Using polygenic methods and pedigrees to understand within-disorder and cross-disorder genetic architecture and heterogeneity

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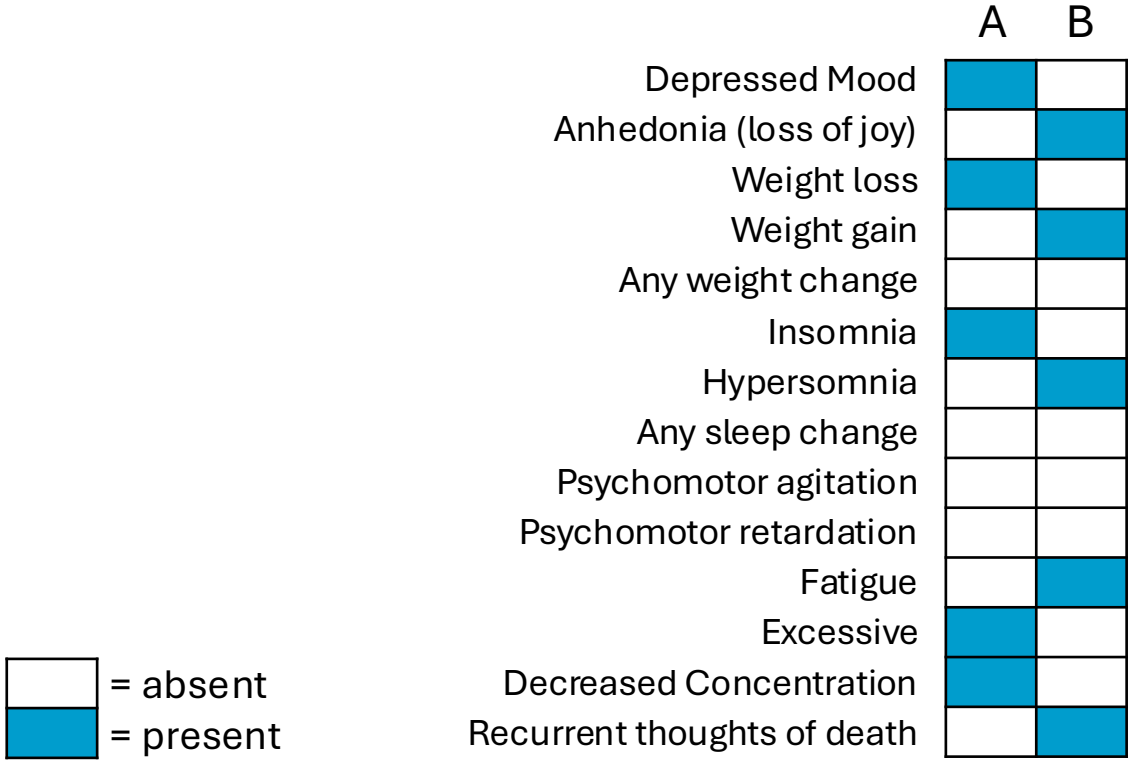
38th ECNP Congress
October 12th 2025, Amsterdam

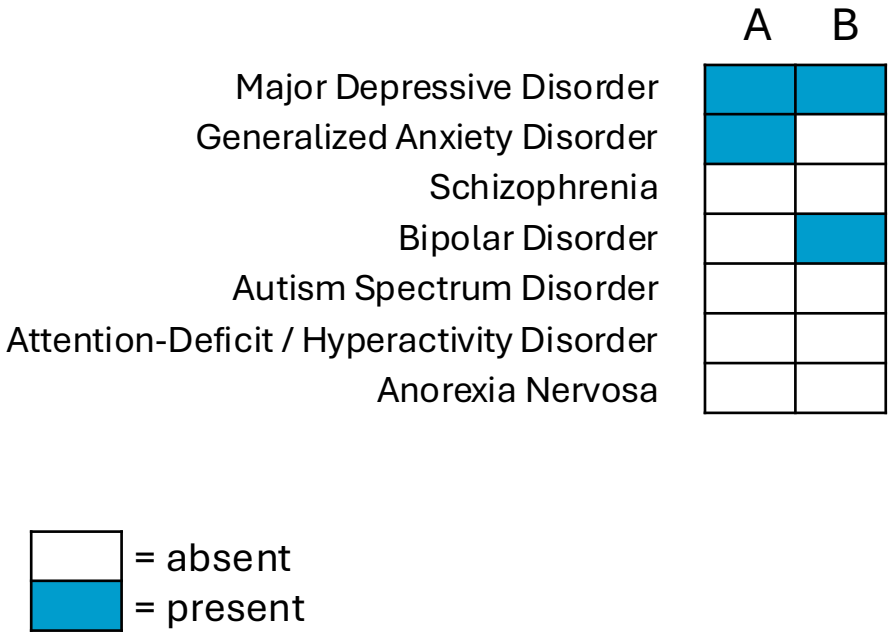
Disclosures

Nothing to disclose

Major Depressive Disorder heterogeneity: symptom presentations



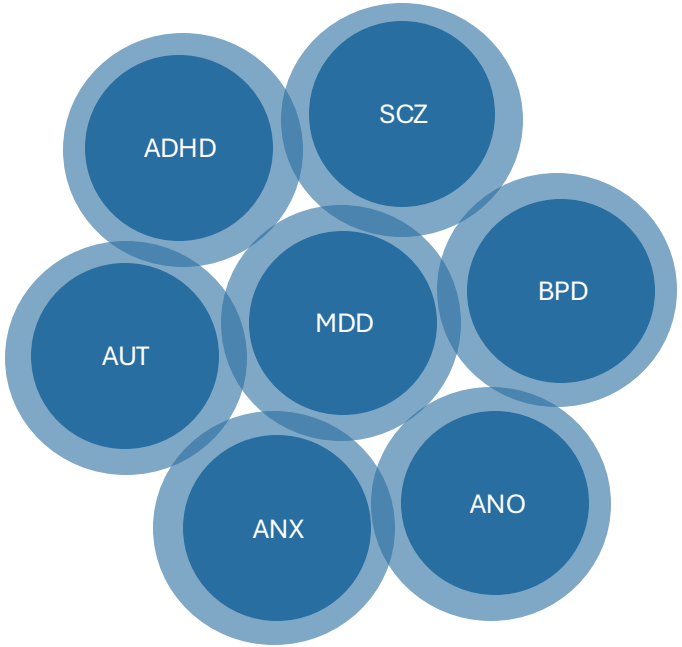
Major Depressive Disorder heterogeneity: comorbid disorders



Major Depressive Disorder heterogeneity: comorbid disorders

	A	B
Major Depressive Disorder	■	■
Generalized Anxiety Disorder	■	
Schizophrenia		
Bipolar Disorder		■
Autism Spectrum Disorder		
Attention-Deficit / Hyperactivity Disorder		
Anorexia Nervosa		

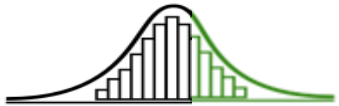
□ = absent
■ = present



Refine psychiatric diagnoses and disentangle heterogeneity into meaningful, biologically driven subtypes.

Additive genetic liability

Disorder A



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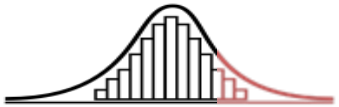
Disorder B



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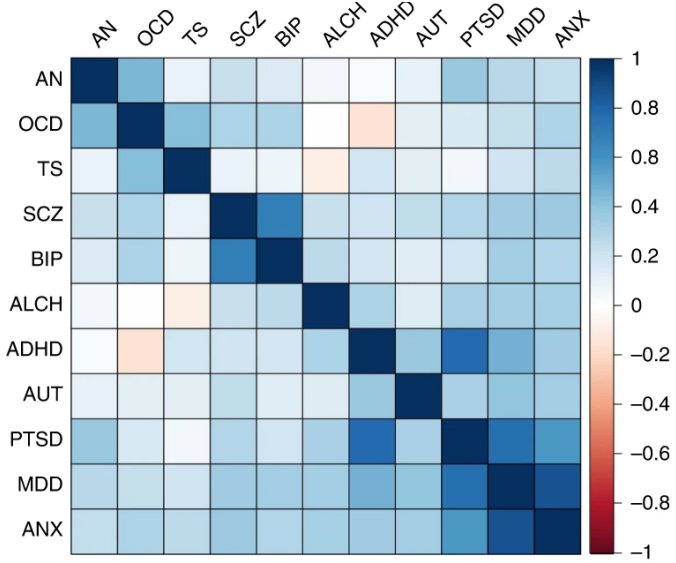
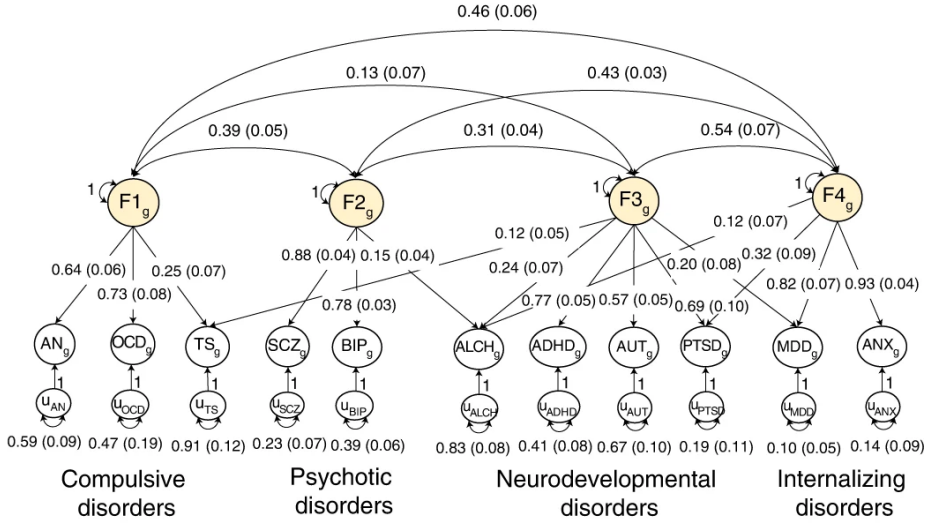
Comorbid phenotype

