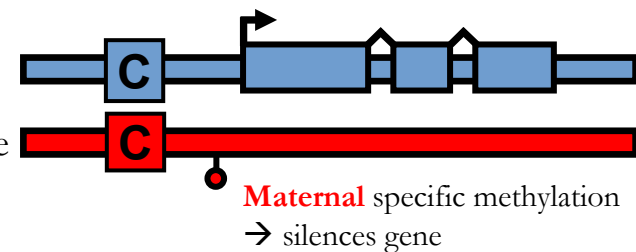
**Genomic imprinting:**  
Parent-specific  
mono-allelic expression

## Bi-allelic expression



Paternal haplotype

Maternal haplotype

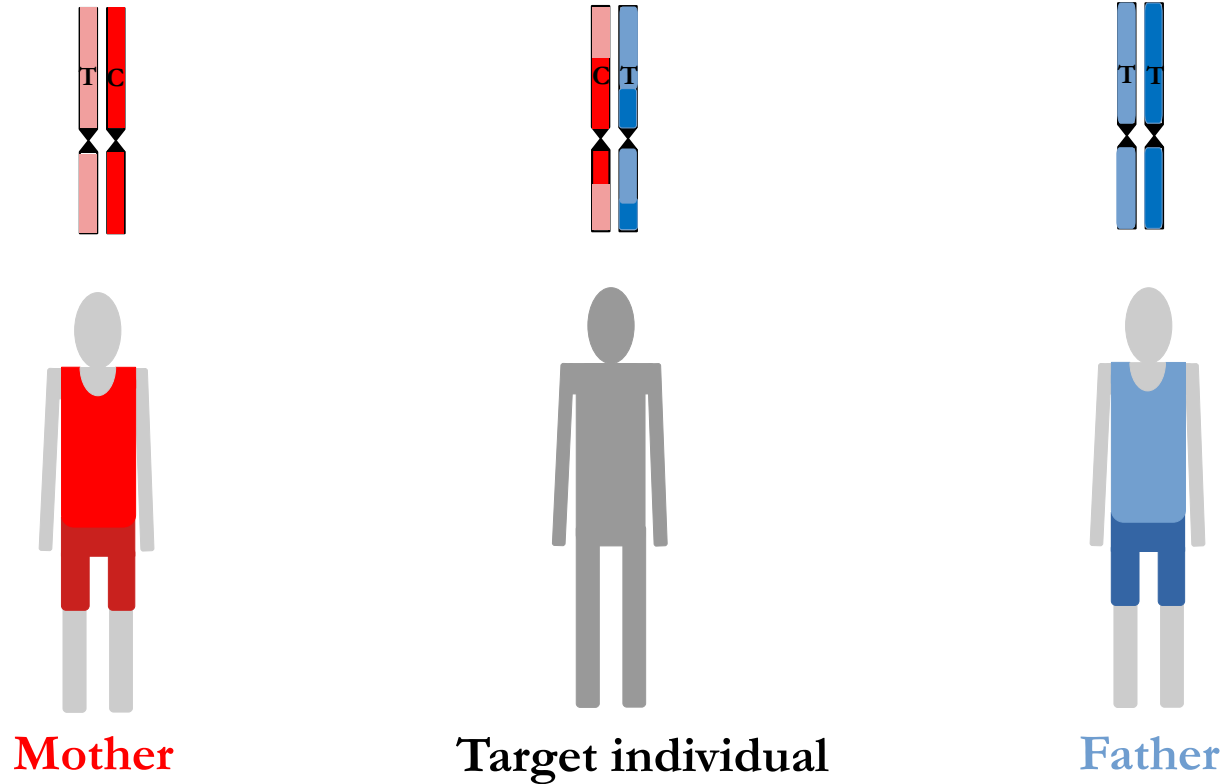


# How to infer the allele origins?

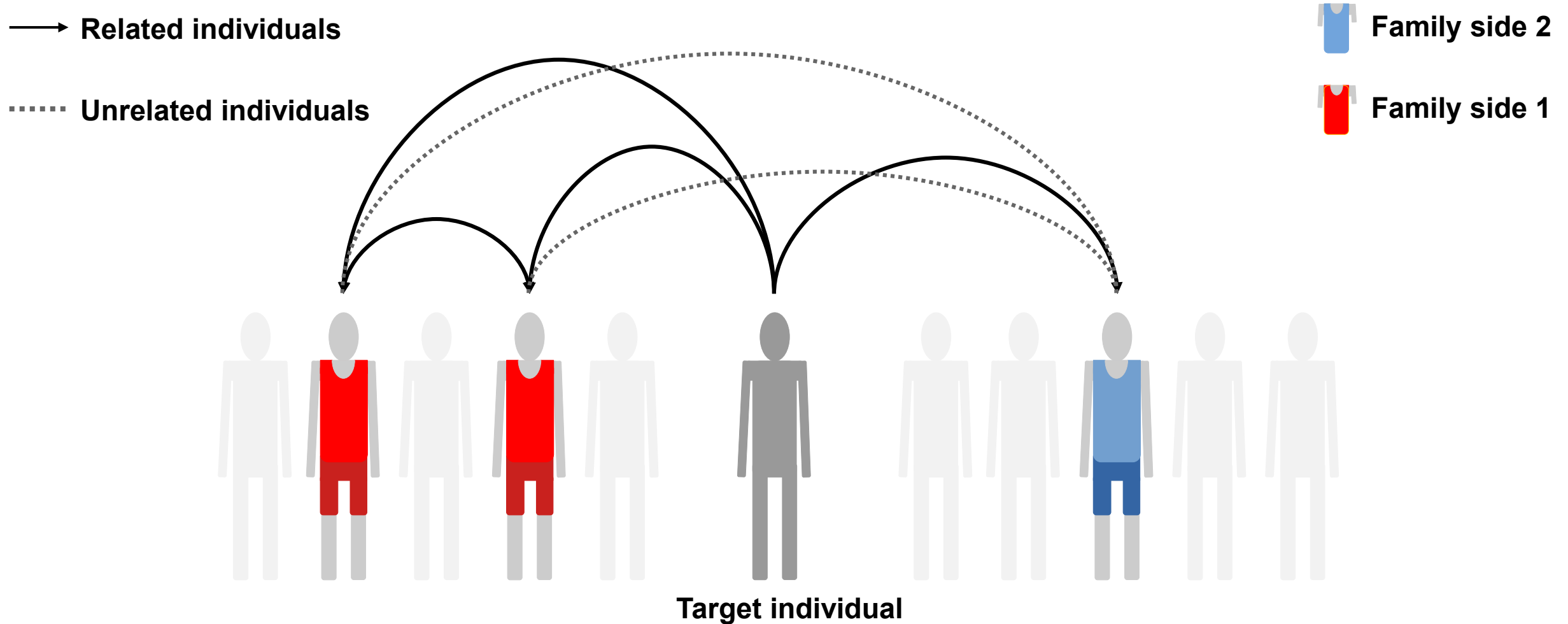


Target individual

# How to infer the haplotype origins?

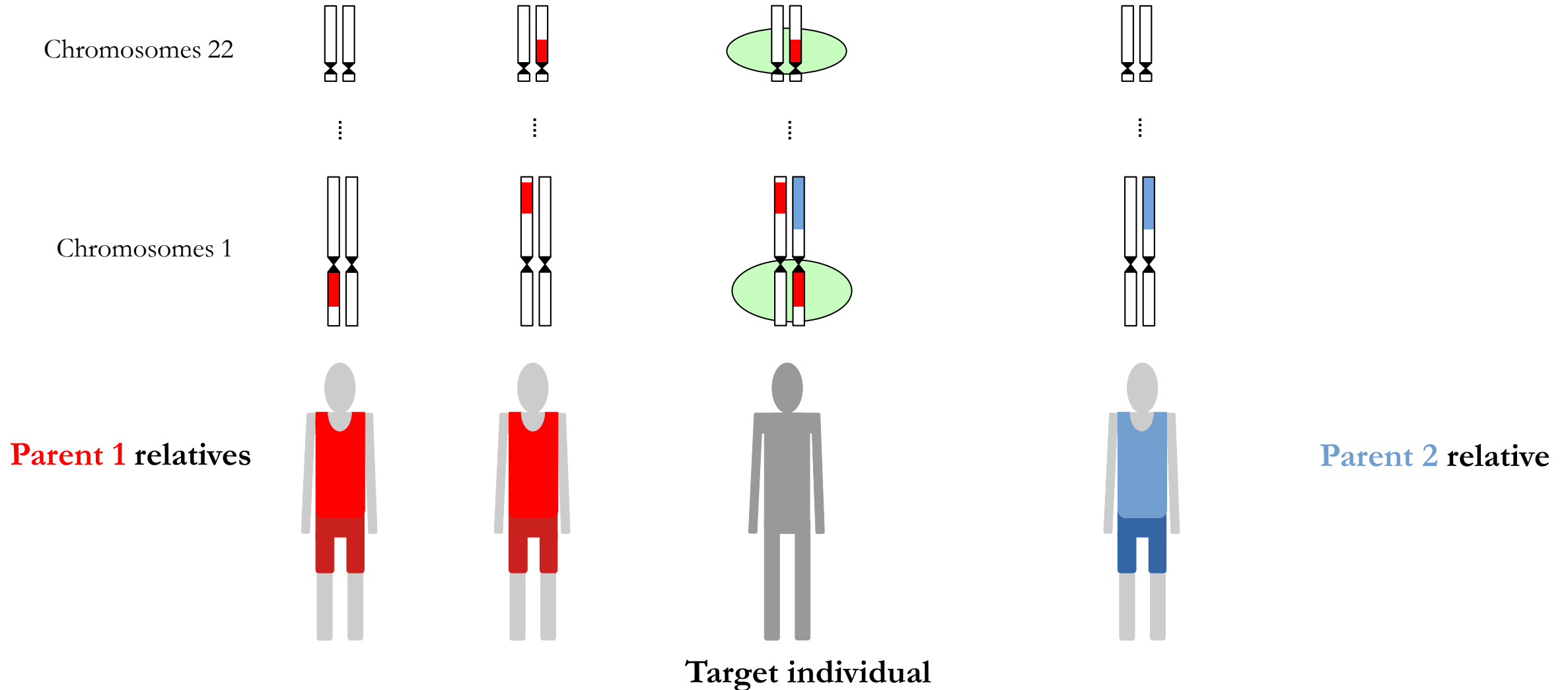


# What if we do not have parents?



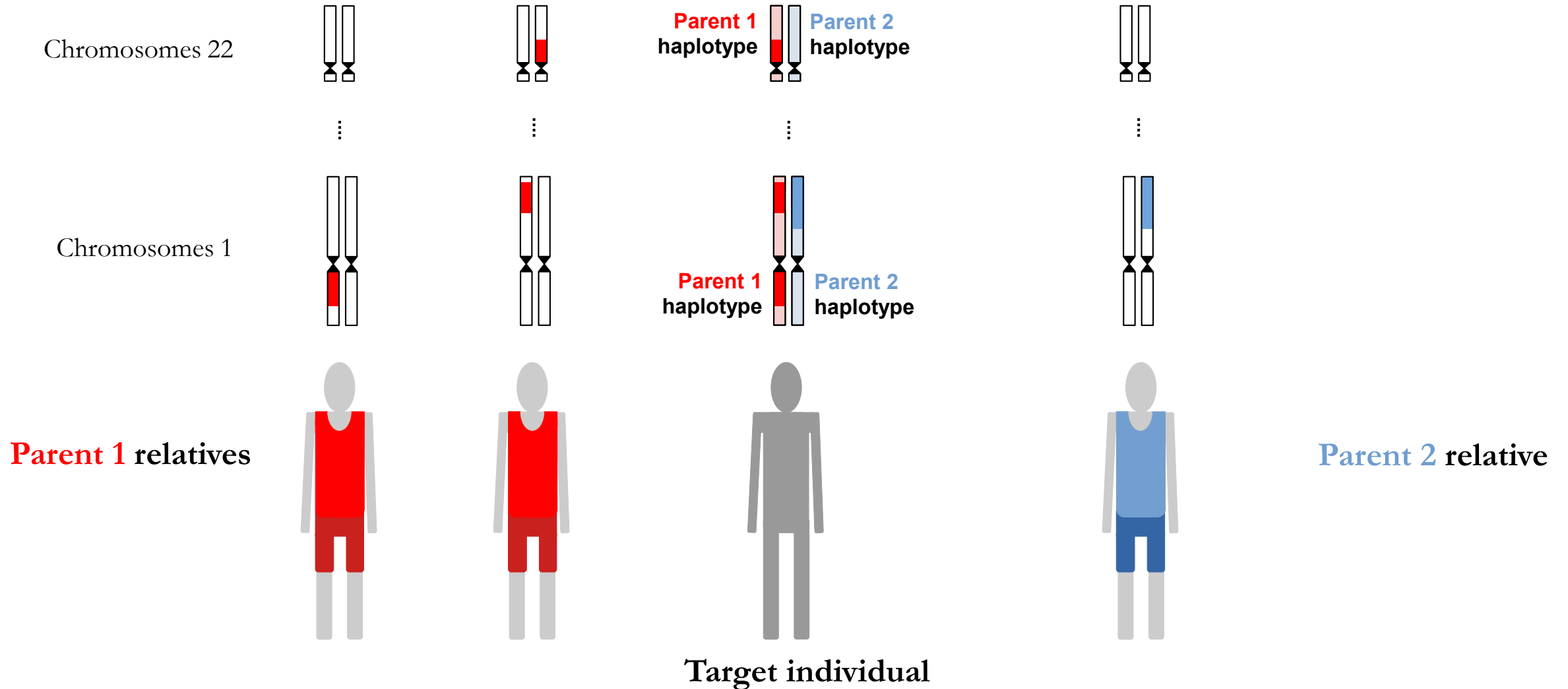
