

Coordinated Epistasis Reveals Symptom-Driven Pathways Towards Major Depressive Disorder

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Myshok, Andrew Schork, Andrew Dahl, Na Cai

Major Depressive Disorder (MDD)

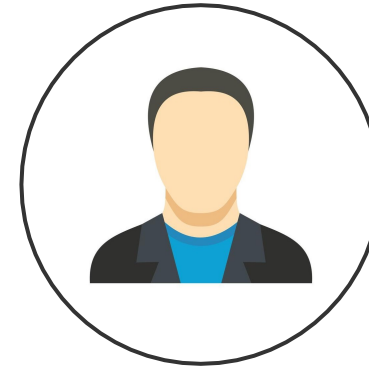
5 out of *14* symptoms for a duration of two weeks,
including either depressed mood or anhedonia

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including either depressed mood or anhedonia

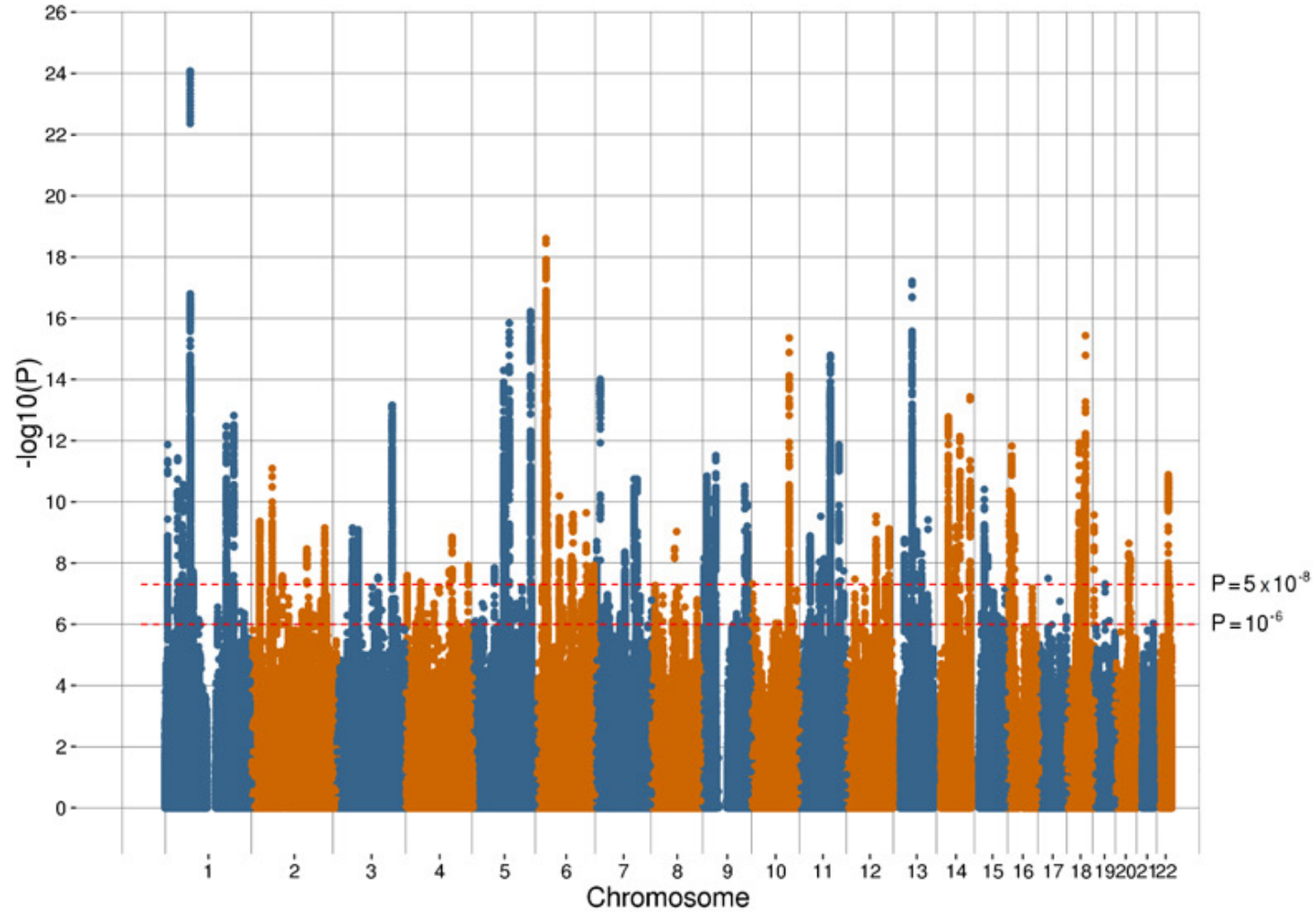


Depressed mood
Weight loss
Waking too early
Feeling worthless
Lost focus



Loss of joy
Weight gain
Insomnia
Fatigue
Suicidal ideation

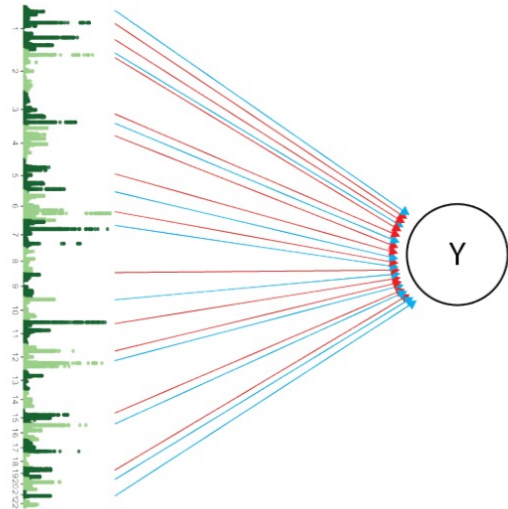
Complex and polygenic



To identify polygenic pathway
leading to MDD

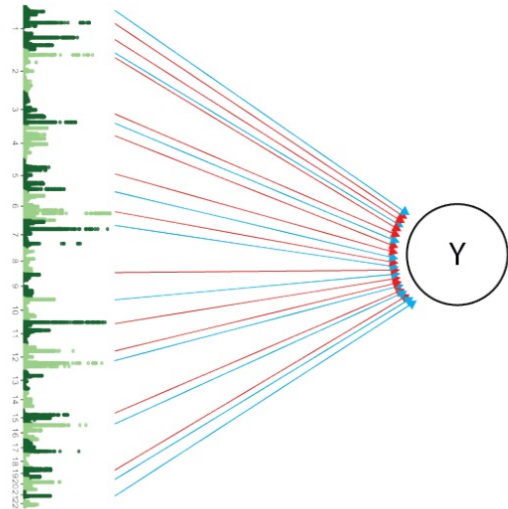
additive

a.



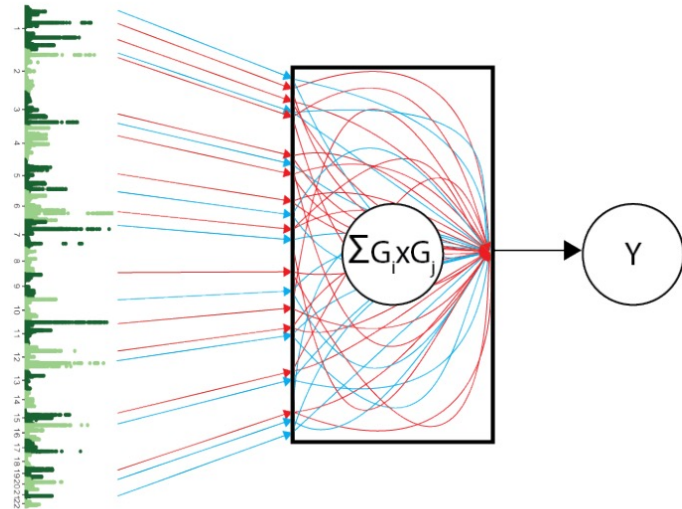
additive

a.