Examples of investigations of shared genetic variation

Genetic Correlation



Genomic Structural Equation Modelling

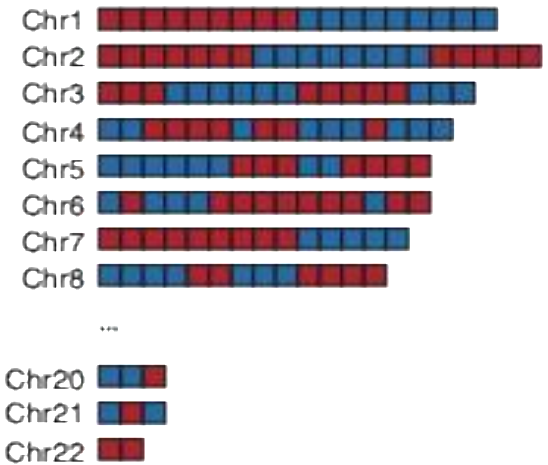


Grotzinger et al. 2022

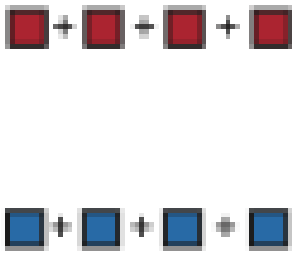
We look beyond additivity

Representing genetic risk as a **genetic set**

GWAS



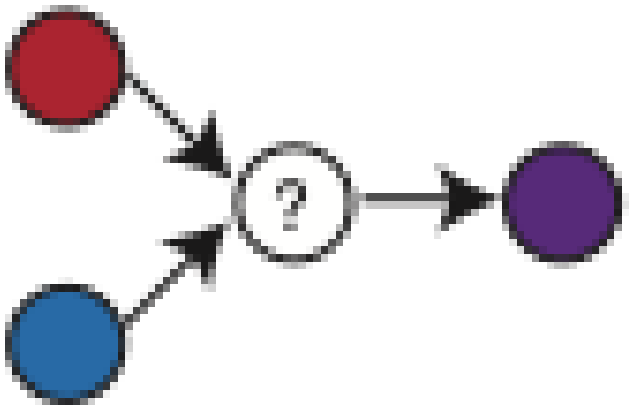
SNP's associating with outcome



Genetic Set
(proxy: Polygenic Risk Scores)

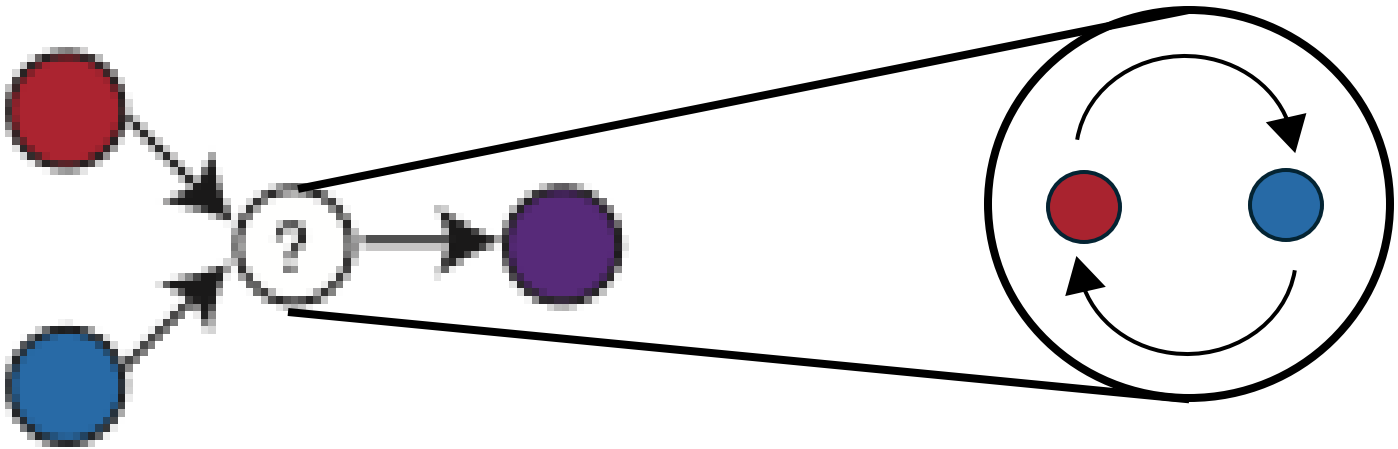
Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

Do these genetic sets influence each other?



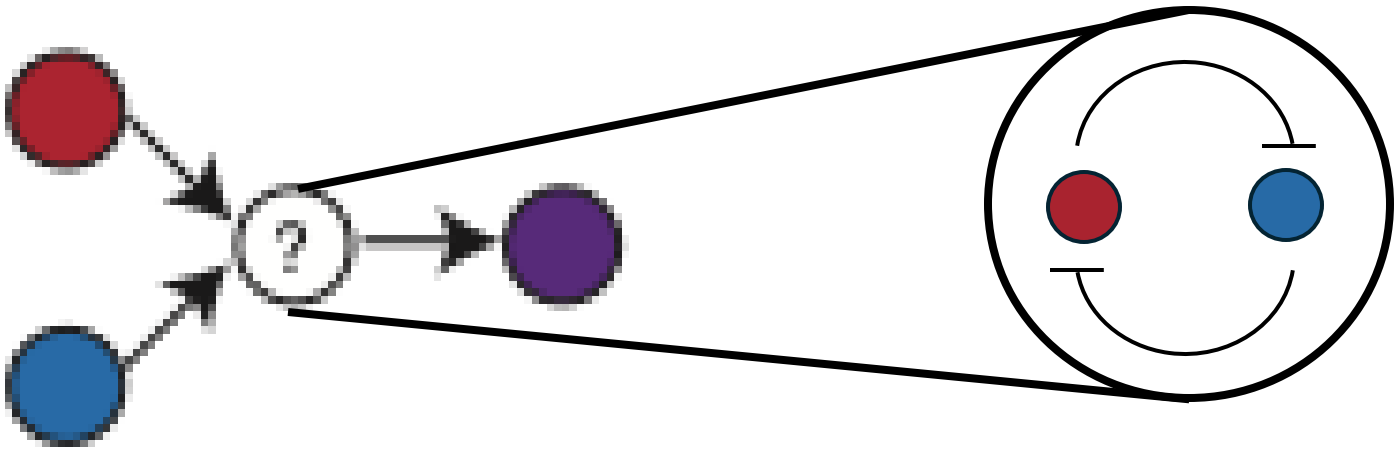
Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

Genetic sets influence eachother through positive-feedback-loop



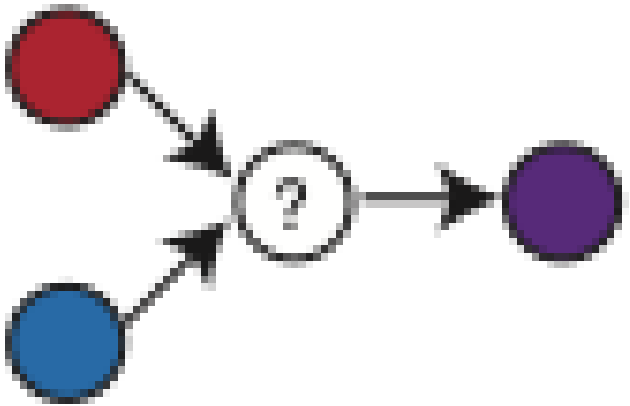
Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

Genetic sets influence eachother through negative-feedback-loop



Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

Testing for interaction between genetic sets



$$y \sim \alpha_i \boldsymbol{GS_i} + \alpha_j \boldsymbol{GS_j} + \boldsymbol{\gamma_{i,j}}\ \boldsymbol{GS_i}^*\ \boldsymbol{GS_j}$$

GS = Genetic Score

i = disorder A
j = disorder B

Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

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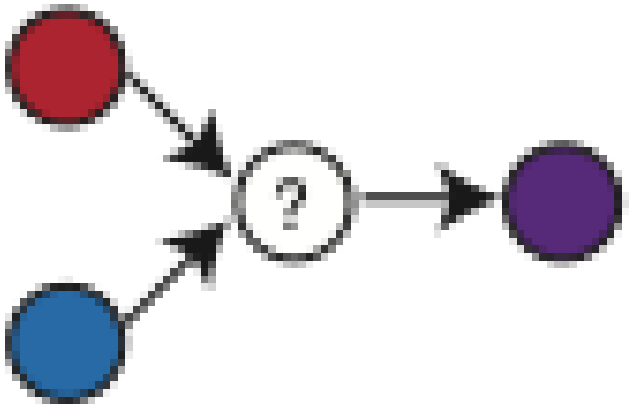