# Interchromosomal phasing

Identity-By-Descent (**IBD**) segments = inherited from a common ancestor

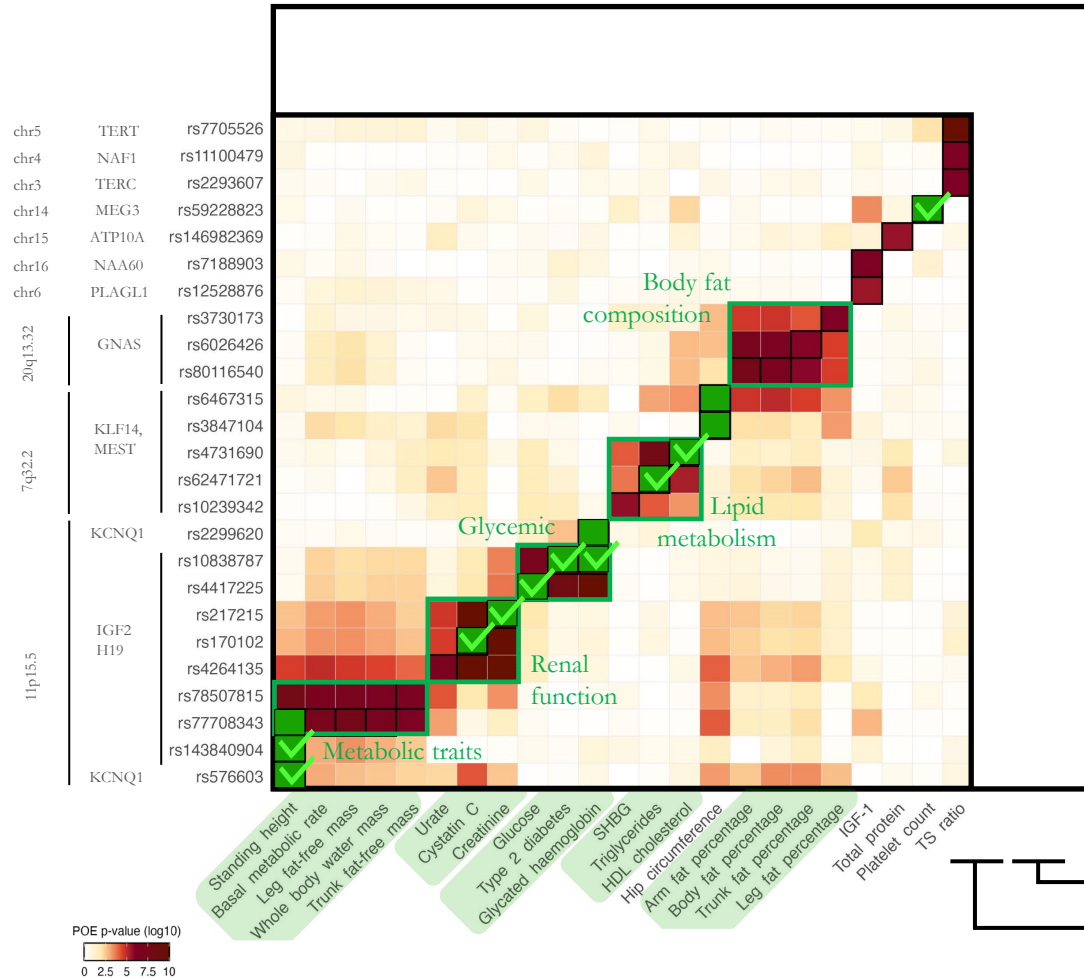


# Interchromosomal phasing

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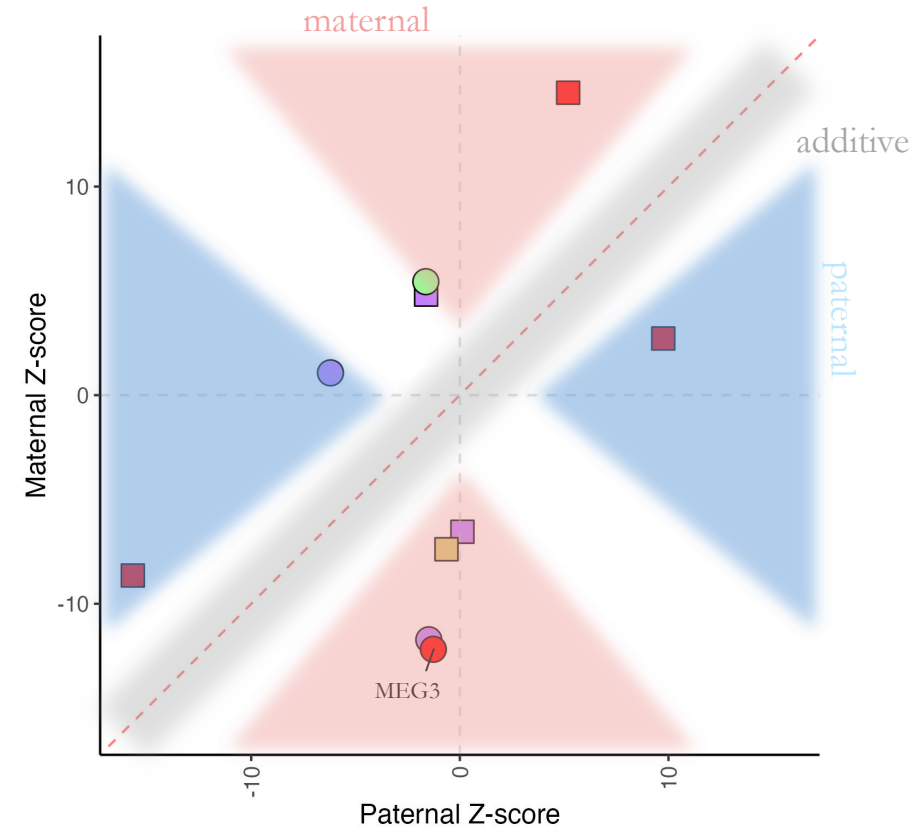
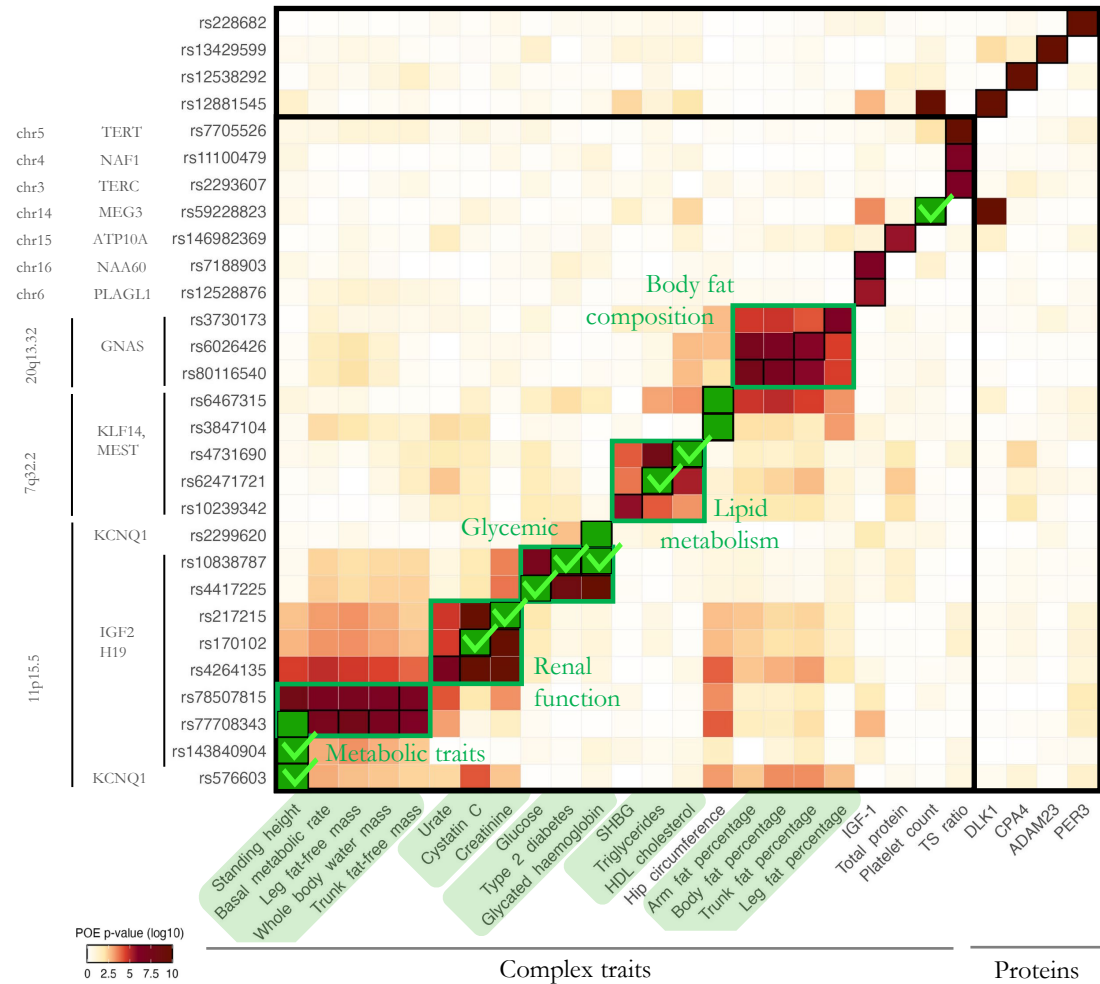
# Results overview



## Replication in 90,000 Estonian Biobank individuals:

- 14/30 POEs assessed (phenotypes are available in EstBB)
- >70% (10/14) replicated (60% of independent snp-trait pairs)