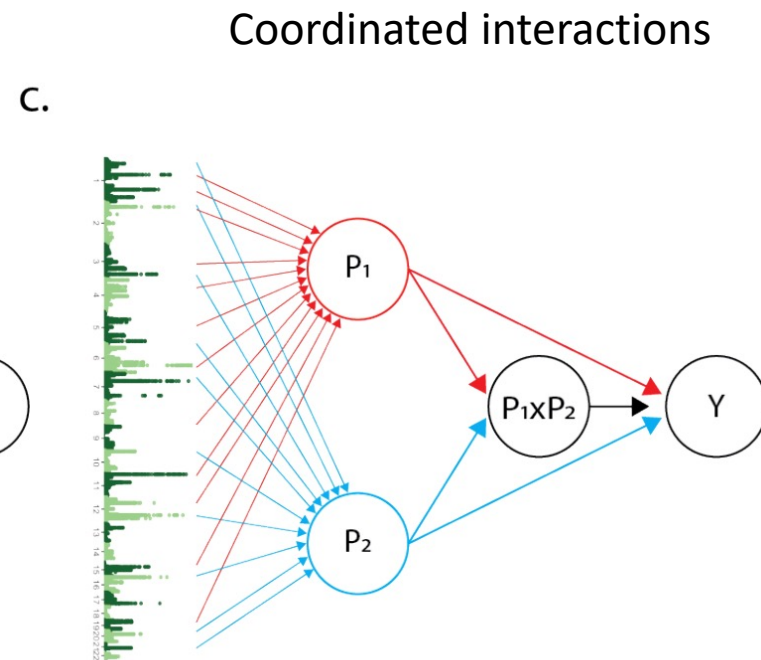
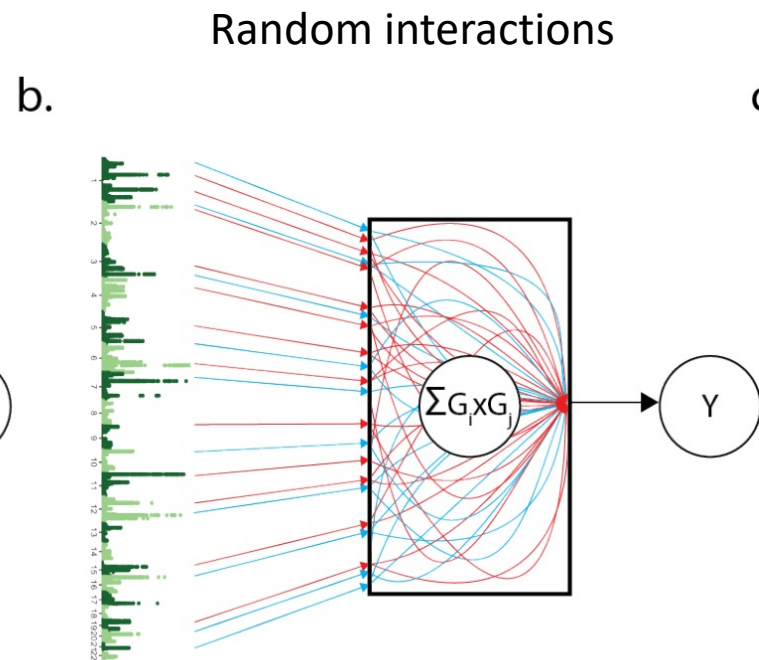
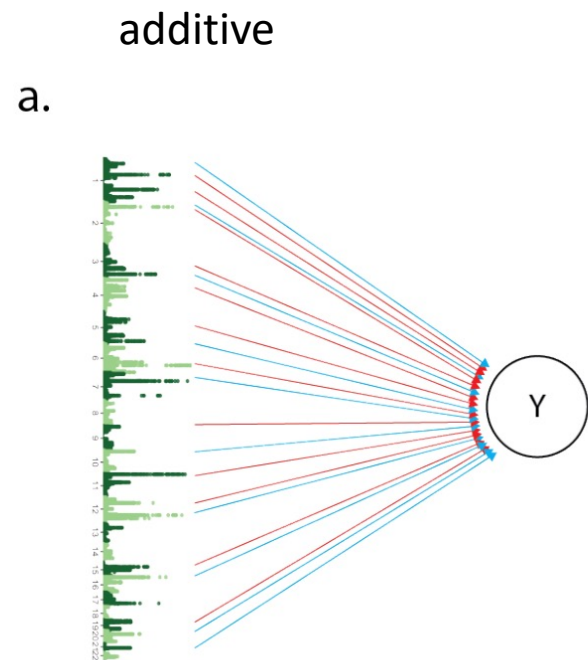


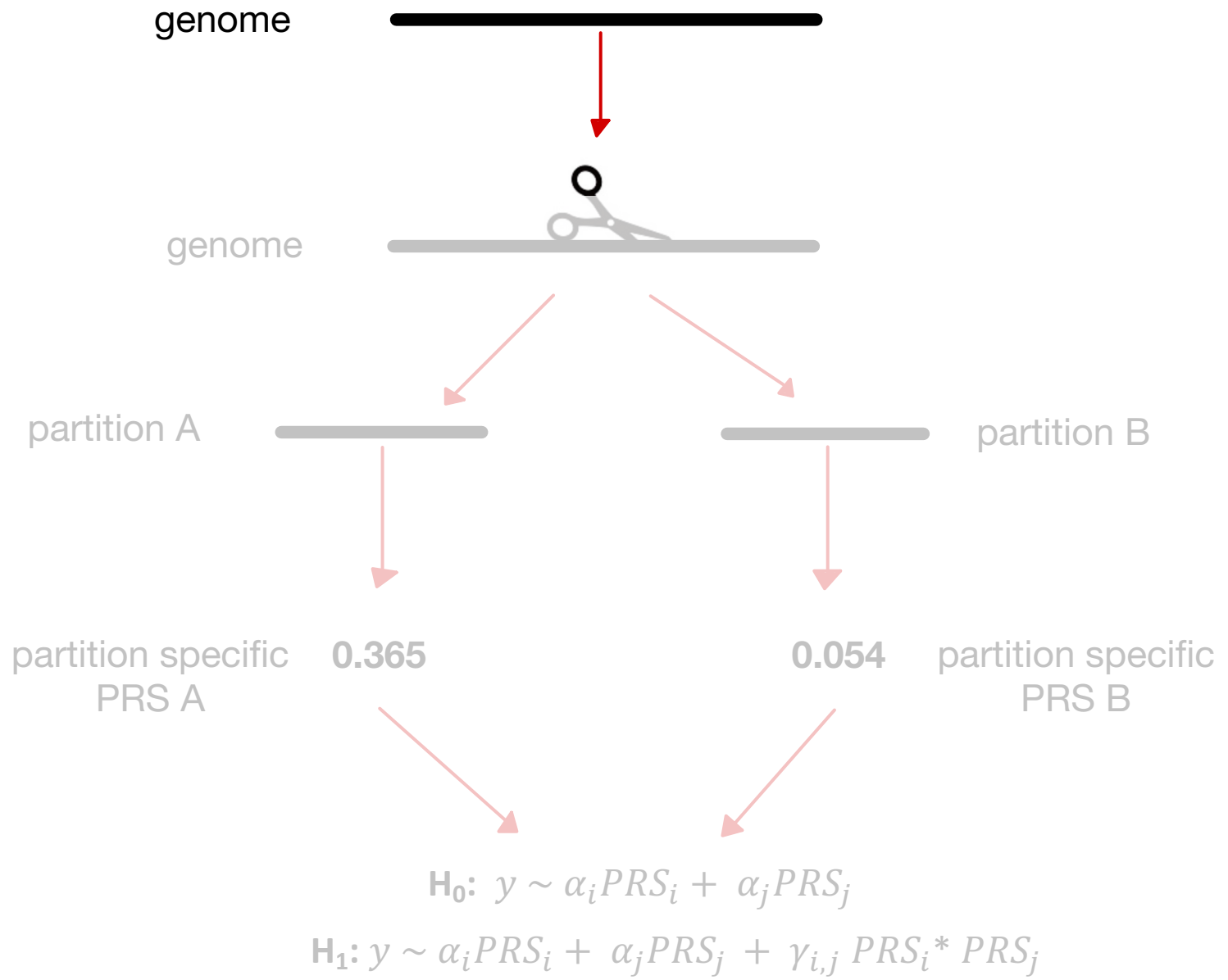
Random interactions

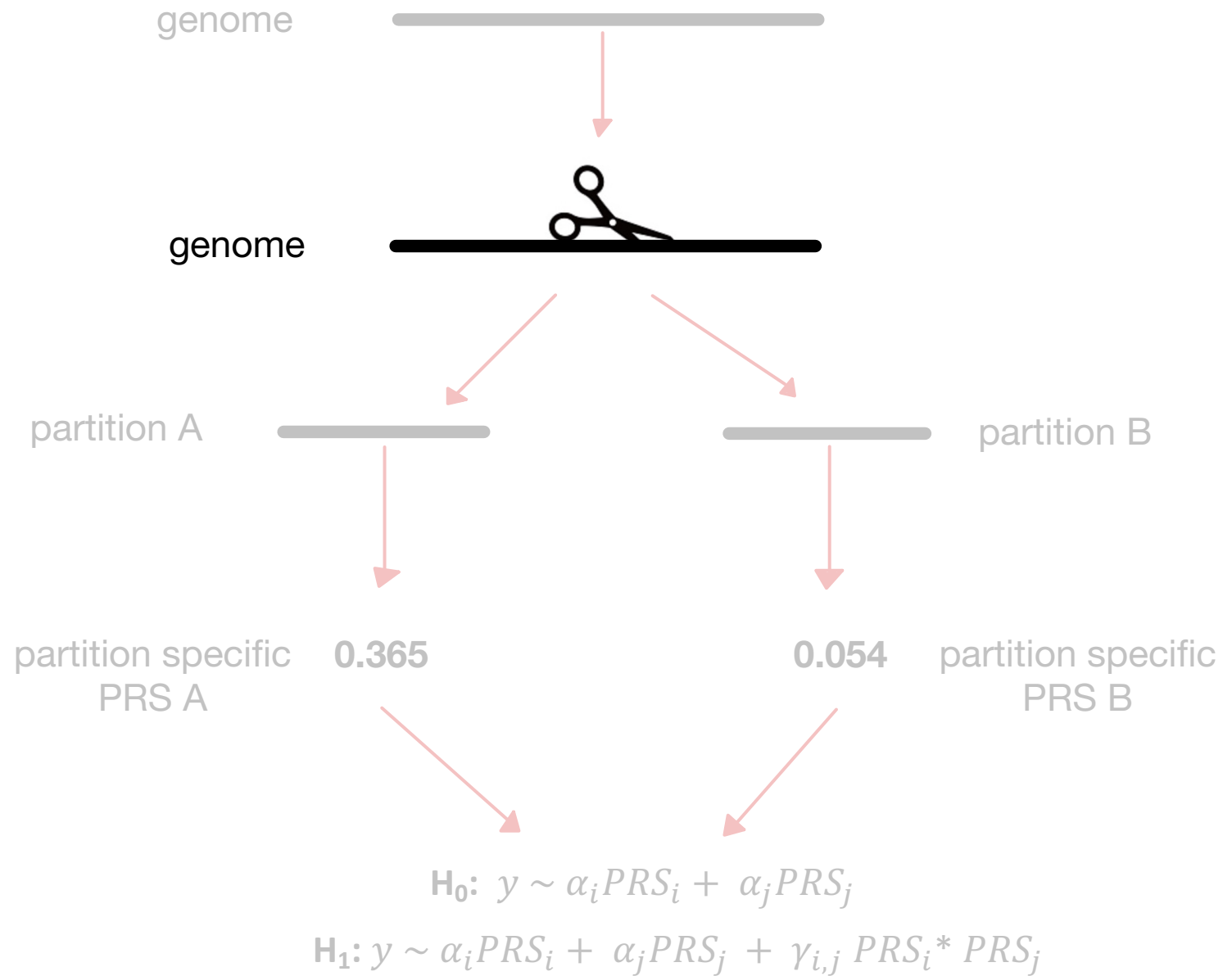
b.