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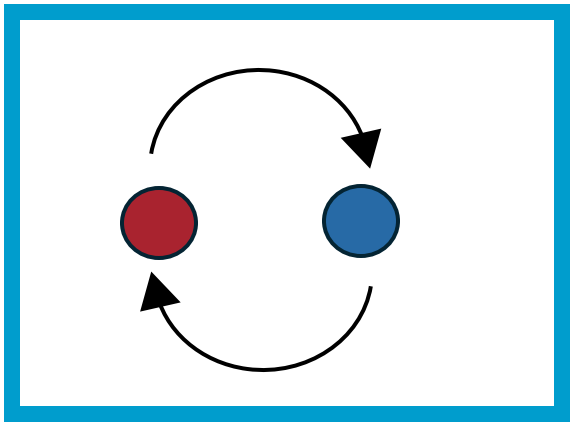
Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

$\gamma_{i,j}$ informative of interplay between variant sets

Positive feedback loop



$\gamma_{i,j} > 0$

Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

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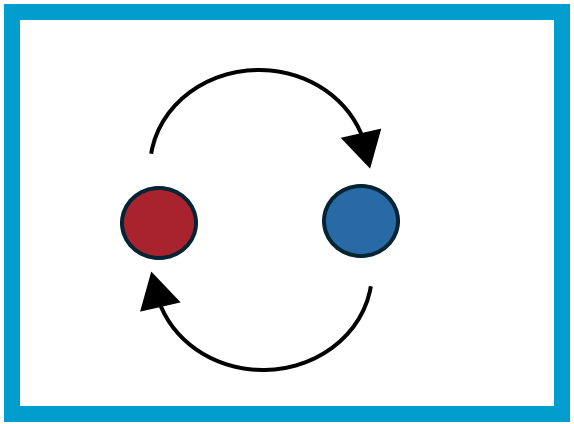

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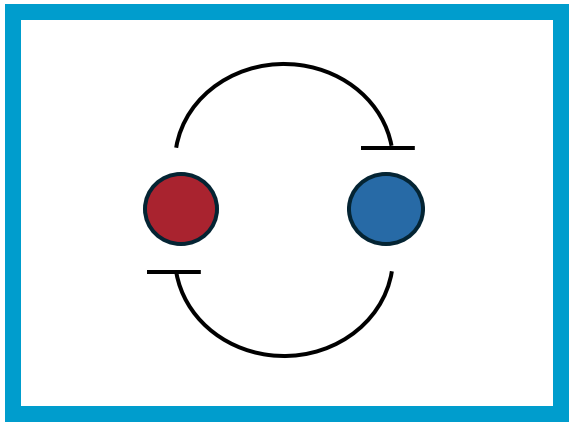
Negative feedback loop



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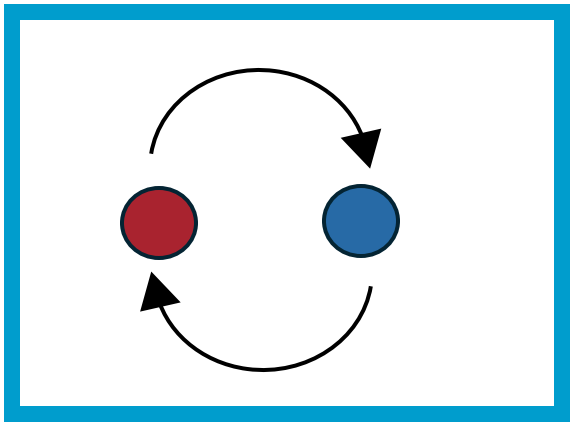

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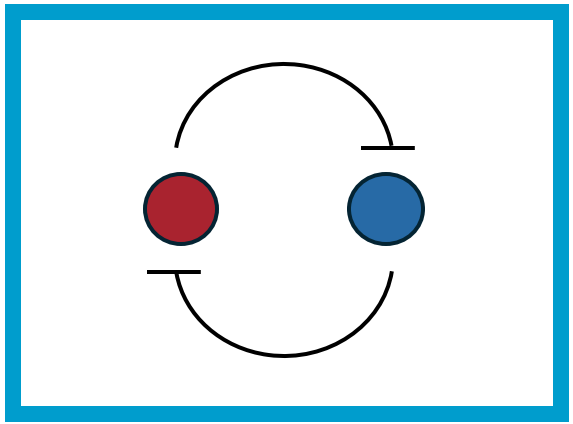
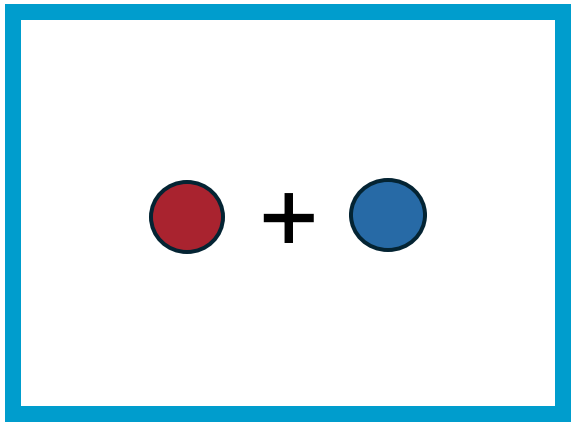


$\gamma_{i,j} < 0$

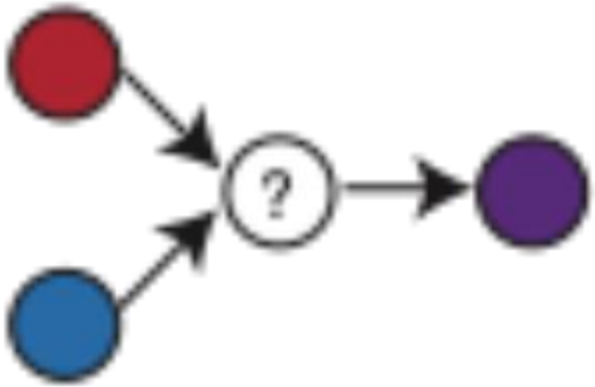
Additive



$\gamma_{i,j} = 0$

Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022

Testing for interaction between genetic sets



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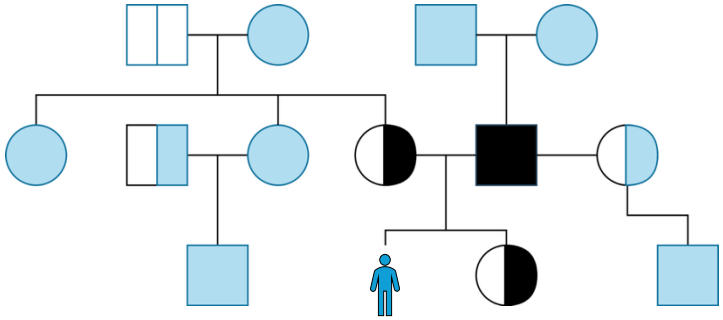
GS = Genetic Score

i = disorder A
j = disorder B

Representing **sets** of genetic effects on psychiatric outcomes

Polygenic Score

Family Genetic Score

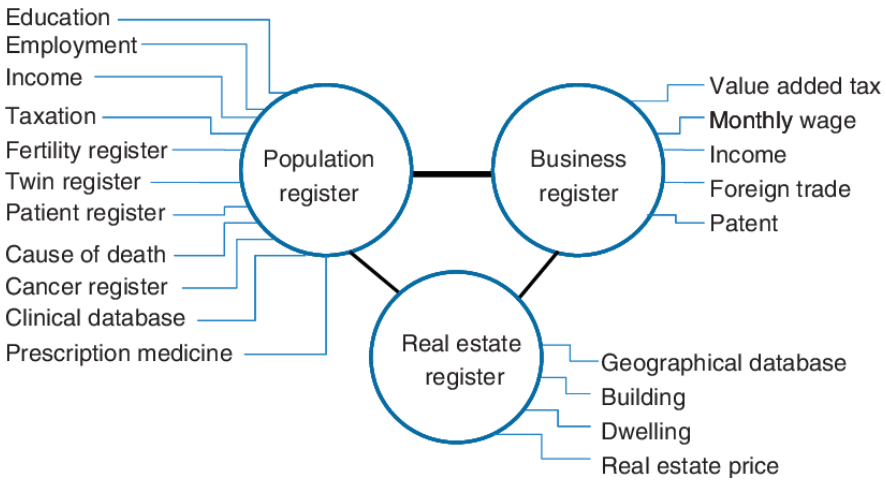


Krebs et al. 2025, AJHG

The Danish Register

CPR: Centrale Person Register

CPR	Adress	Mother	Father
DDMMYY-SSSS	postalcode	DDMMYY-SSSS	DDMMYY-SSSS
DDMMYY-SSSS	postalcode	DDMMYY-SSSS	DDMMYY-SSSS