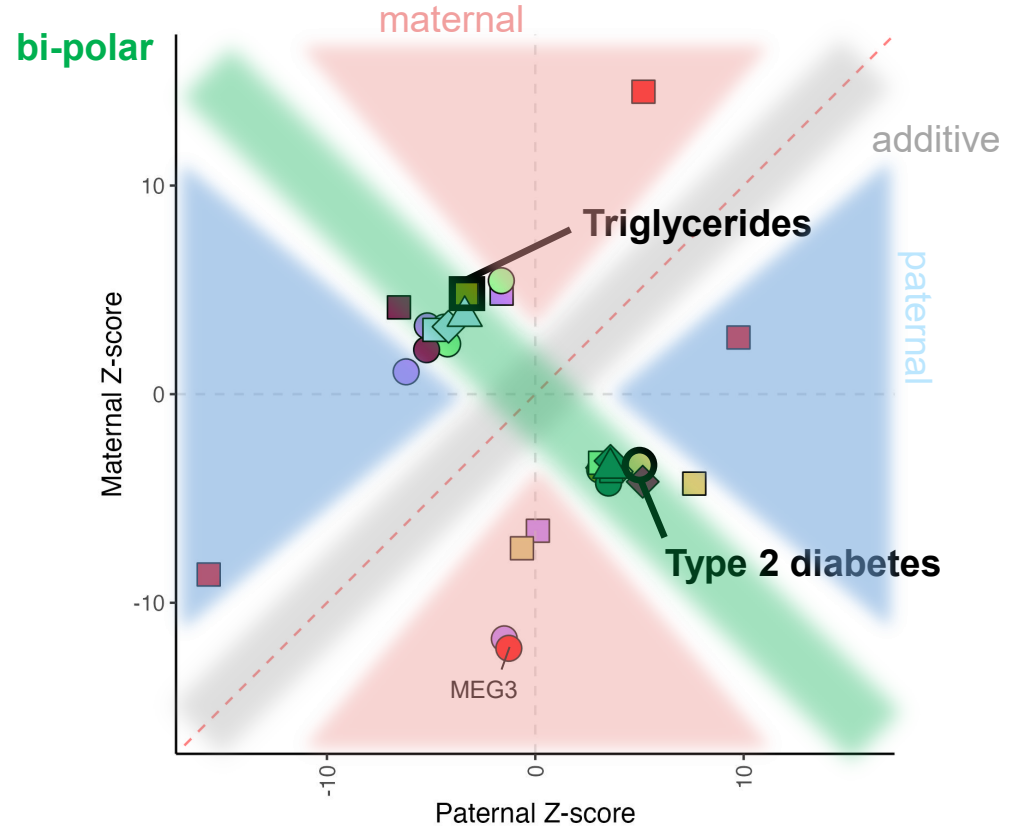
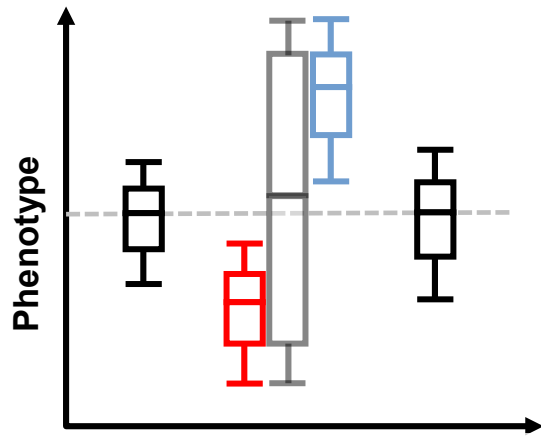
# Results overview



- Type 2 diabetes
- Glycated haemoglobin
- Glucose
- Basal metabolic rate
- Leg fat-free mass
- Whole body water mass
- Trunk fat-free mass
- Arm fat percentage
- Body fat percentage
- Trunk fat percentage
- Leg fat percentage
- Urate
- Cystatin C
- Creatinine
- HDL cholesterol
- Leg fat percentage
- Triglycerides
- SHBG
- Platelet count
- Total protein
- IGF-1