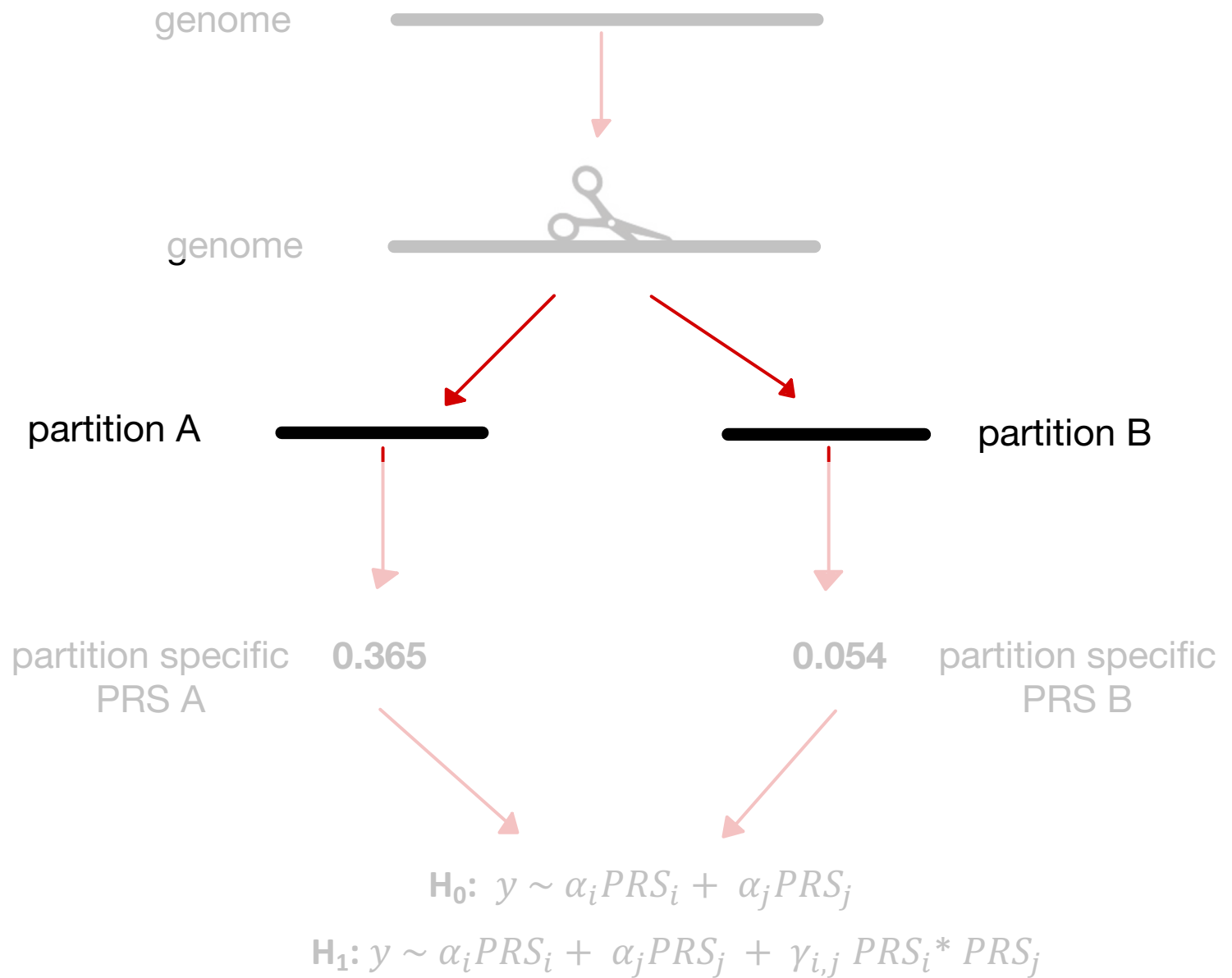


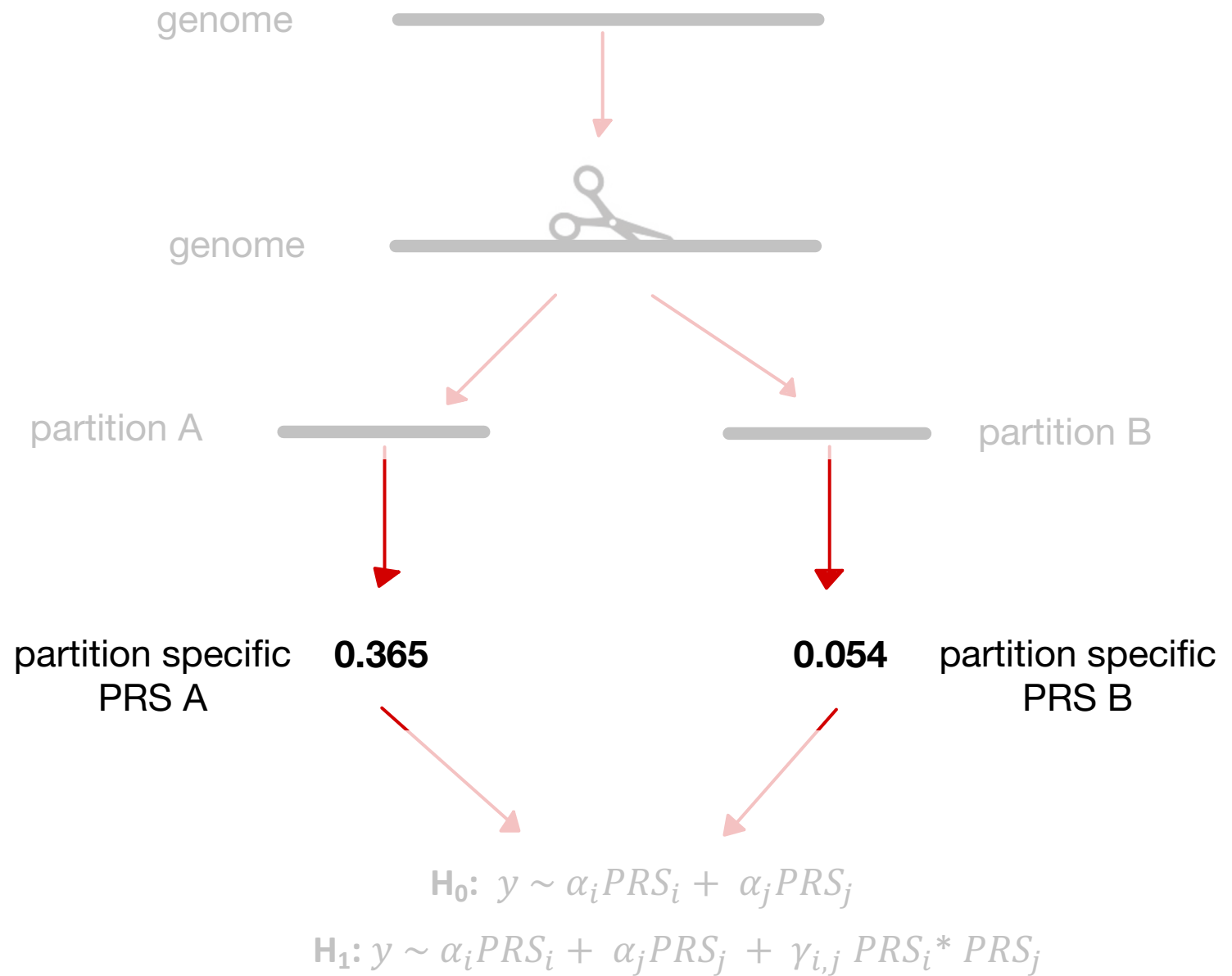
c.