Thygesen et al. 2011; Lynge, Sandegaard and Rebolj 2011

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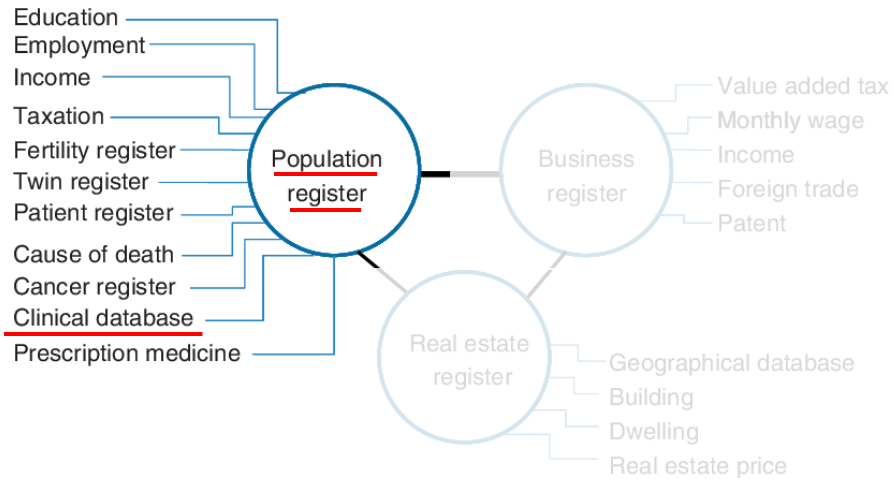
DDMMYY-SSSS	postalcode	DDMMYY-SSSS	DDMMYY-SSSS



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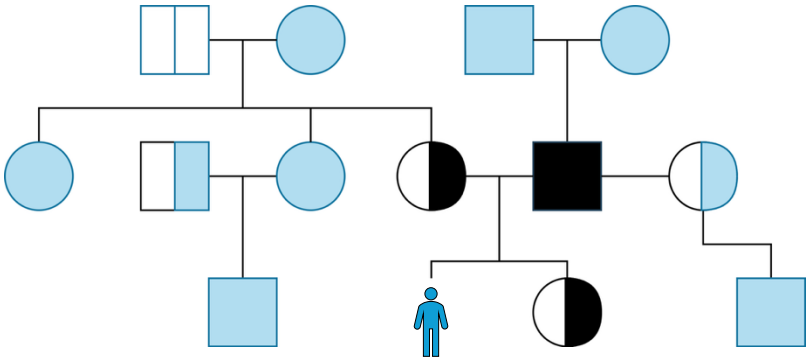
Liability scores to represent genetic sets



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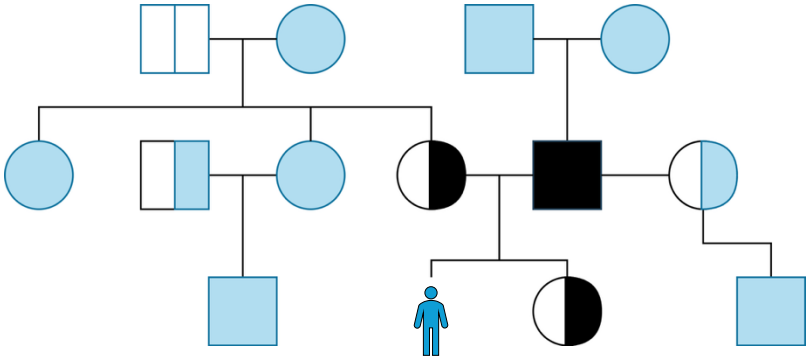
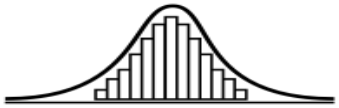
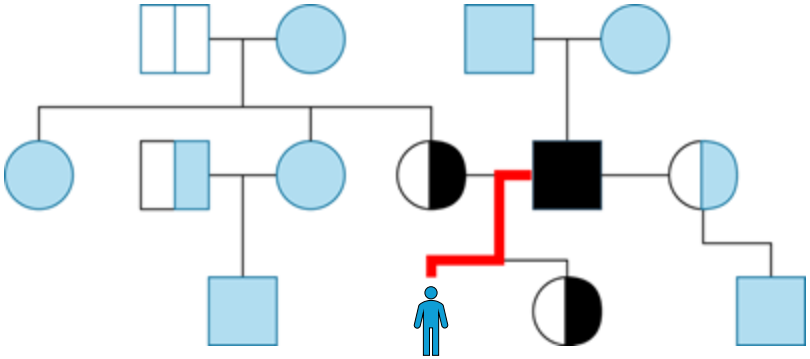


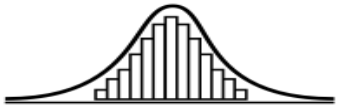


mean = 0
standard error = 1

Krebs et al. 2025, AJHG

Liability scores to represent genetic sets





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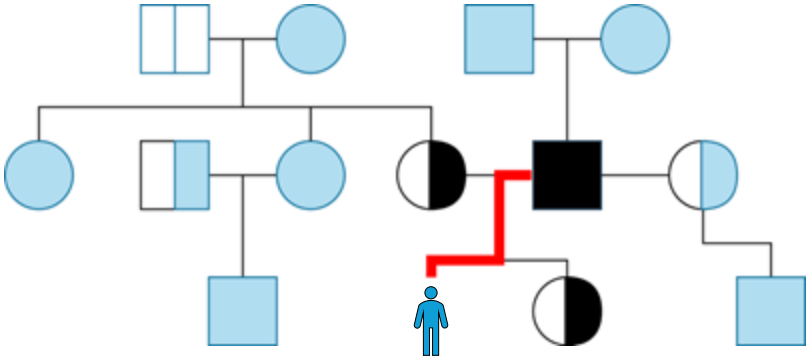

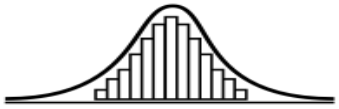

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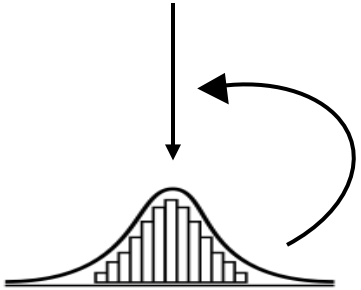

Adjusting using relatedness, phenotype, covariates

Krebs et al. 2025, AJHG

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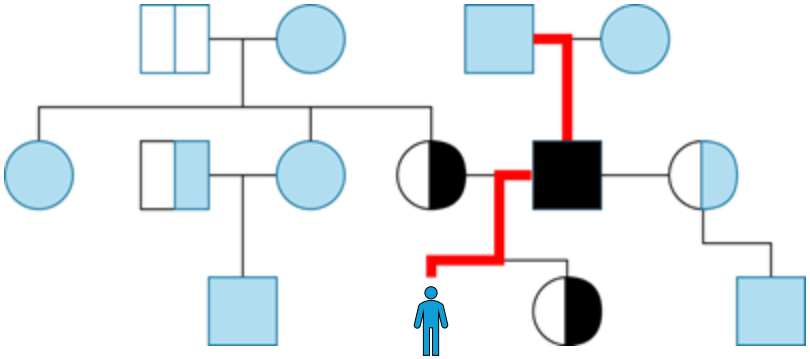

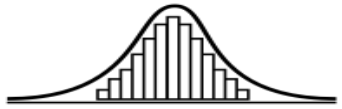

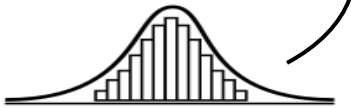

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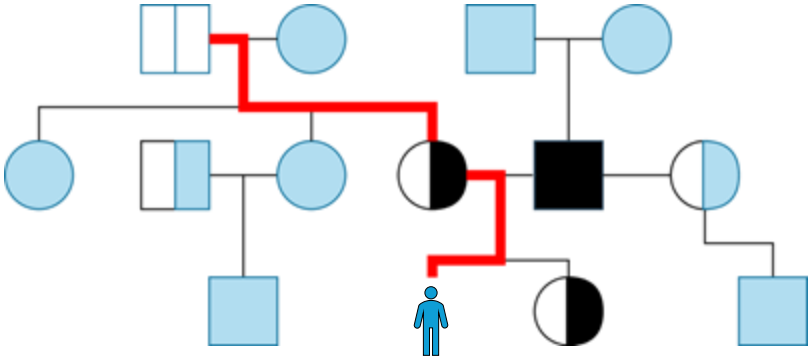

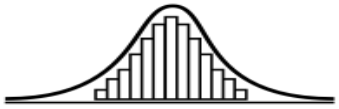

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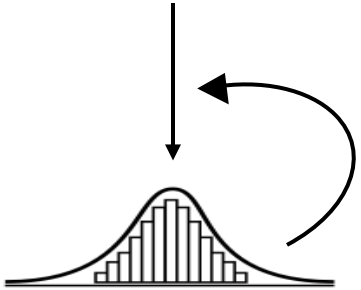

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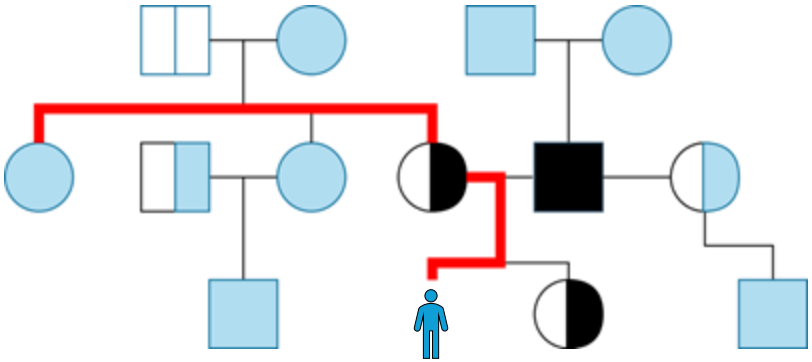