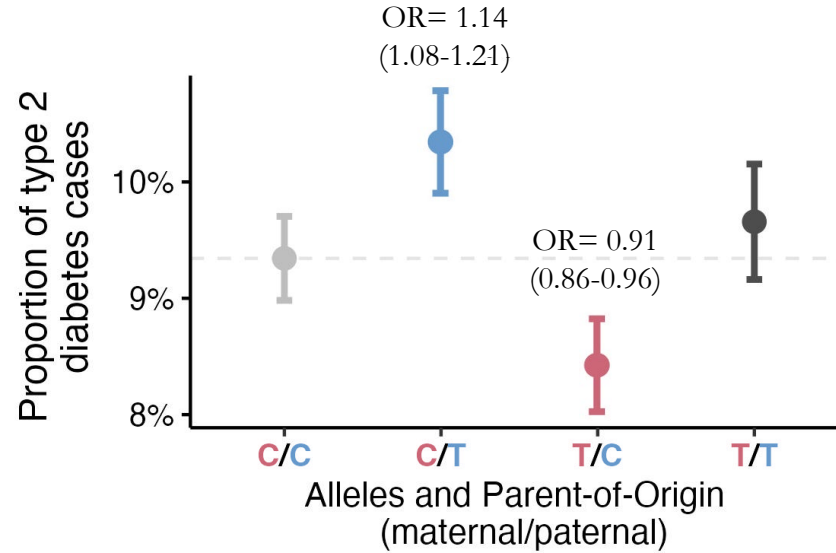
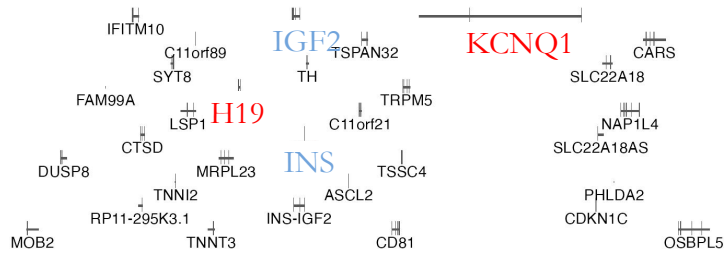
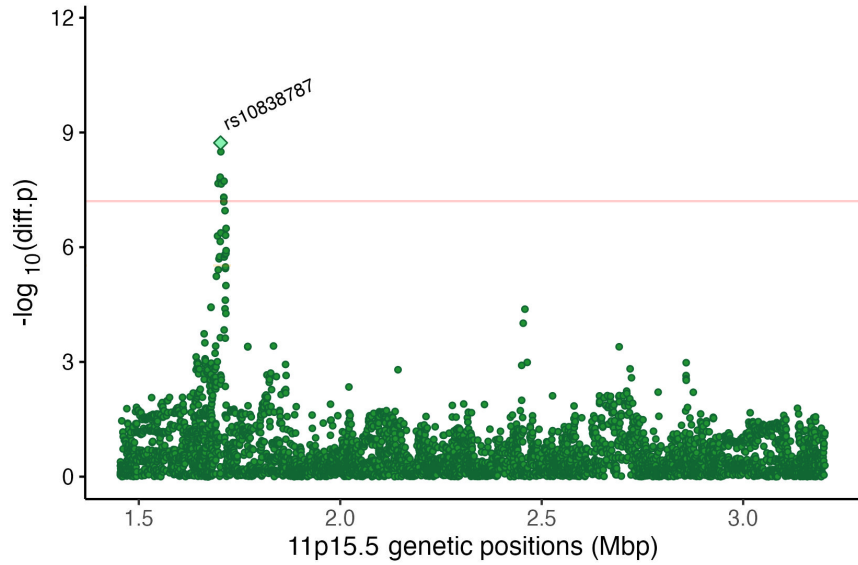
# Results overview

Bi-polar  
parent-of-origin effect



- Type 2 diabetes
- ◇ Whole body water mass
- ▲ Leg fat percentage
- Triglycerides
- Total protein
- Glycated haemoglobin
- △ Trunk fat-free mass
- Urate
- ◇ SHBG
- Platelet count
- ◇ Glucose
- Arm fat percentage
- Cystatin C
- ◇ Standing height
- TS ratio
- Basal metabolic rate
- Body fat percentage
- ◇ Creatinine
- Hip circumference
- Leg fat-free mass
- ◇ Trunk fat percentage
- HDL cholesterol
- IGF-1

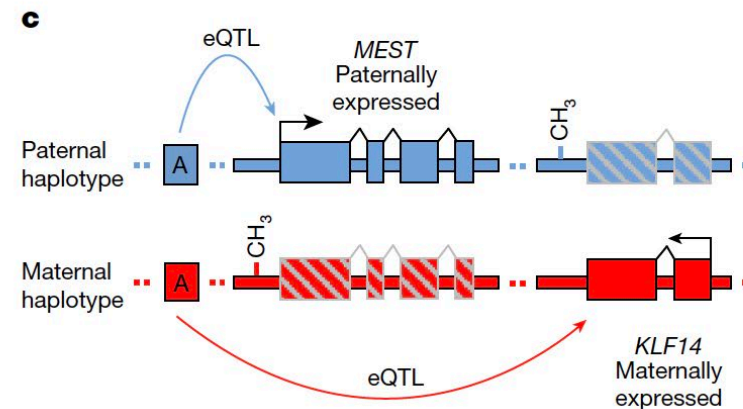
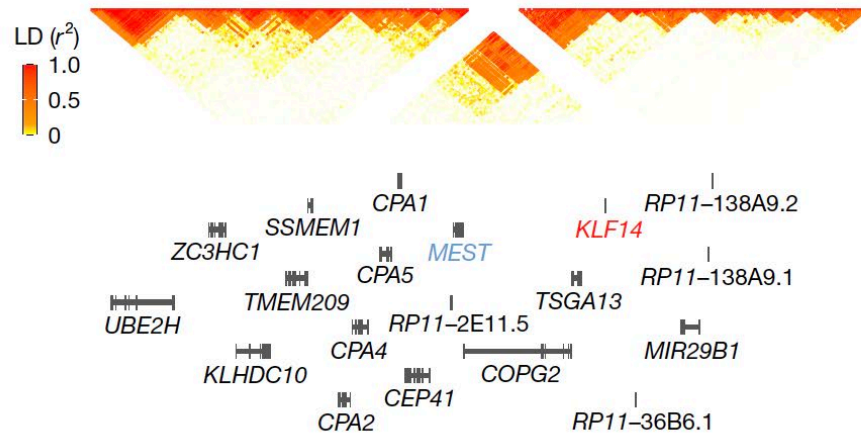
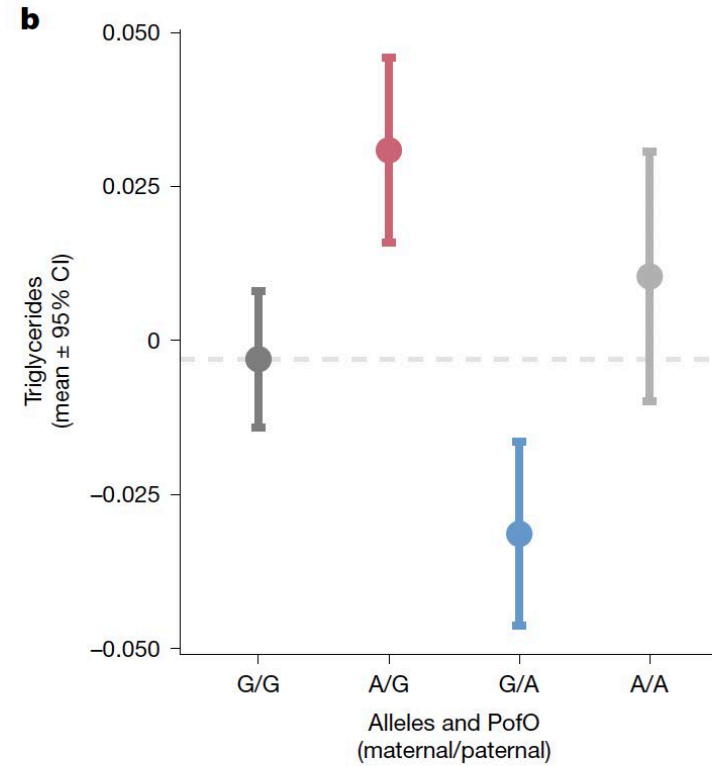
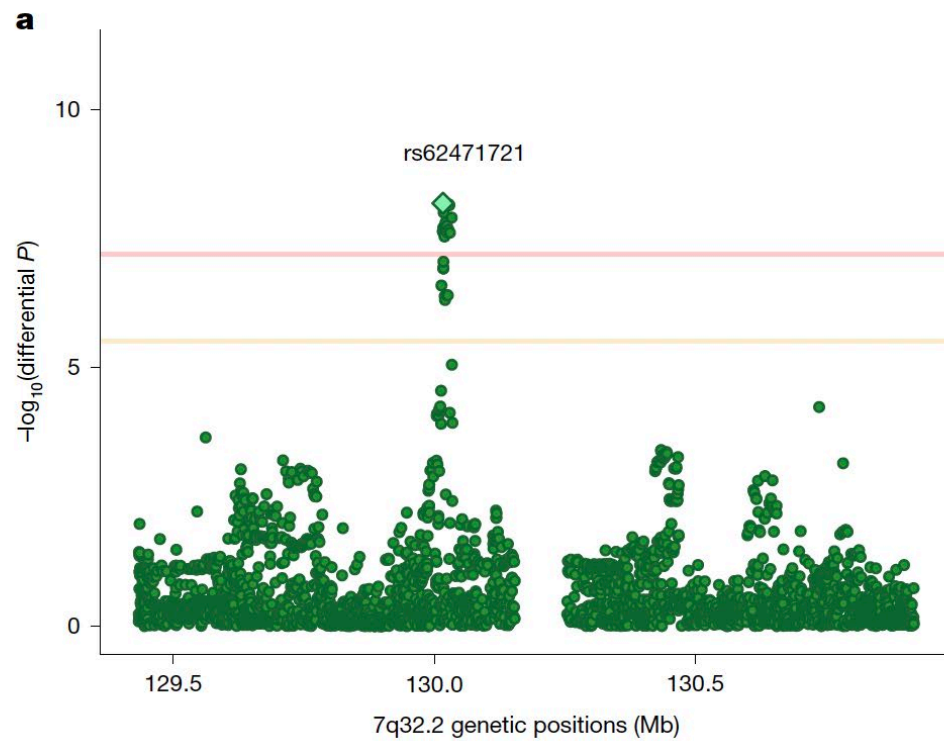
# Results: 11p15.5 & T2D