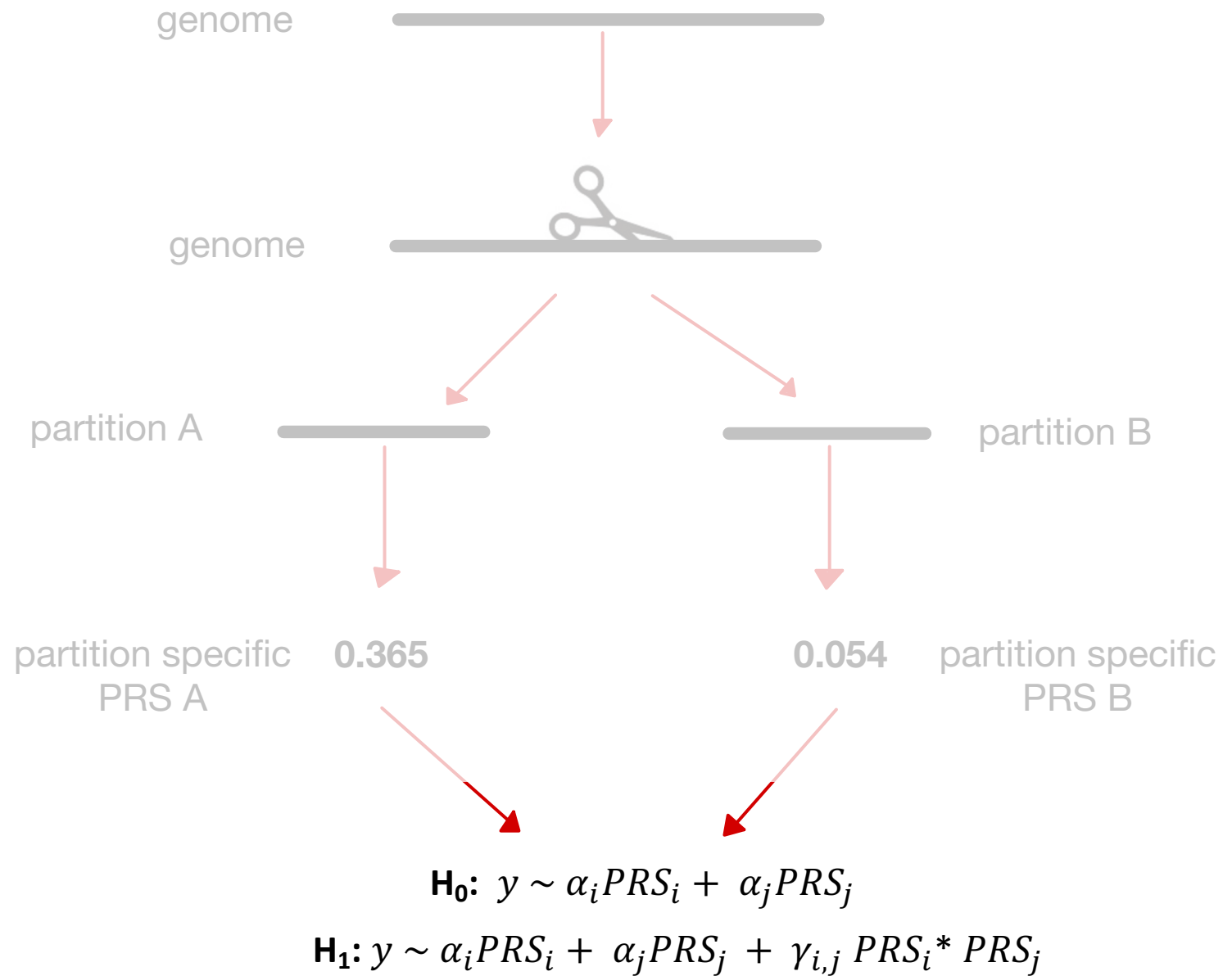


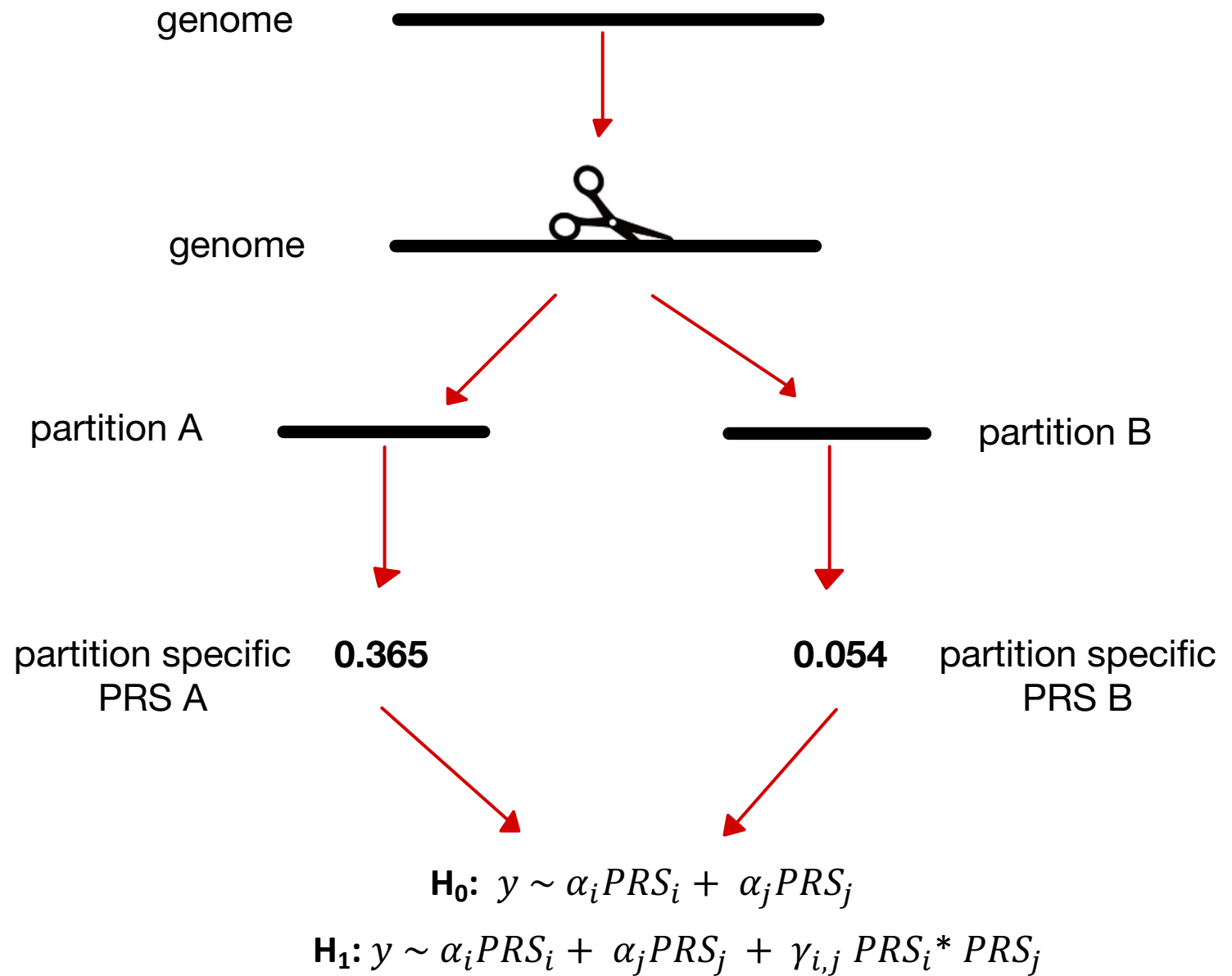


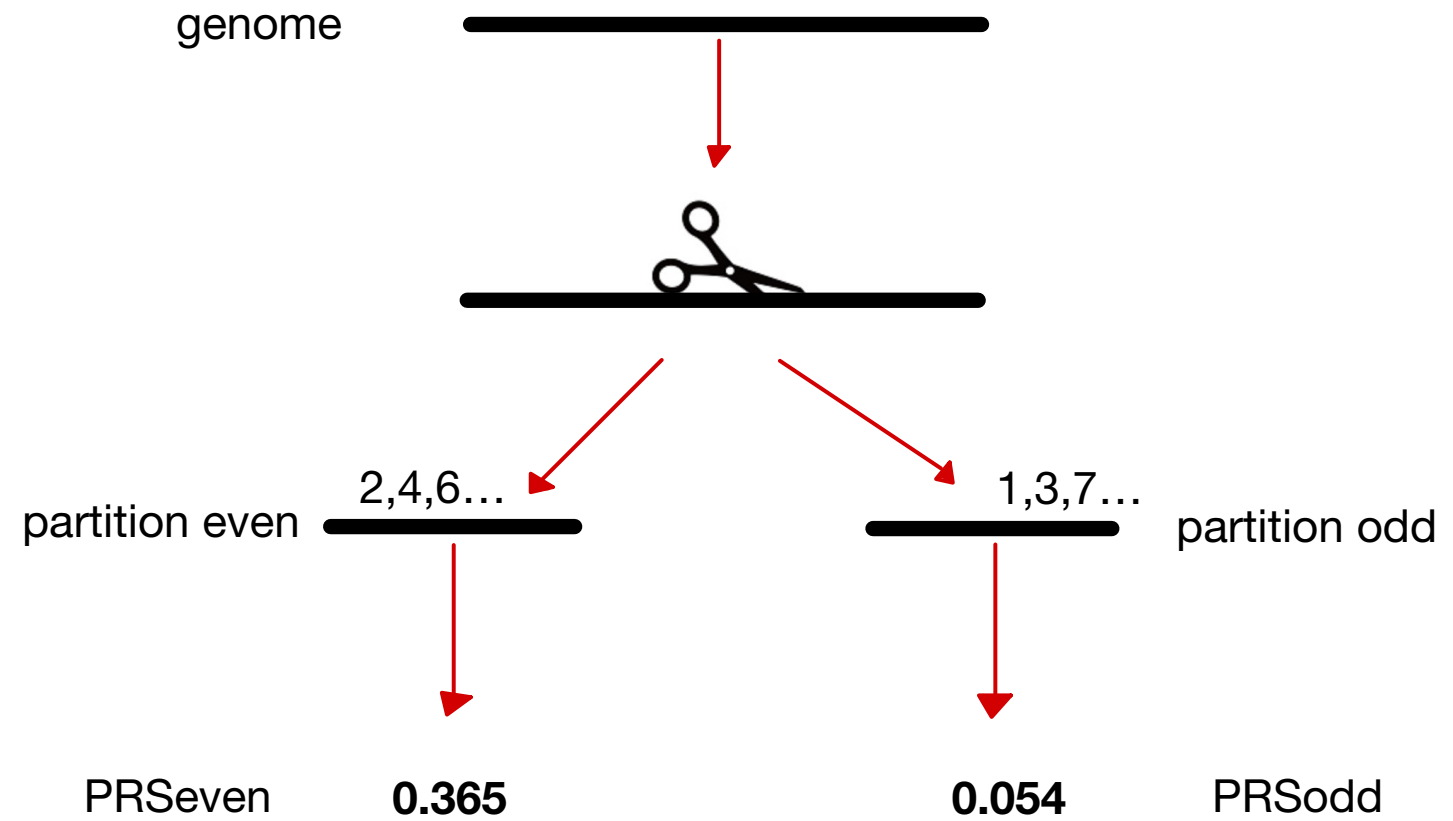




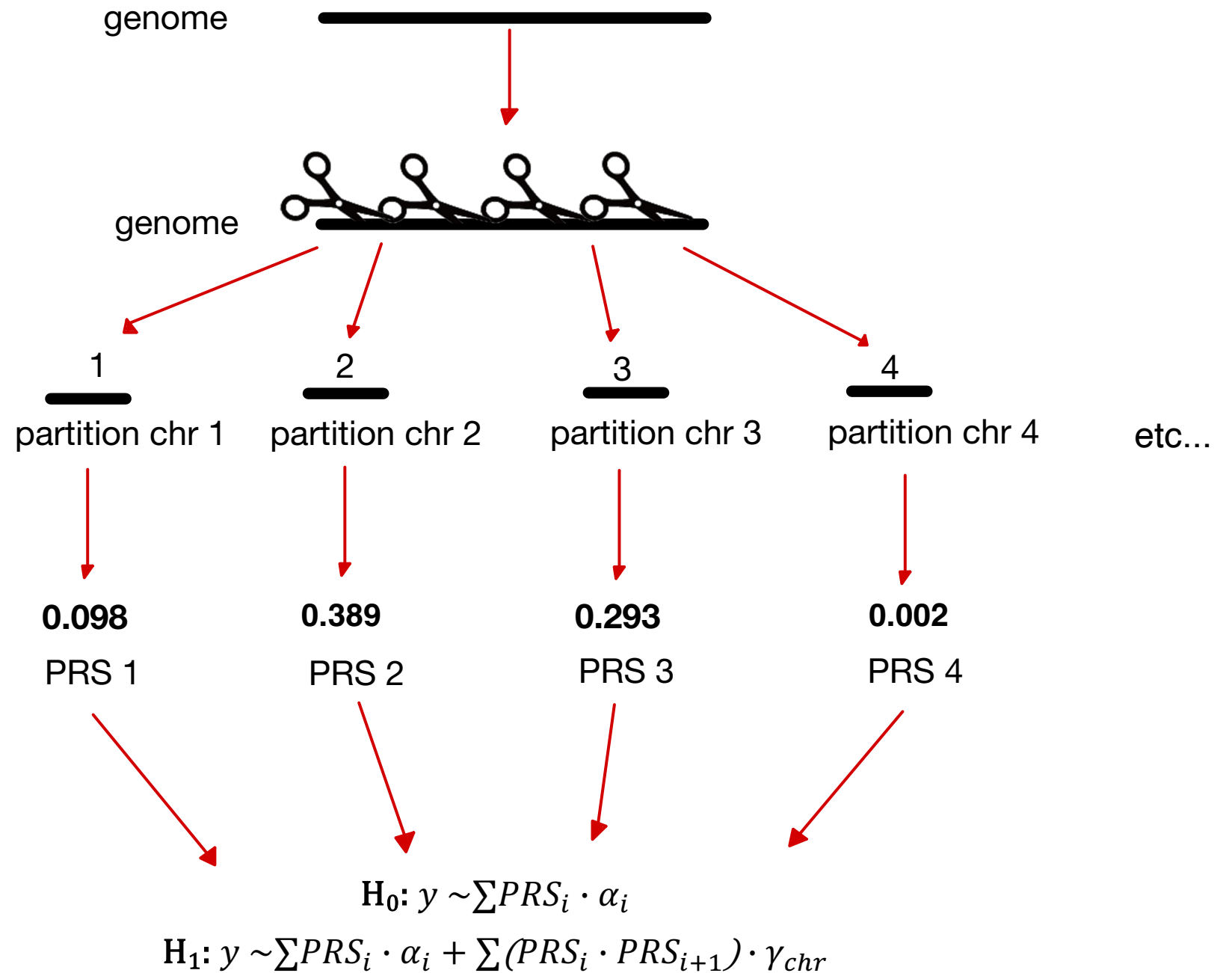






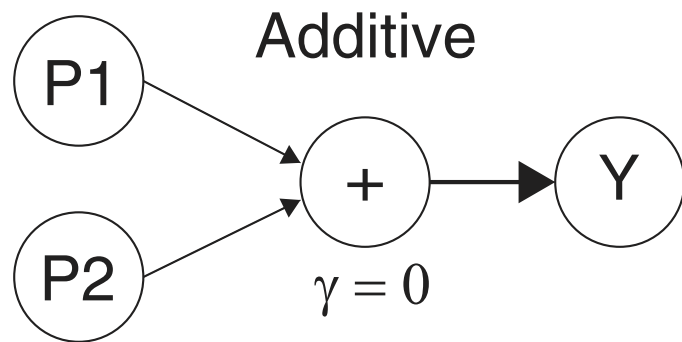


$$\mathbf{H}_0: y \sim \alpha_e PRS_e + \alpha_o PRS_o$$
$$\mathbf{H}_1: y \sim \alpha_e PRS_e + \alpha_o PRS_o + \gamma_{e,o} PRS_e * PRS_o$$

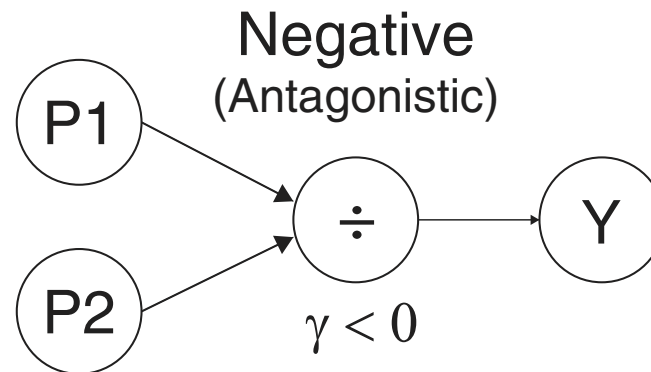
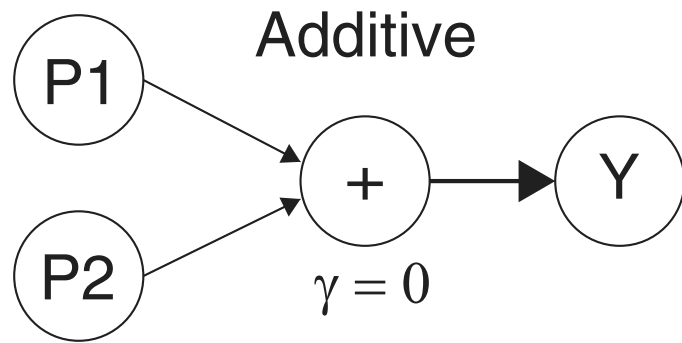