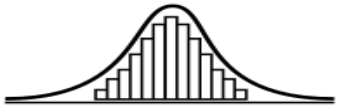

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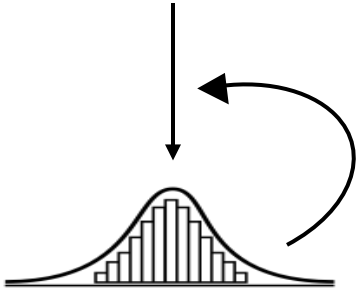

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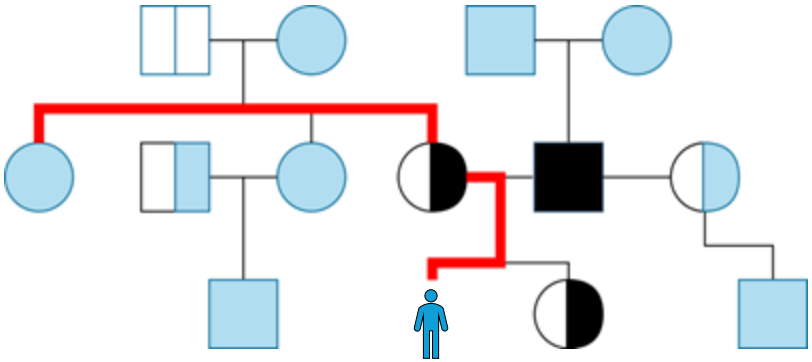
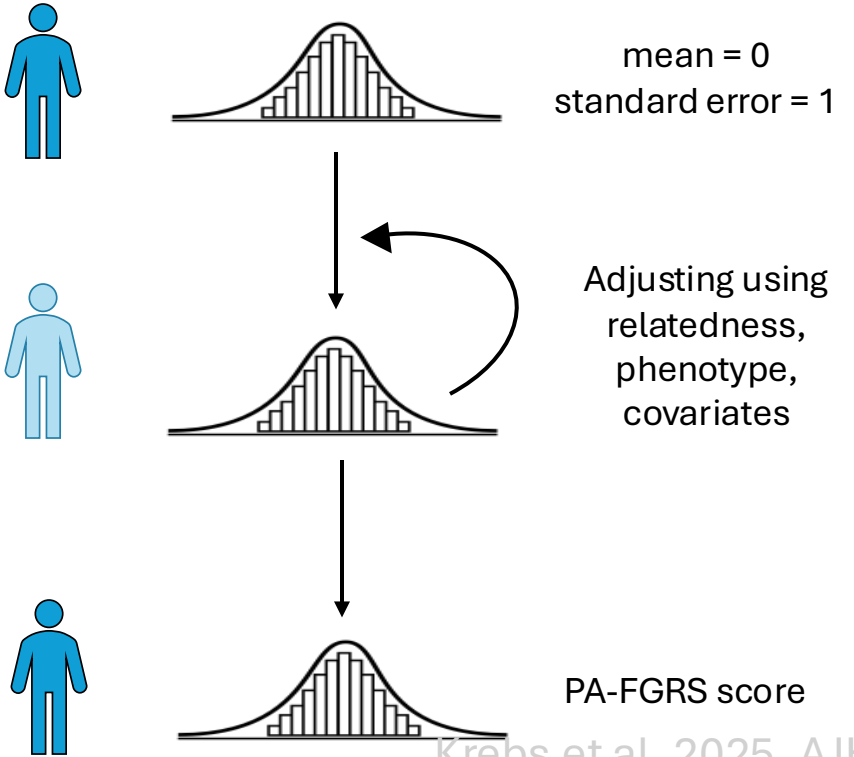
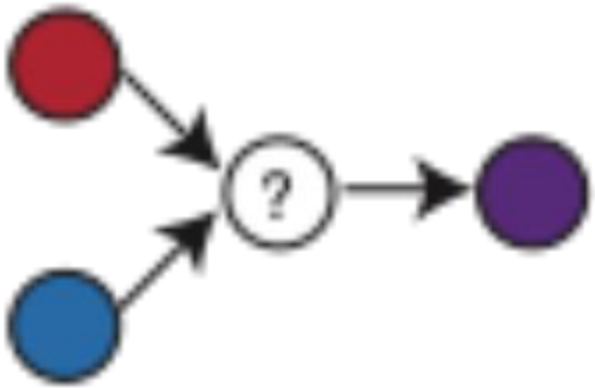




Krebs et al. 2025, AJHG

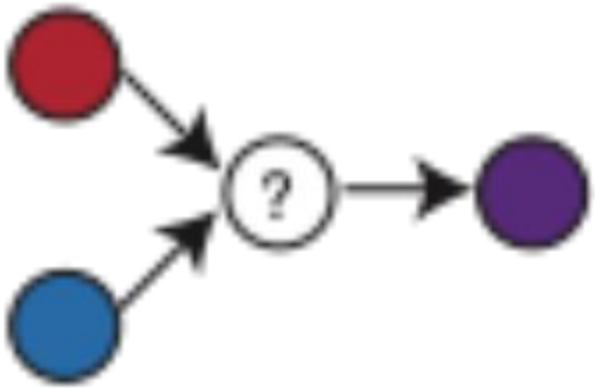
Many questions, One method



Research Question:
Are there genetic sets (as proxies of pathways) interacting with each other to influence platelet volume?

Sheppard et al. 2020

Many questions, One method



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Are there genetic sets (as proxies of pathways) interacting with each other to influence platelet volume?

Sheppard et al. 2020

Research Question:

Are MDD variants part of same set as ADHD variants?

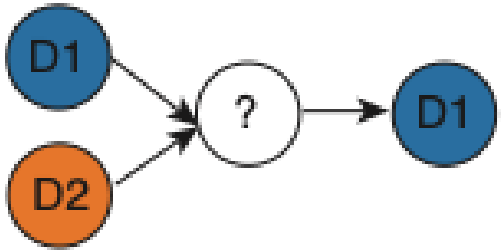
Many questions, One method

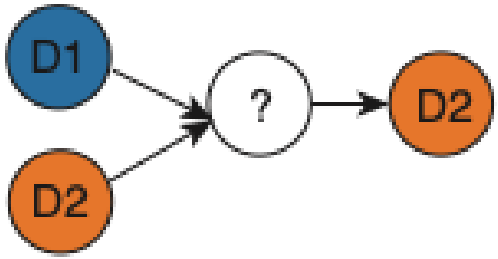
Research Question: Are MDD variants part of same set as ADHD variants?

Input:

PA-FGRS of MDD

PA-FGRS of ADHD





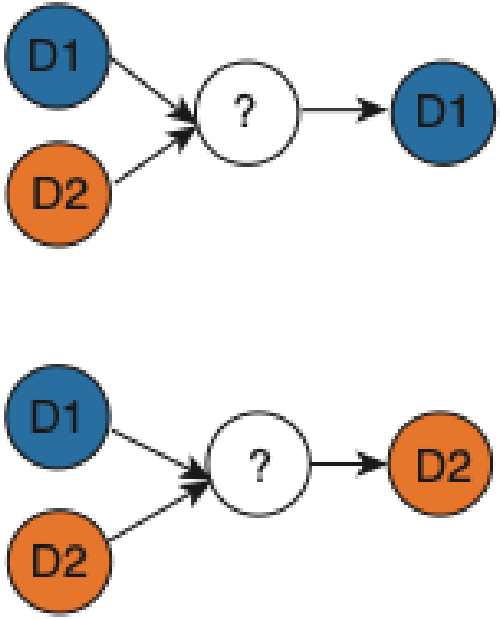
Output:

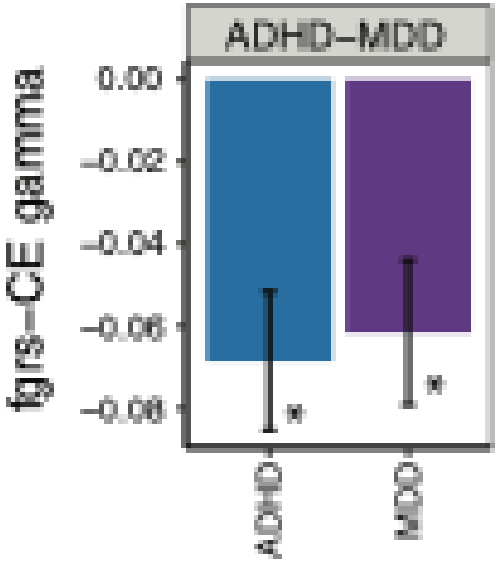
MDD case/control

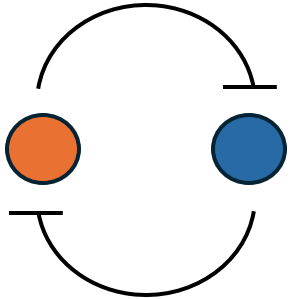
OR

ADHD case/control

ADHD and MDD genetic variants distinct







$\gamma_{i,j} < 0$

* = 10% FDR

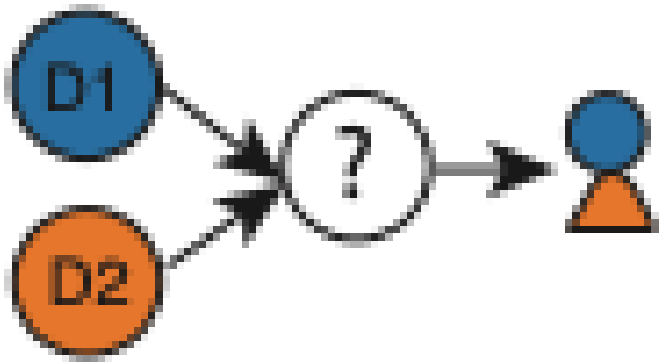
Many questions, One method

Research Question: Are MDD variants and ADHD variants part of same set as comorbid variants?