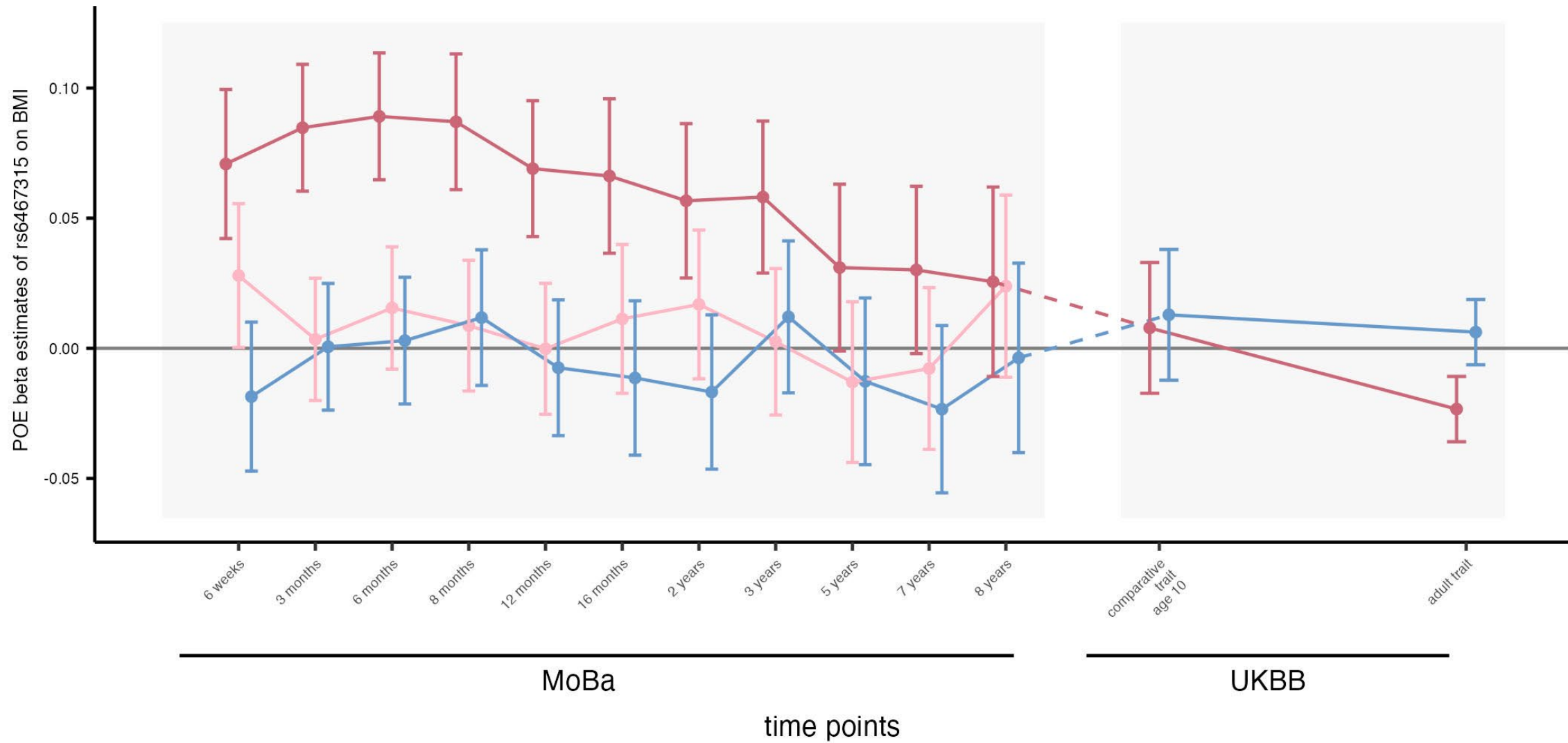
$$OR_{\text{pat vs. mat}} = 1.25$$

Compared to OR ~ 1.4 for the strongest SNP effect on T2D (TCF7L2)

# POE: hinting mechanisms at 7q32.2



# POE across life course: BMI

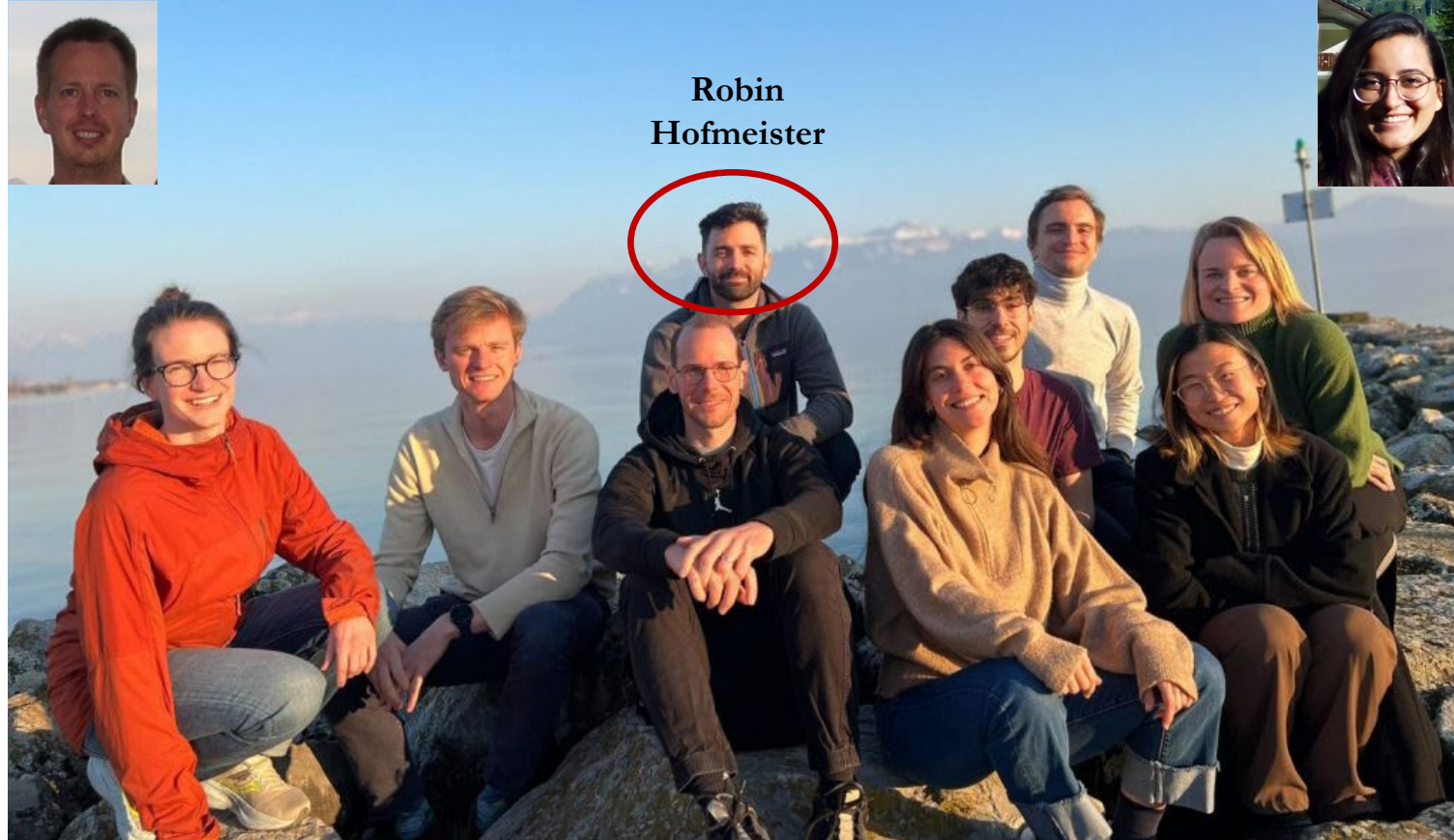


# Acknowledgements

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## Statistical Genetics Group

Liza  
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Lili Milani (POE)



University of Bergen  
Stefan Johansson (POE)