$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \gamma_{i,j} PRS_i^* PRS_j$$

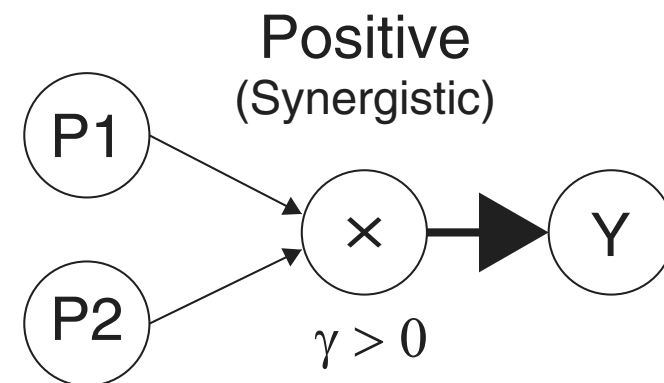
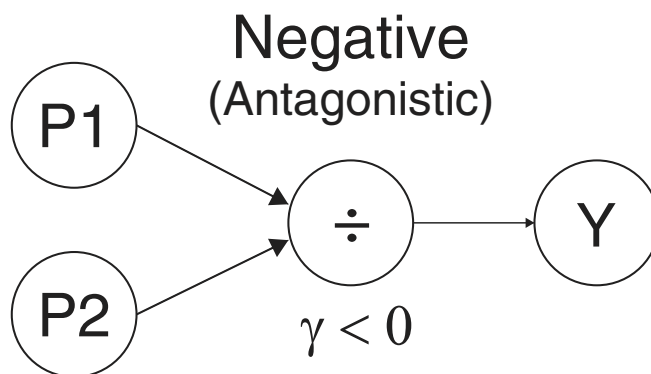
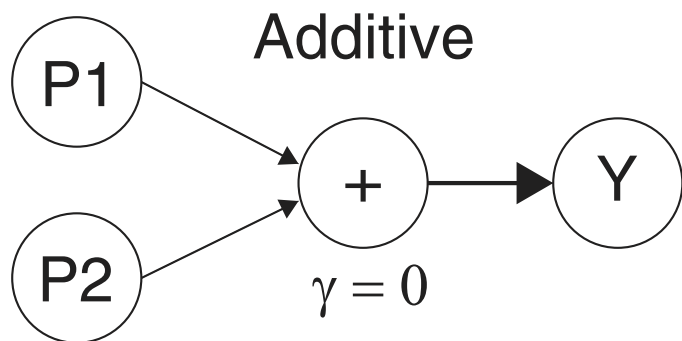
$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \boldsymbol{\gamma}_{i,j} PRS_i * PRS_j$$



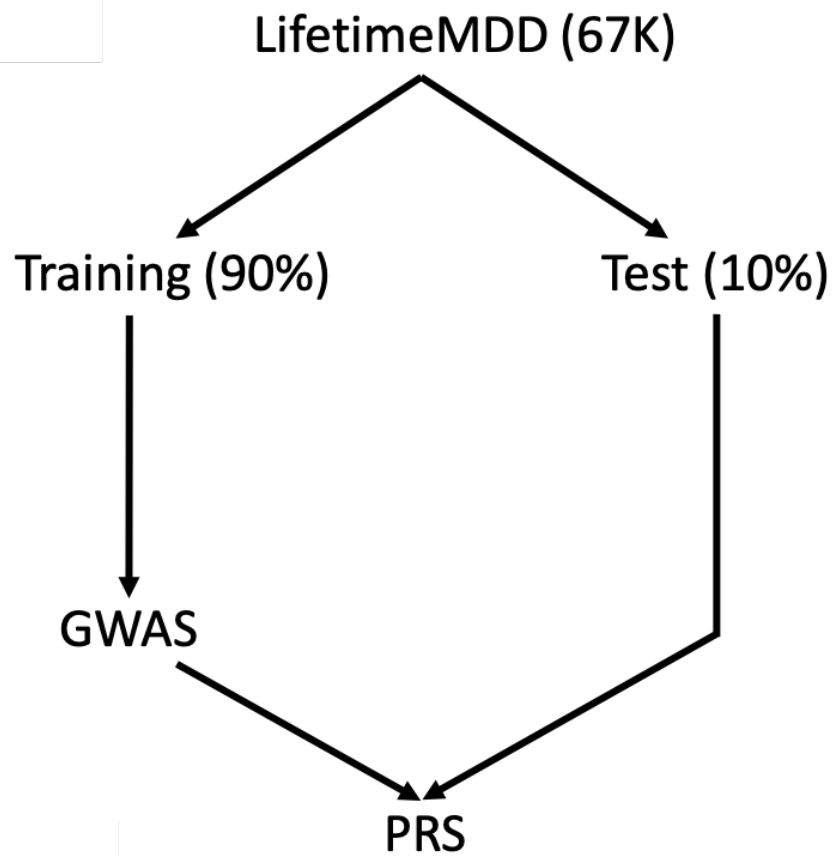
$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \boldsymbol{\gamma}_{i,j} PRS_i * PRS_j$$