Input:

PA-FGRS of MDD

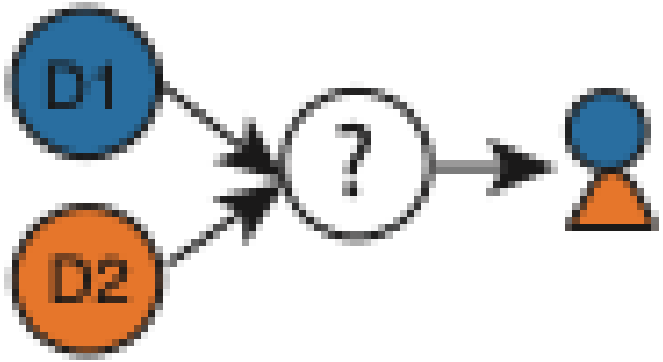
PA-FGRS of ADHD

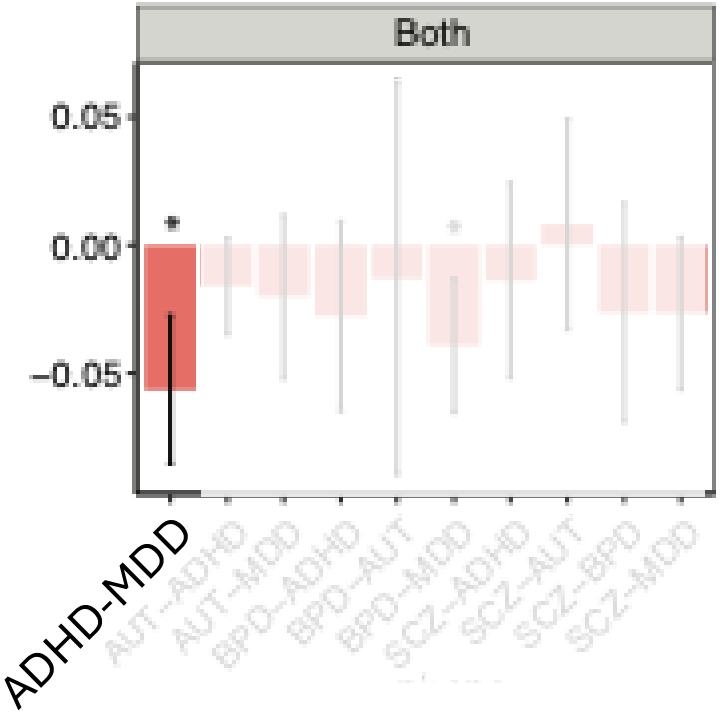


Output:

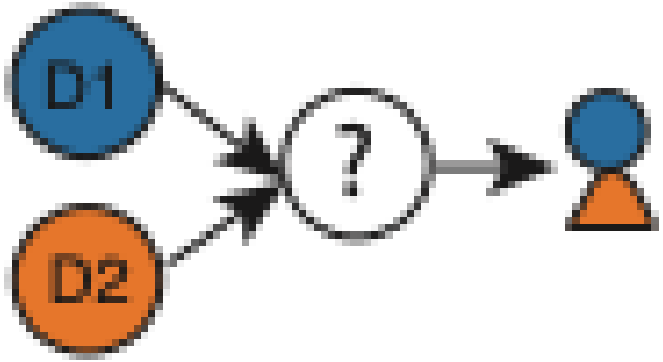
Comorbidity case/control

ADHD and MDD genetic variants distinct from comorbidity



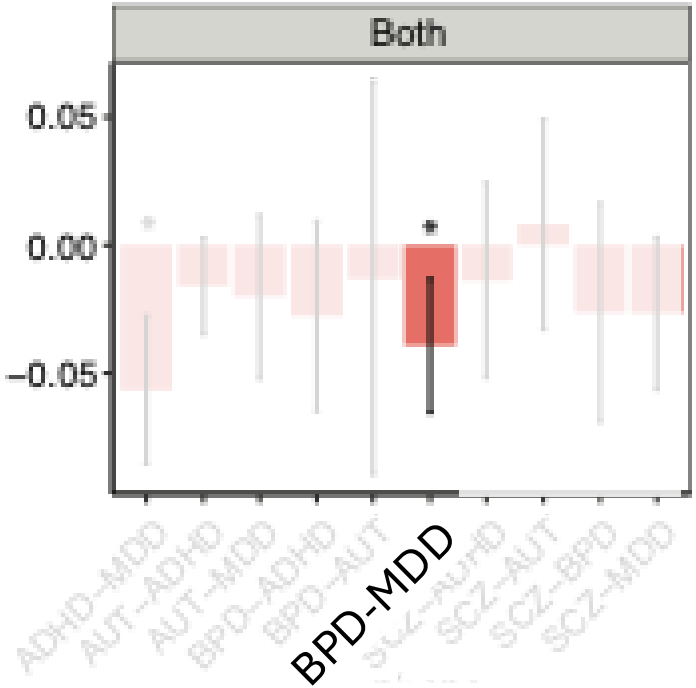


BPD and MDD genetic variants distinct from comorbidity

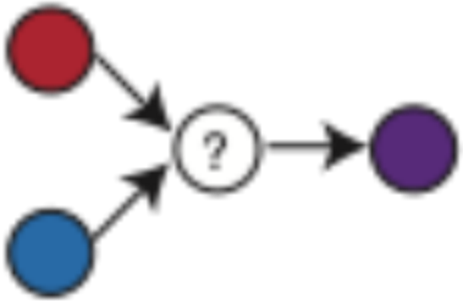


PA-FGRS of MDD

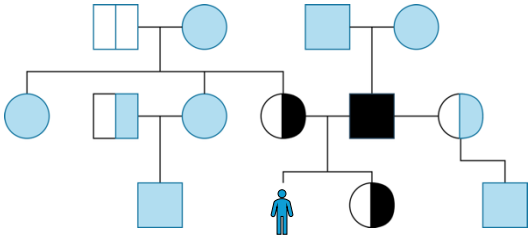
PA-FGRS of BPD



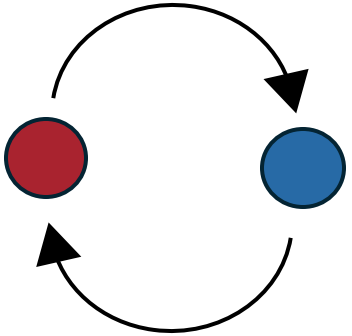
Summary



CE framework elegantly answers many research questions depending on applied context



PA-FGRS within CE framework capture disorder-specific effects



Genetic sets of disorder pairs MDD-ADHD and MDD-BPD not likely part of a synergistic genetic set

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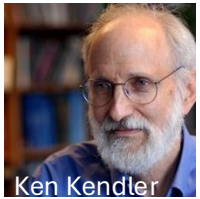
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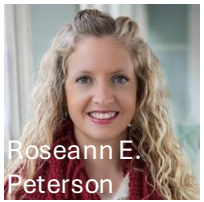
Noah Zaitlen


Bertram Müller-Myshok


Bastian Rieck


Roseann E. Peterson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Cai Lab

van Loo Lab

iPSYCH

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Technische Universität München

Thank you

Pre-print

“Genetic Risk Effects on Psychiatric Disorders Act in Sets”