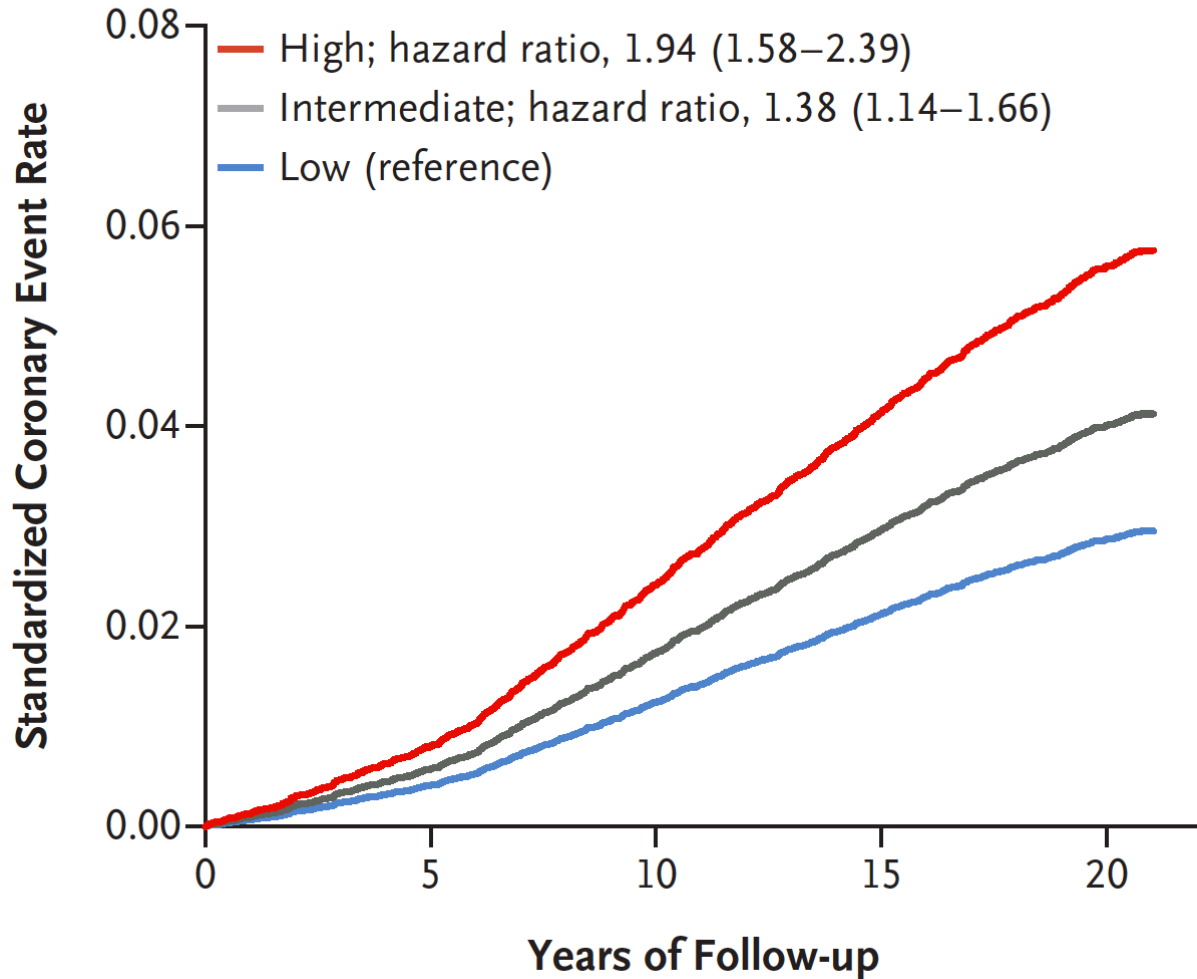


# Supplementary slides

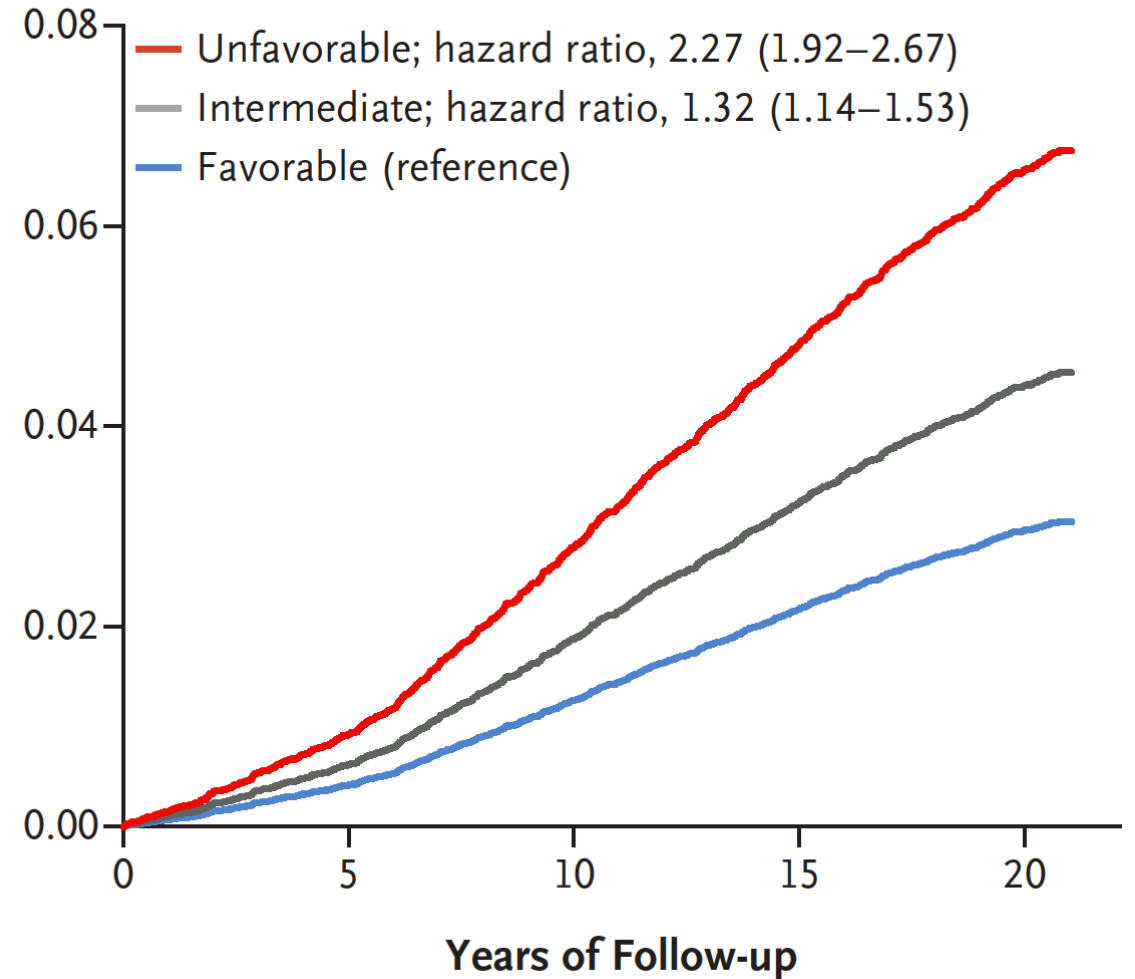
# Predicting coronary events

## Women's Genome Health Study

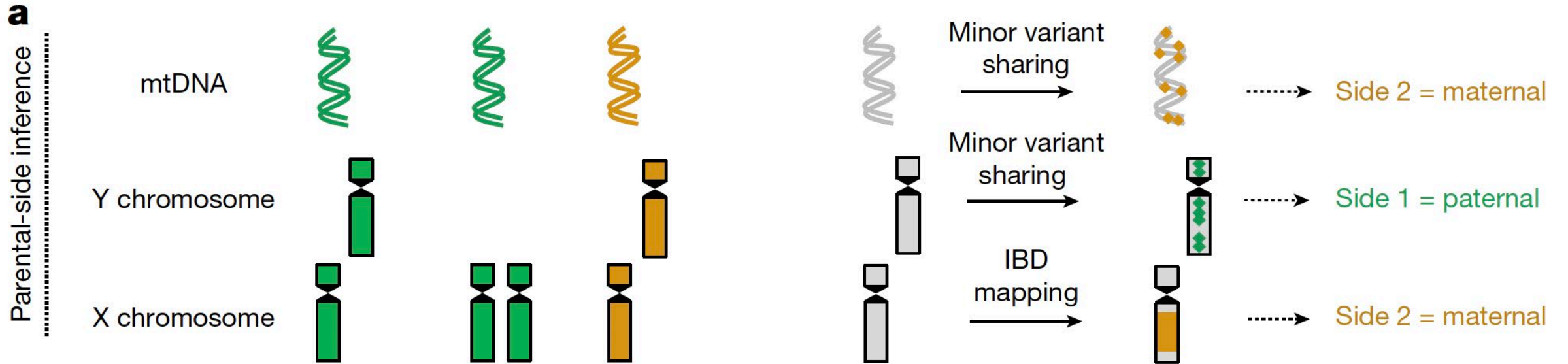
### Genetic Risk



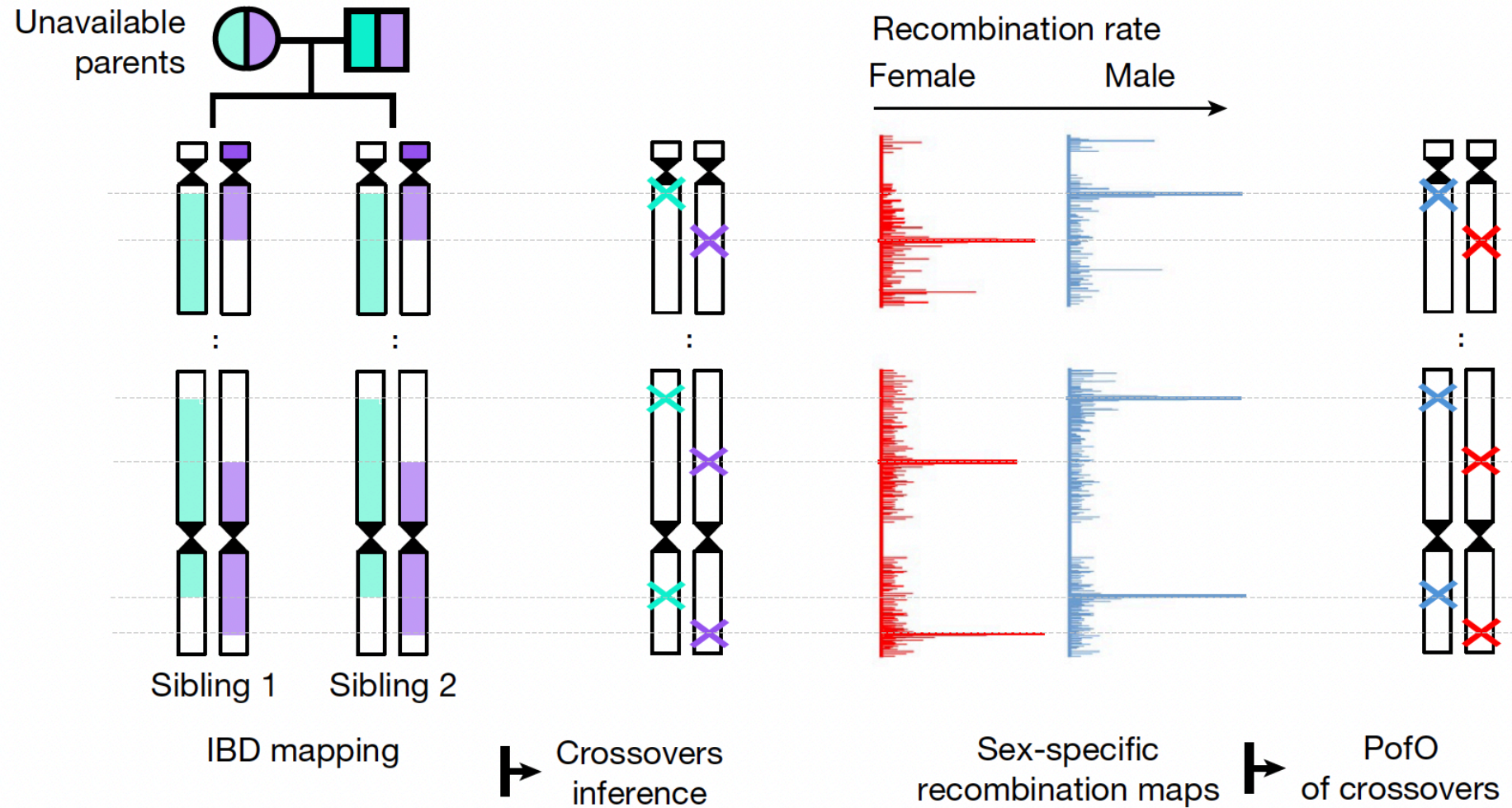
### Lifestyle Risk



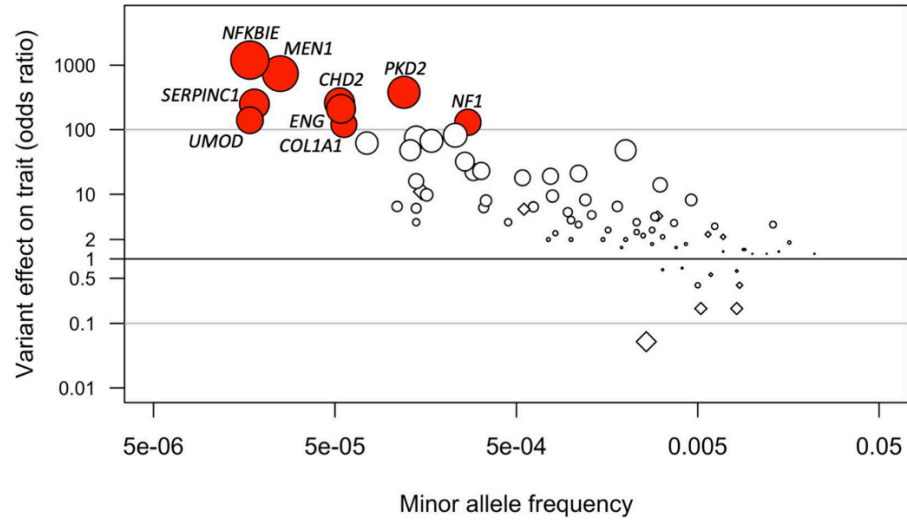
# Which parent?



# What about siblings?



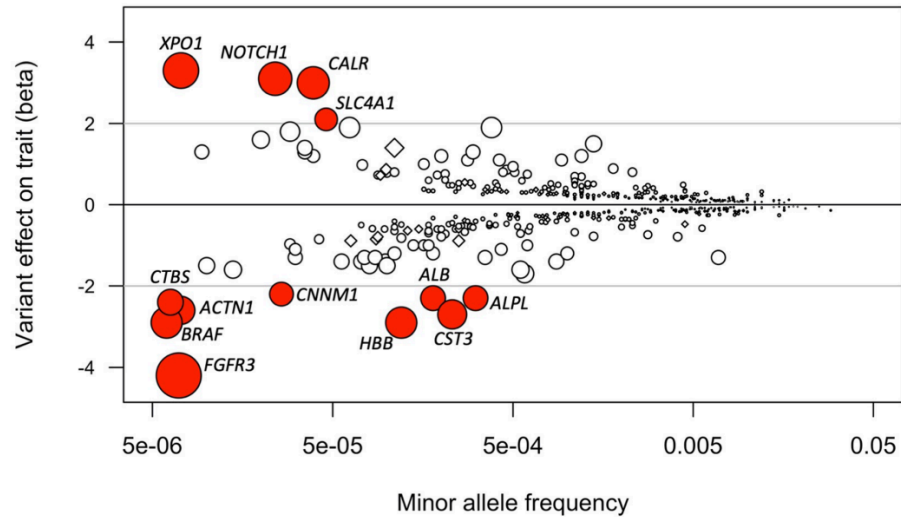