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Testing for CE in MDD

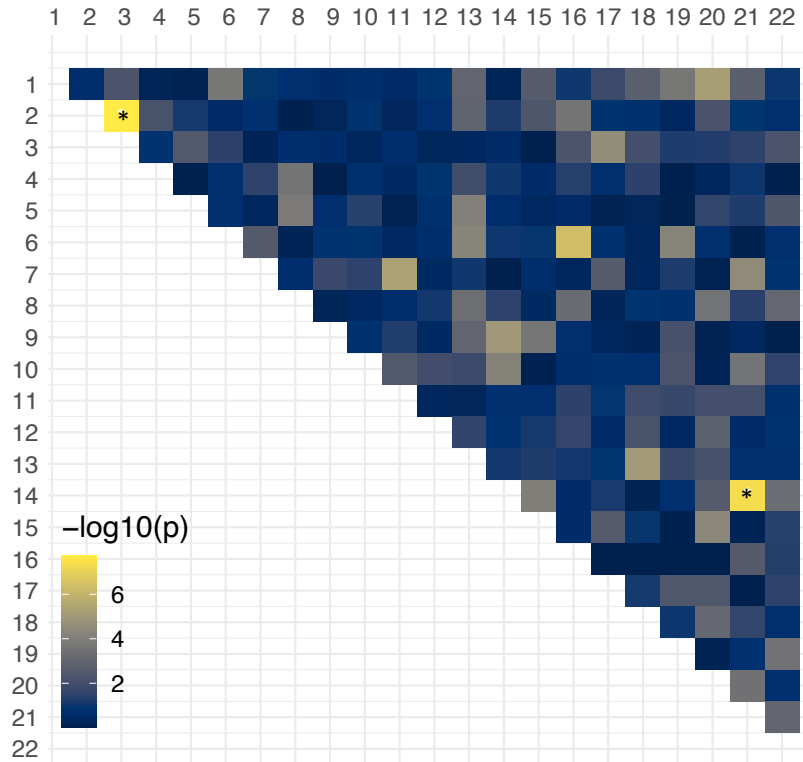


10 fold \rightarrow $\sum PRS_{test} =$ 10-fold CV
partition-specific PRS

$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \gamma_{i,j} PRS_i * PRS_j$$

Lifetime MDD in UK Biobank

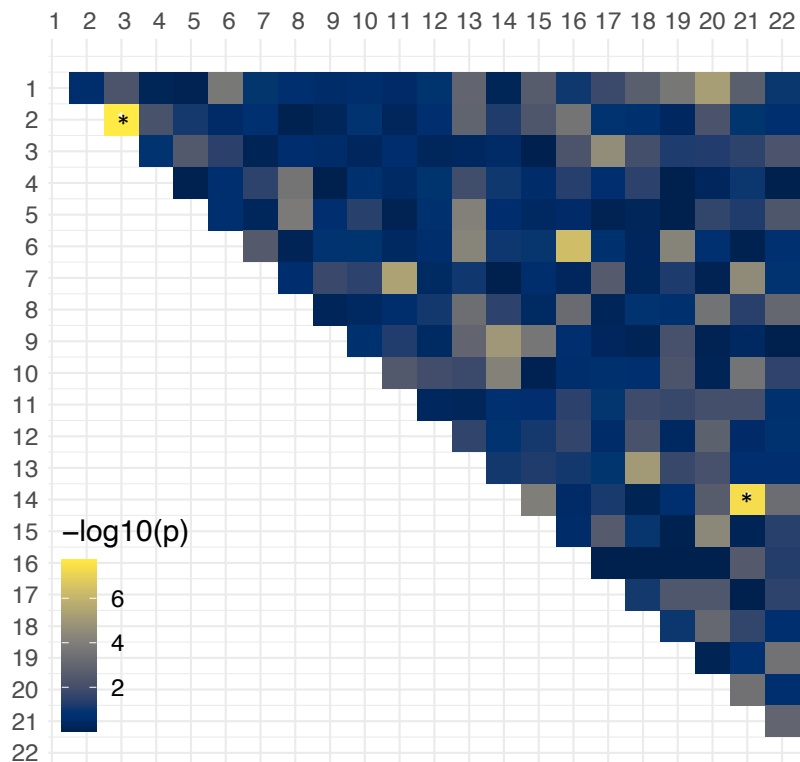
$p_{EO} = 3.00E-02$	$p_{chr} = 9.52E-12$
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* = FDR 10%

Lifetime MDD in UK Biobank

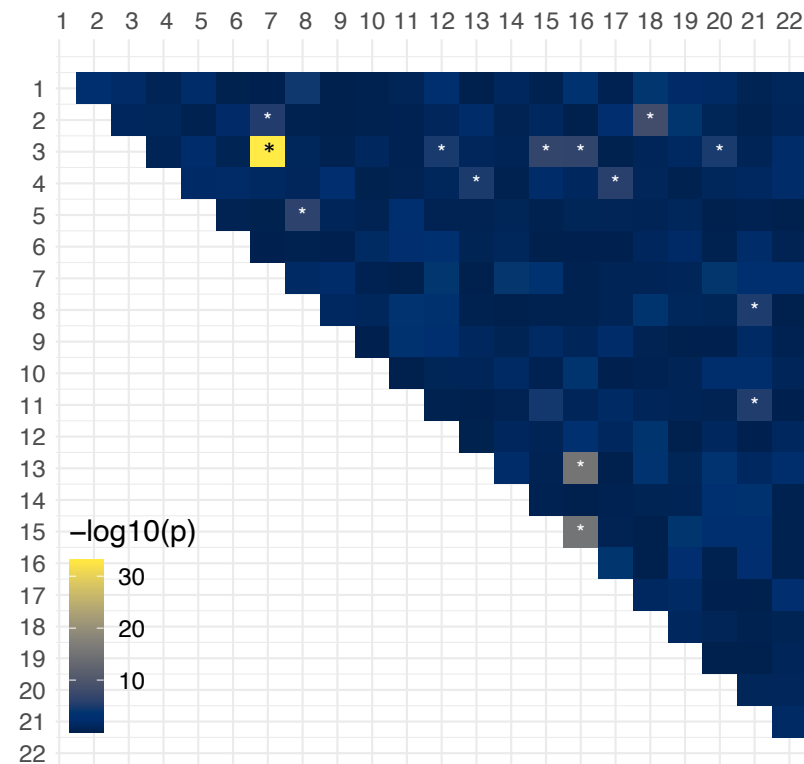
$p_{EO} = 3.00E-02$	$p_{chr} = 9.52E-12$
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* = FDR 10%

MDD in 23&Me summarystatistics predicting in UK Biobank

$p_{EO} = 9.68E-03$	$p_{chr} = 1.79E-58$
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* = FDR 10%

Are MDD symptoms complex phenotypes with interacting pathways?

CE in MDD symptoms

	γ_{EO}	p_{EO}	$\bar{\gamma}_{chr}$	p_{chr}
Depressed mood	-1.41E-04	9.76E-01	-2.83E-04	8.77E-15
Anhedonia	5.24E-03	5.34E-01	-1.59E-03	1.73E-08
Weight	1.96E-02	6.25E-02	1.66E-03	5.30E-04
Weight gain	2.83E-02	1.74E-01	3.26E-03	8.75E-08
Weight loss	-9.82E-03	1.89E-01	-2.46E-03	3.3-E-04
Weight change	2.12E-01	1.05E-02	2.51E-03	3.76E-05
Sleep	-9.41E-02	6.98E-02	4.46E-03	1.35E-07
Insomnia	3.71E-03	7.39E-01	1.85E-03	8.04E-03
Hypersomnia	8.71E-03	6.60E-01	1.61E-03	2.04E-04
Early up	-8.95E-02	1.57E-01	-2.52E-03	1.31E-02
Fatigue	2.06E-01	2.83E-02	-1.23E-03	1.13E-06
Worthless	3.21E-02	6.73E-02	-1.09E-03	1.26E-06
Focus loss	3.25E-03	6.82E-01	-2.87E-03	1.22E-11
Suicidal	-3.59E-03	8.14E-01	8.99E-04	2.43E-06

CE in MDD symptoms

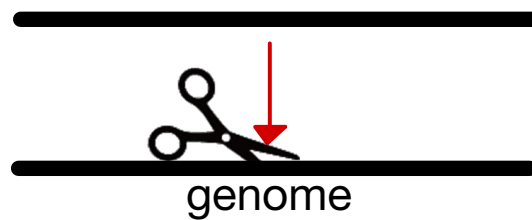
	γ_{EO}	p_{EO}	$\bar{\gamma}_{chr}$	p_{chr}
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CE in MDD symptoms

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Characterization of interaction
effect estimates