Connect

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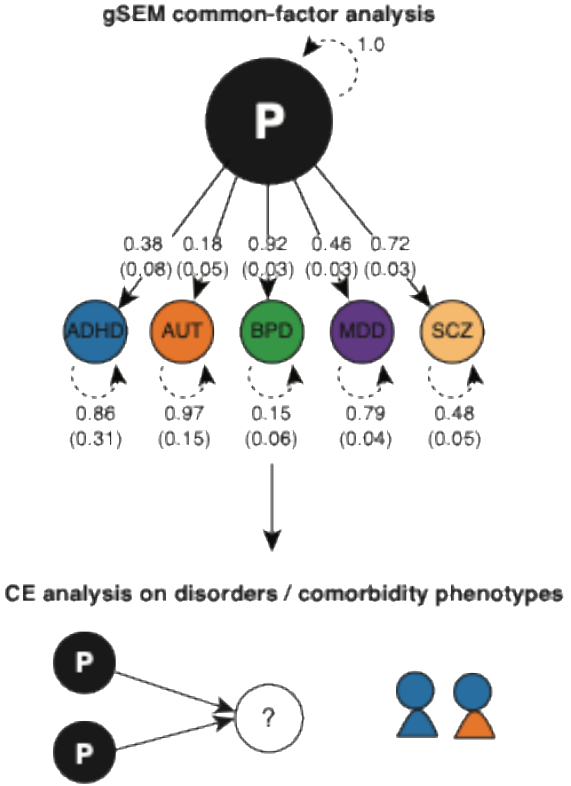
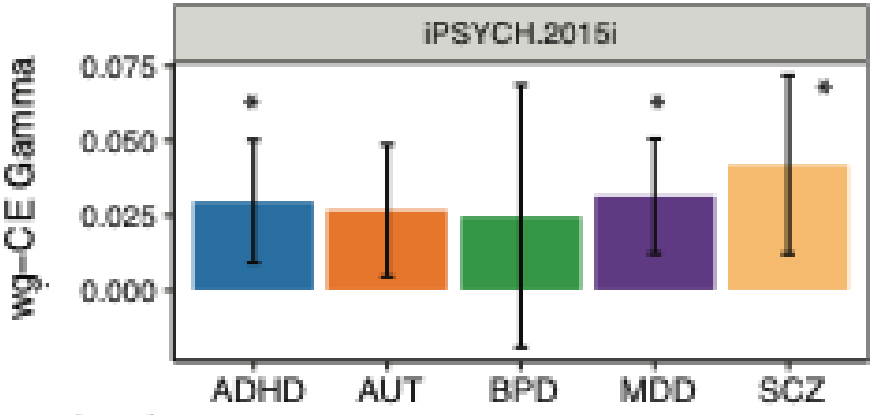
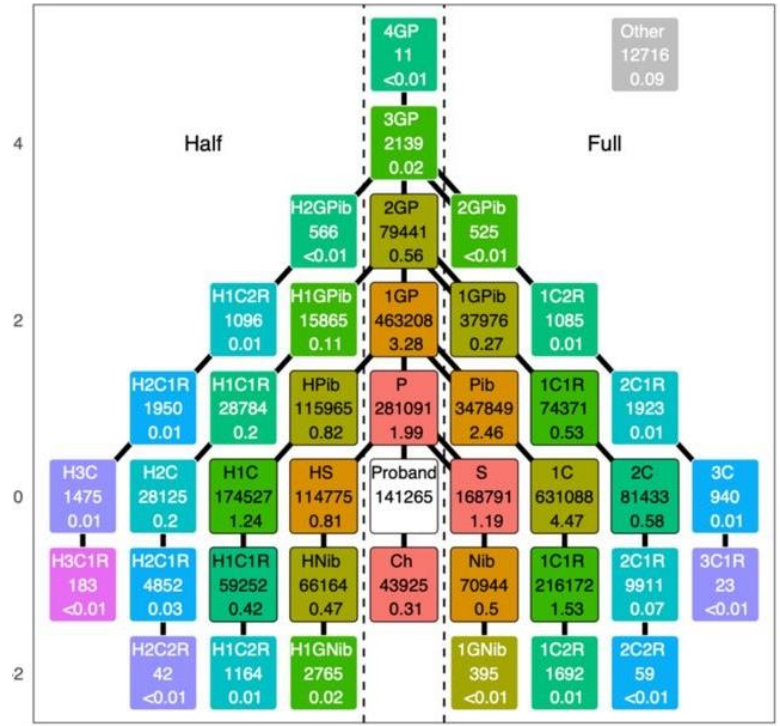
Genetic sets of disorder-specific factors part of same set as P-factor





The Danish Registers



iPSYCH

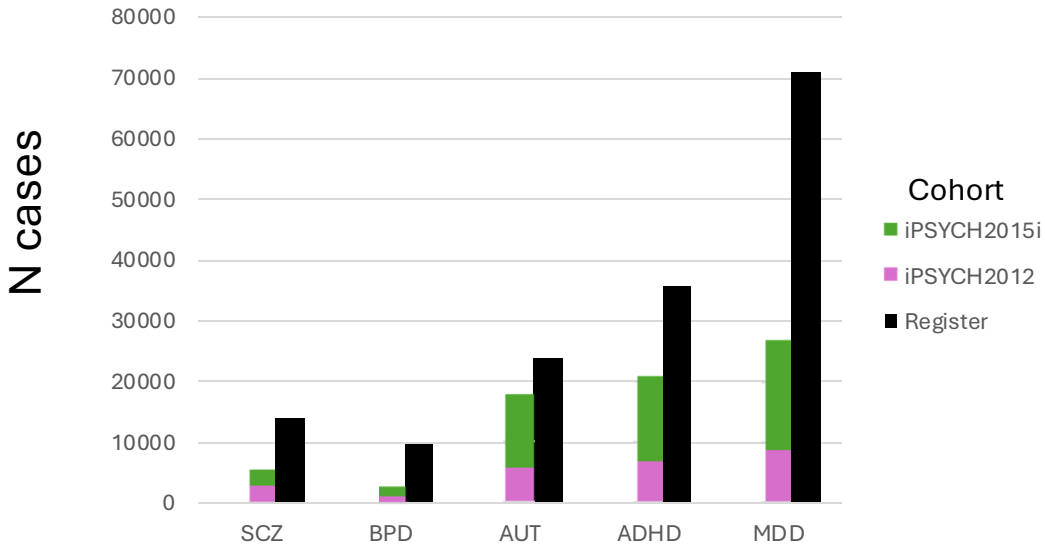
Danish medical register and linked genealogy data

All Danish individuals with psychiatric disorders

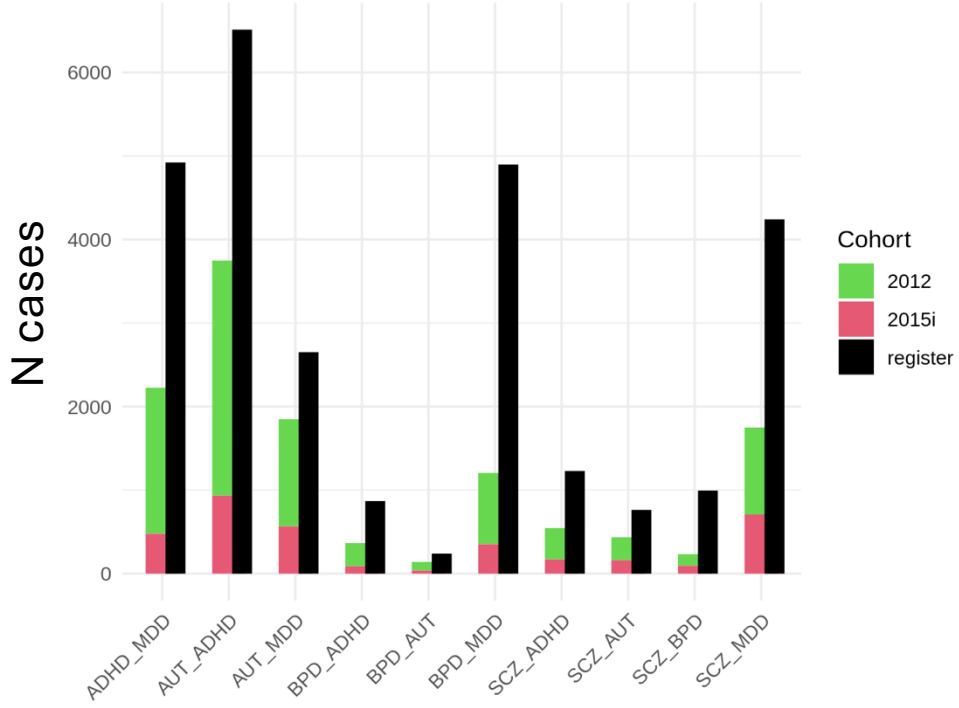
Genotyped individuals in iPSYCH2012 and iPSYCH2015i (combined = iPSYCH2015)