**a 80 genes for which the lead association was with a binary trait**



**Genes with an odds ratio >100:**

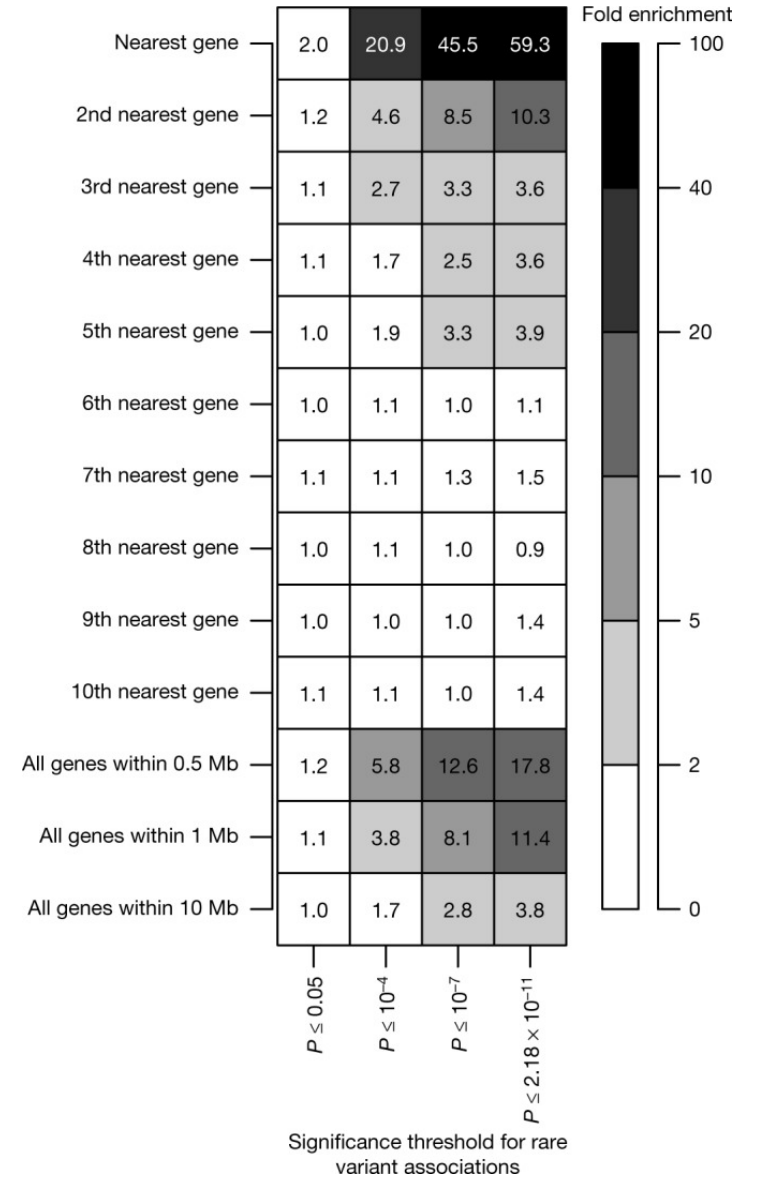
Gene	Most associated binary trait
<i>CHD2</i>	Chronic lymphocytic leukemia of B-cell type
<i>COL1A1</i>	Bone disorder
<i>ENG</i>	Hereditary hemorrhagic telangiectasia
<i>MEN1</i>	Hyperparathyroidism
<i>NF1</i>	Benign neoplasm of peripheral nerves
<i>NFKBIE</i>	Chronic lymphocytic leukemia of B-cell type
<i>PKD2</i>	Cystic kidney disease
<i>SERPINC1</i>	Coagulation defects
<i>UMOD</i>	Chronic kidney disease