genome



partition A

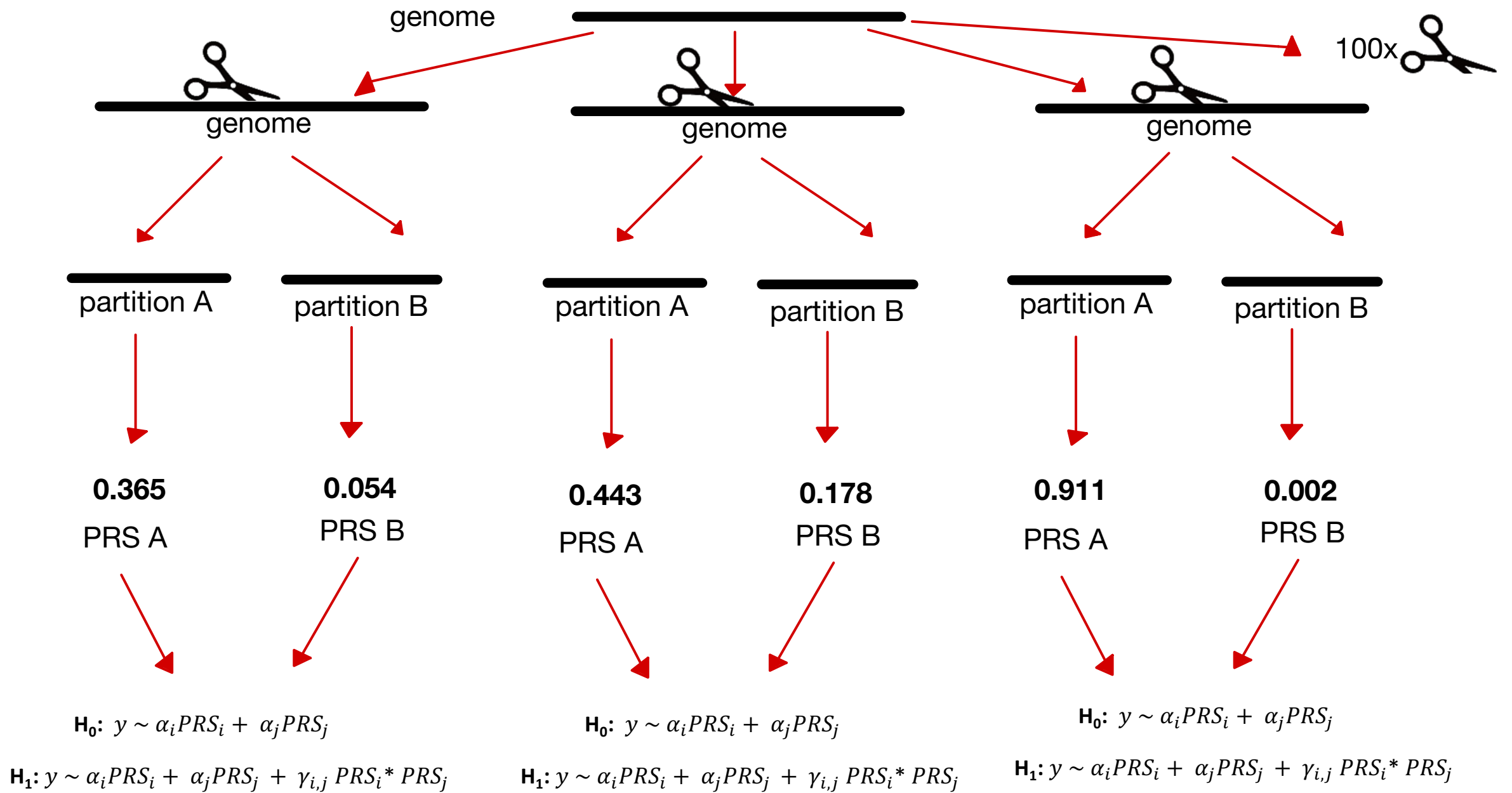
partition B

0.443
PRS A

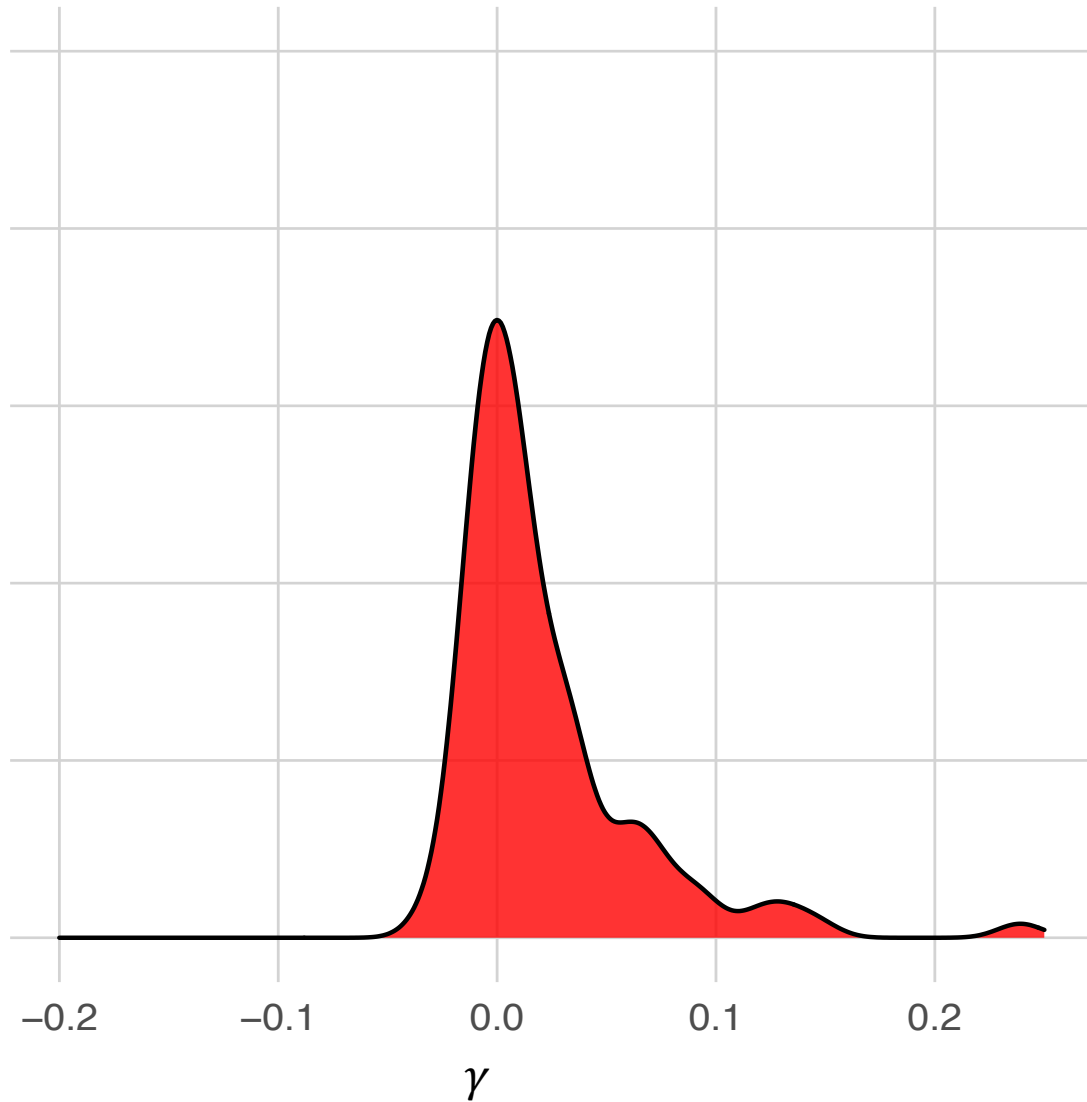
0.178
PRS B

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$$H_1: y \sim \alpha_i PRS_i + \alpha_j PRS_j + \gamma_{i,j} PRS_i * PRS_j$$



LifetimeMDD



Investigating gamma



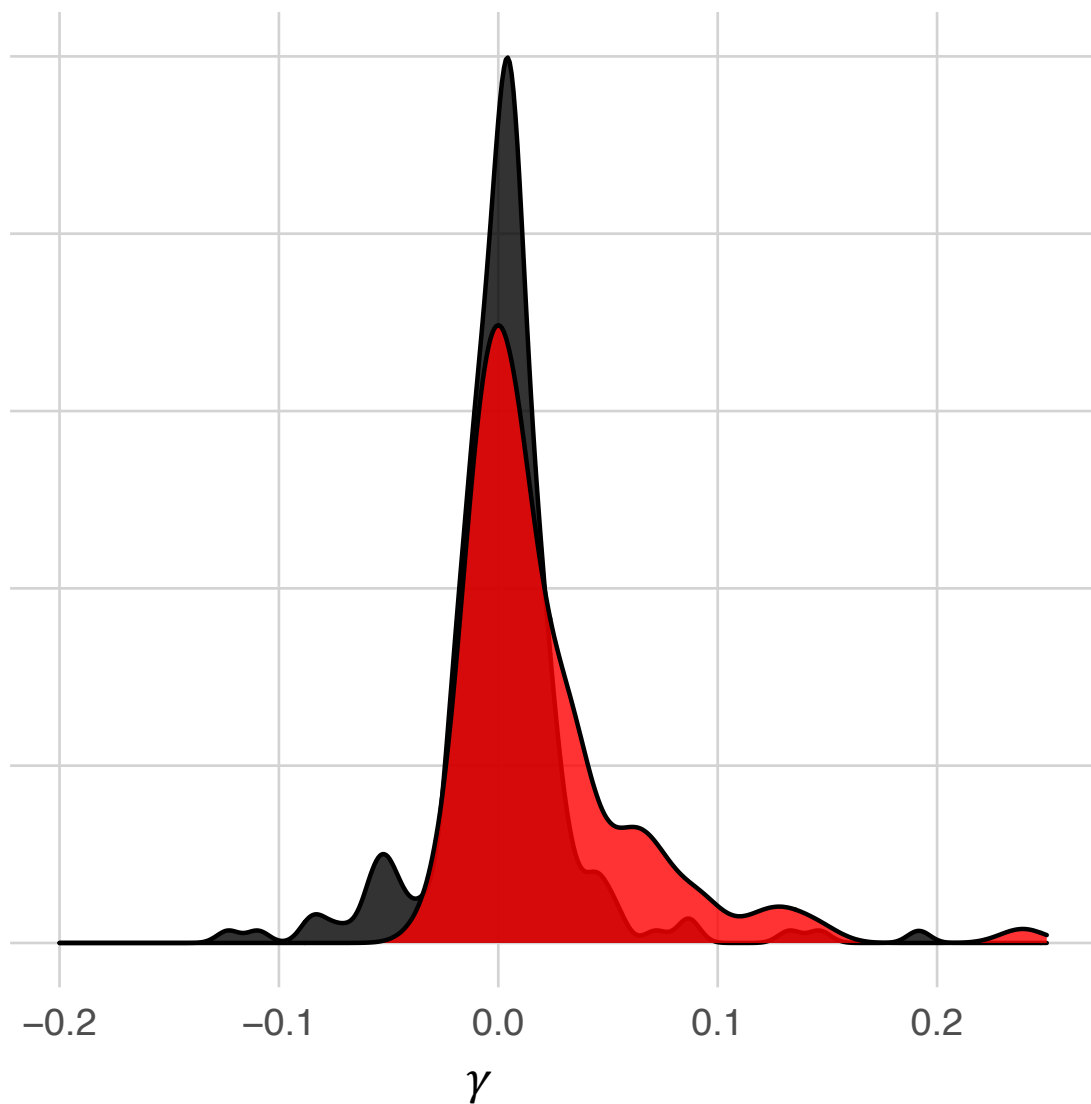
100 dissecting partitions

$$y \sim \alpha_i PRS_i + \alpha_j PRS_j + \gamma_{i,j} PRS_i * PRS_j$$

$i = 11$ **random** chromosomes

$j = 11$ **random** chromosomes

LifetimeMDD



Investigating gamma



100 dissecting partitions

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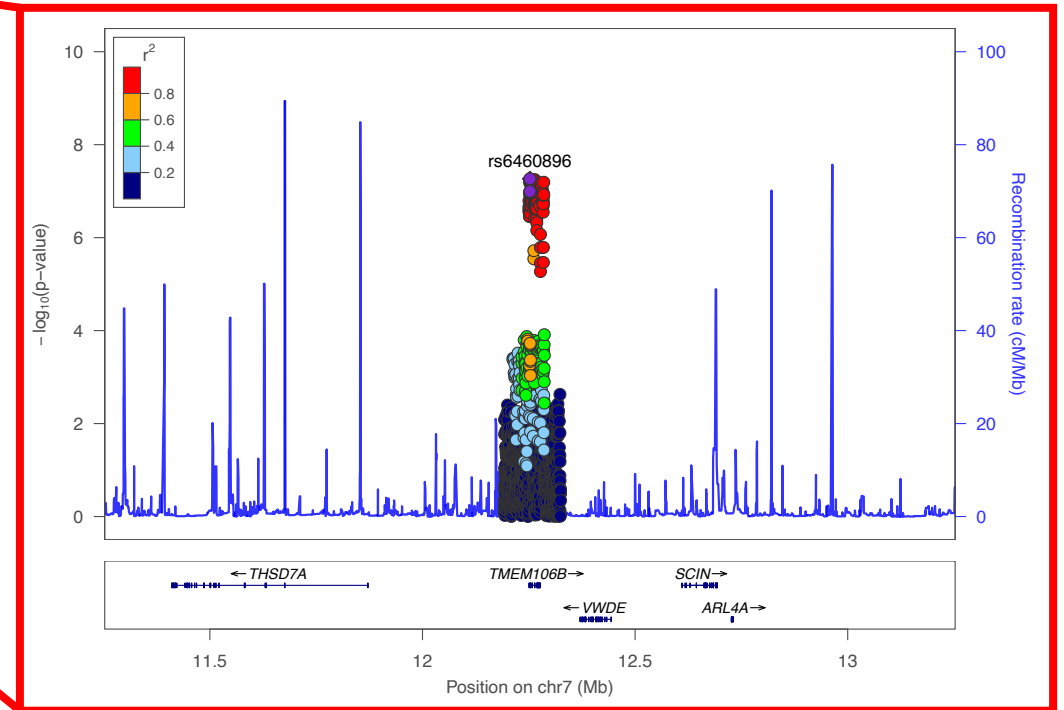
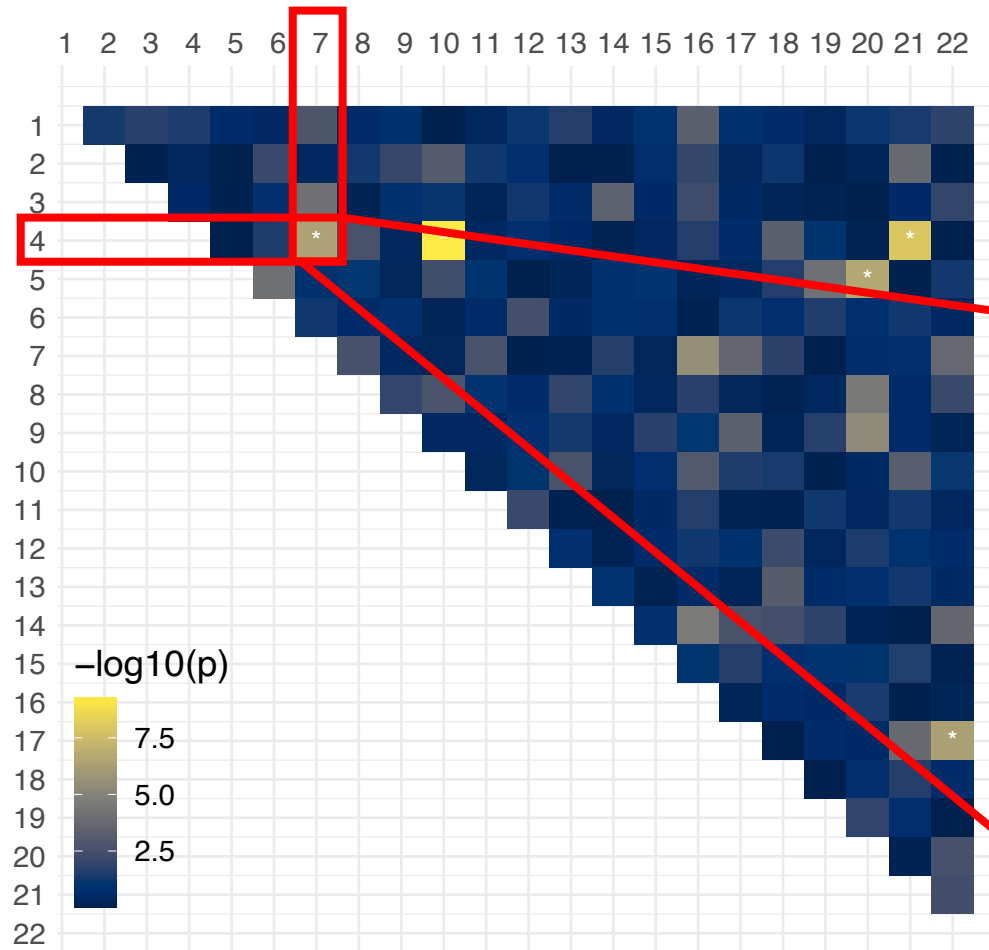
Chromosome partition

$$y \sim \sum PRS_i \cdot \alpha_i + \sum (PRS_i \cdot PRS_{i+1}) \cdot \gamma_i$$

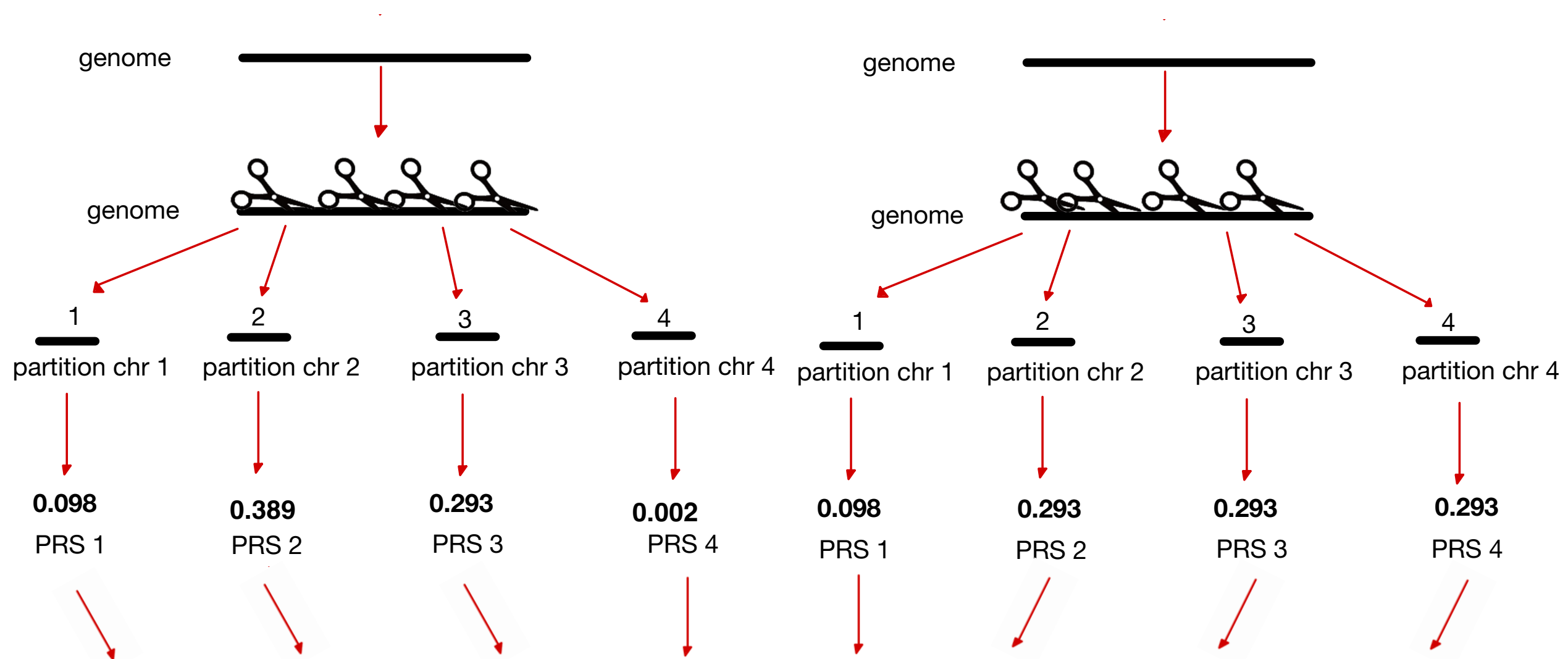
Can we increase CE framework
resolution?

Chromosome partitions in UK Biobank Phenotype: MDD Symptom A6 Fatigue

To select chromosome pairs for SNP * PRS analysis



Are there symptom interactions
towards MDD?



$$H_0: y \sim \sum PRS_i \cdot \alpha_i$$

$$H_1: y \sim \sum PRS_i \cdot \alpha_i + \sum_{\gamma_{chr}} (PRS_i \cdot PRS_{i+1})$$

Summary

- We identified Coordinated Epistasis (CE) in Major Depressive Disorder and its symptoms.
- We further characterized gamma: it is a distribution.
- We increase resolution and identified symptom-specific pathway interactions driven by loci related to MDD.
- We extend across symptoms and identify symptom-specific pathway interactions towards MDD.



biobank^{uk}

iPSYCH

lifelines

CONVERGE

SHIP

HELMHOLTZ
MUNICH

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TUM

Thank you