**b 484 genes for which the lead association was with a quantitative trait**

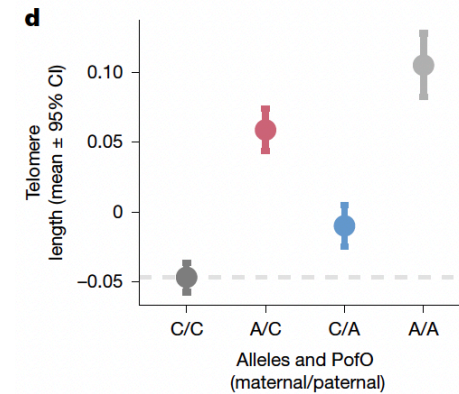
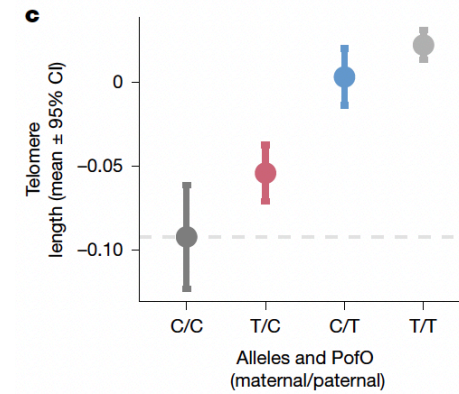
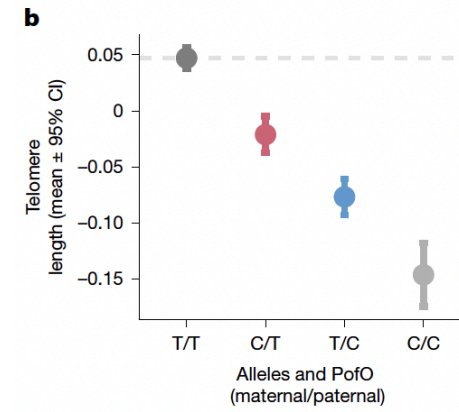
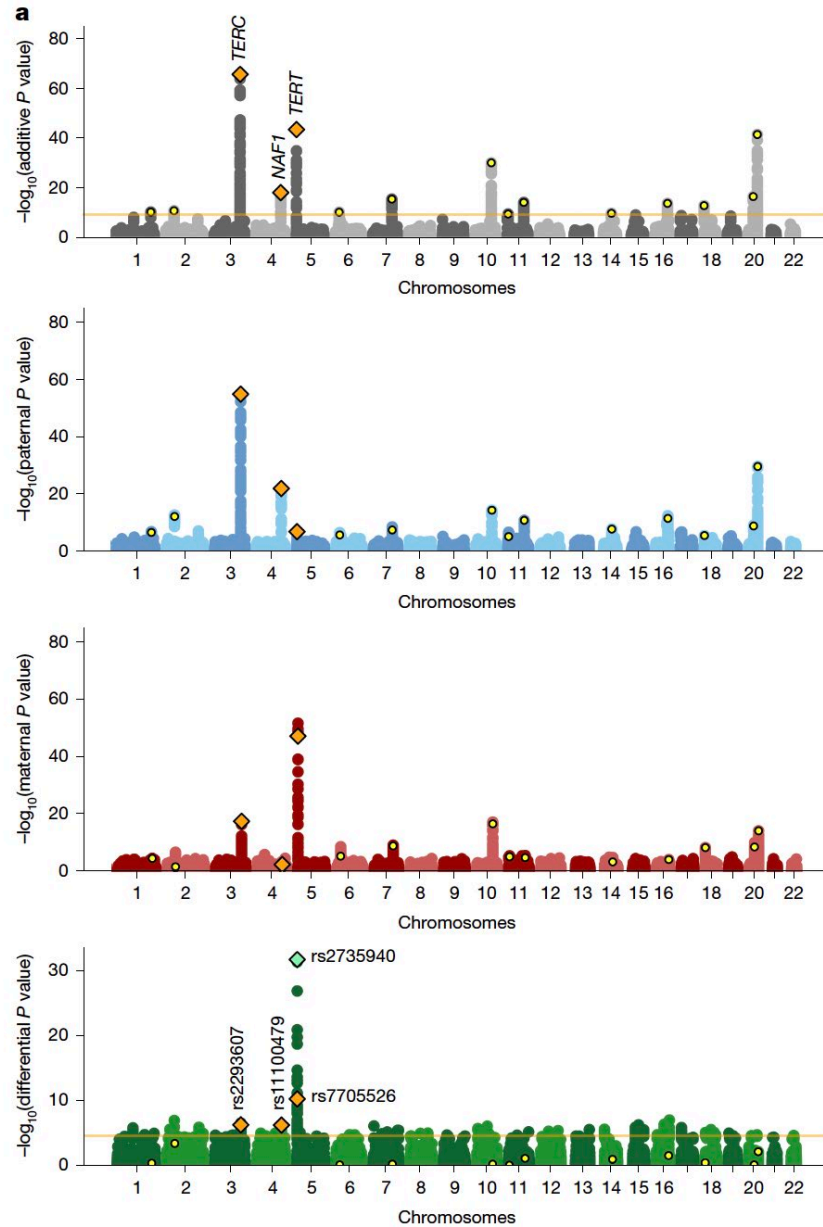


**Genes with leffectl >2:**

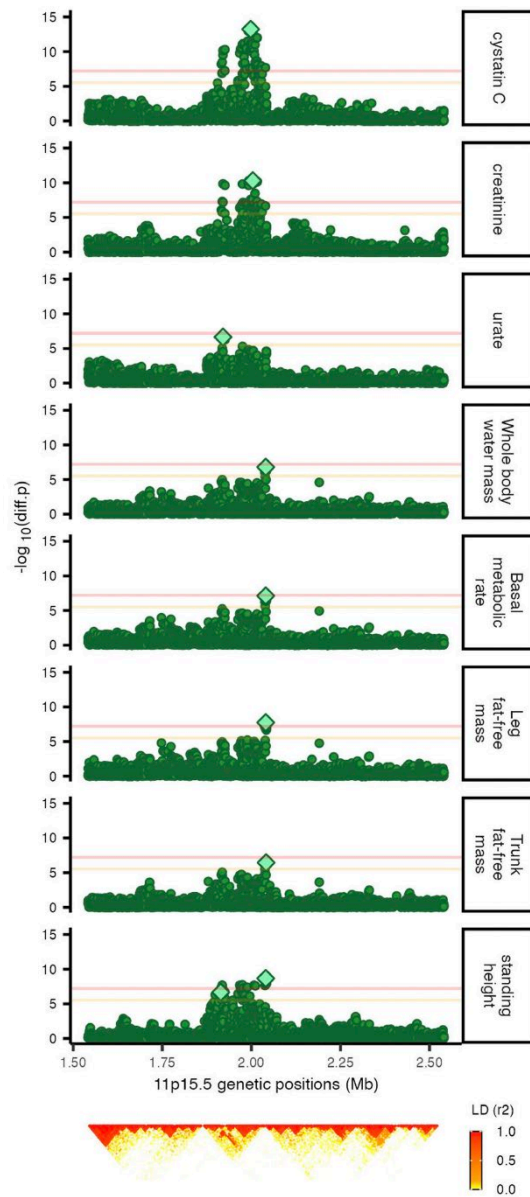
Gene	Most associated quantitative trait
<i>ACTN1</i>	Platelet count
<i>ALB</i>	Albumin
<i>ALPL</i>	Alkaline phosphatase
<i>BRAF</i>	Neutrophil count
<i>CALR</i>	Platelet count
<i>CNNM1</i>	Aspartate aminotransferase
<i>CST3</i>	Cystatin C
<i>CTBS</i>	Peak expiratory flow
<i>FGFR3</i>	Height
<i>HBB</i>	Mean corpuscular volume
<i>NOTCH1</i>	Lymphocyte count
<i>SLC4A1</i>	Reticulocyte percentage
<i>XPO1</i>	Lymphocyte count



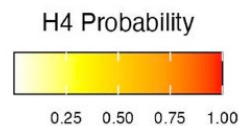
# Whole genome results: telomere length



# POE: pleiotropy



standing height	0	0	0.3	0.93	0.94	0.95	0.92	1
Trunk fat-free mass	0	0.01	0.41	0.94	0.94	0.93	1	0.92
Leg fat-free mass	0	0.01	0.27	0.95	0.96	1	0.93	0.95
Basal metabolic rate	0.01	0.02	0.38	0.95	1	0.96	0.94	0.94
Whole body water mass	0.01	0.02	0.38	1	0.95	0.95	0.94	0.93
urate	0.47	0.81	1	0.38	0.38	0.27	0.41	0.3
creatinine	0.92	1	0.81	0.02	0.02	0.01	0.01	0
cystatin C	1	0.92	0.47	0.01	0.01	0	0	0
	cystatin C	creatinine	urate	Whole body water mass	Basal metabolic rate	Leg fat-free mass	Trunk fat-free mass	standing height



# POE across life course: height

a.