Krebs et al. 2025, AJHG

Sample size: per-disorder

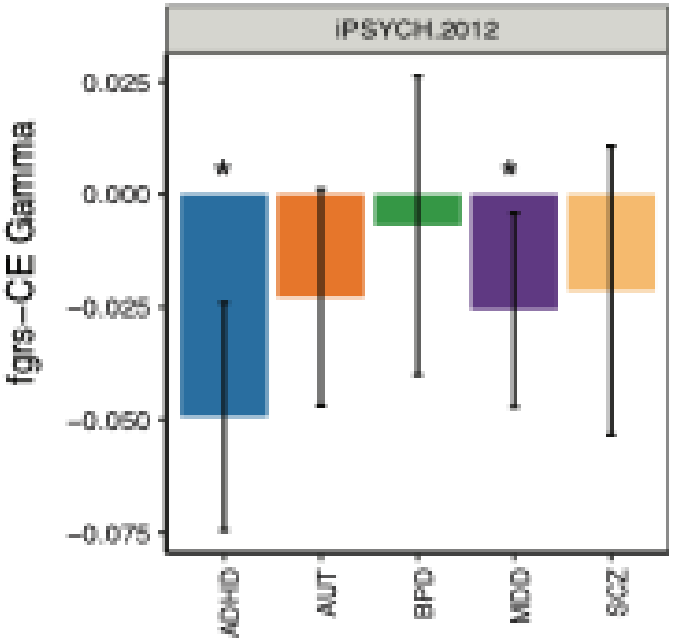


Sample size: comorbidity

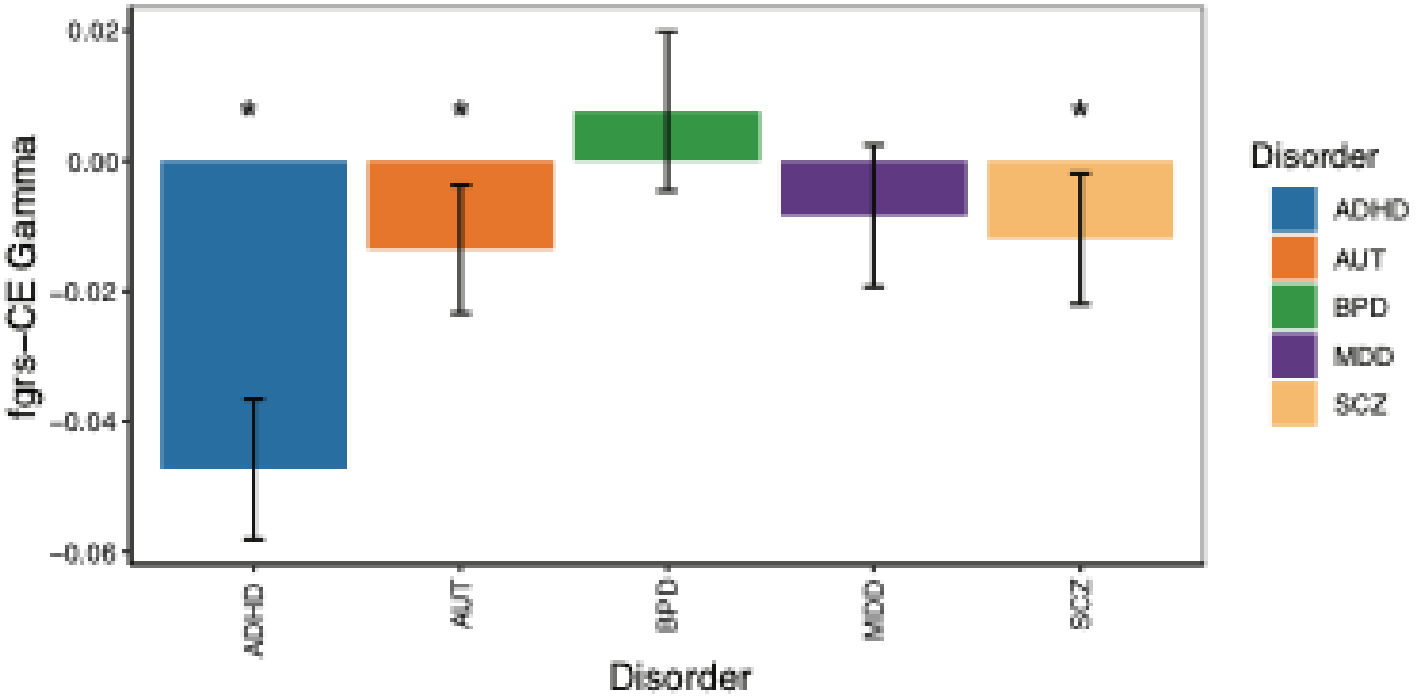


PRS and PA-FGRS mainly differ in power

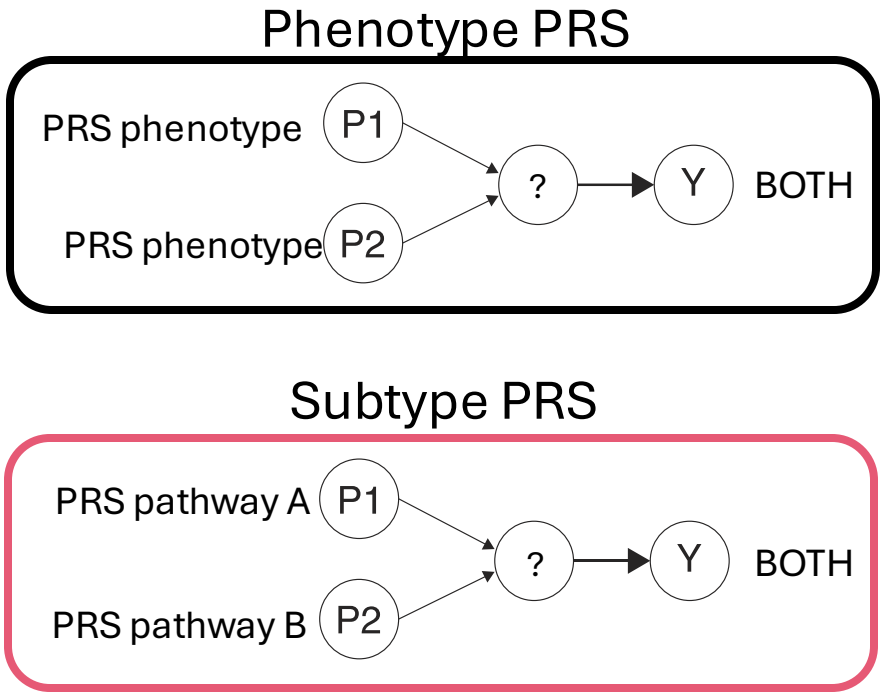
within-pheno
CE with PRS x
PA-FGRS

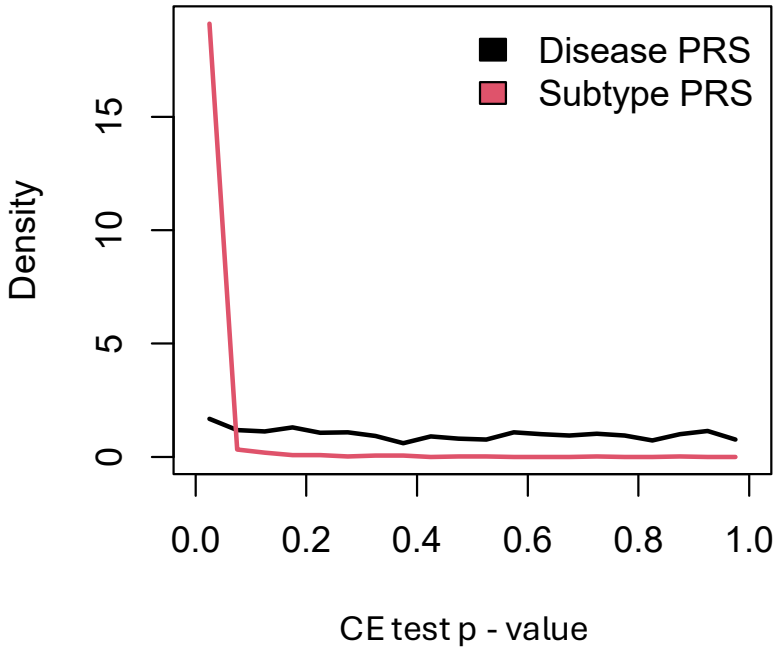


Within-disorder heterogeneity: PA-FGRS



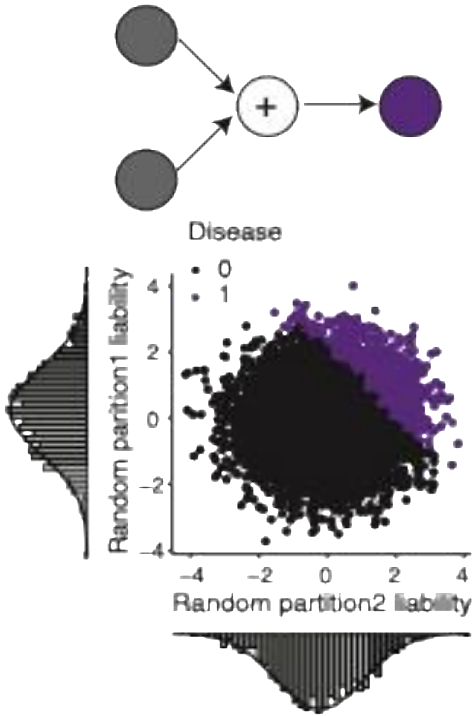
Simulation: knowing subtype = power



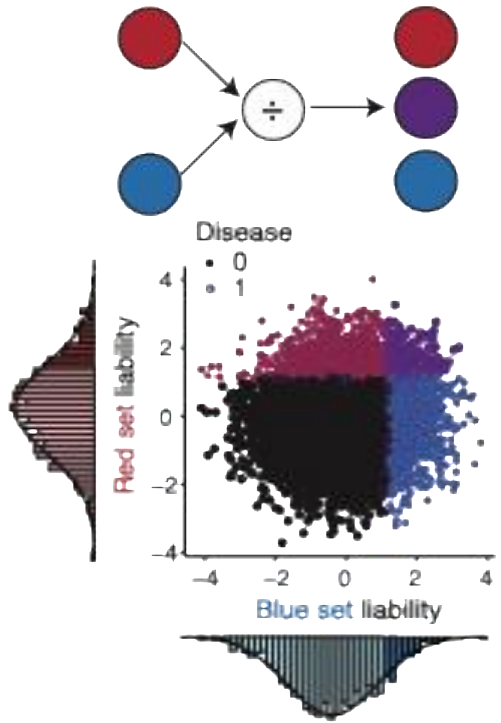


Interplay between genetic sets

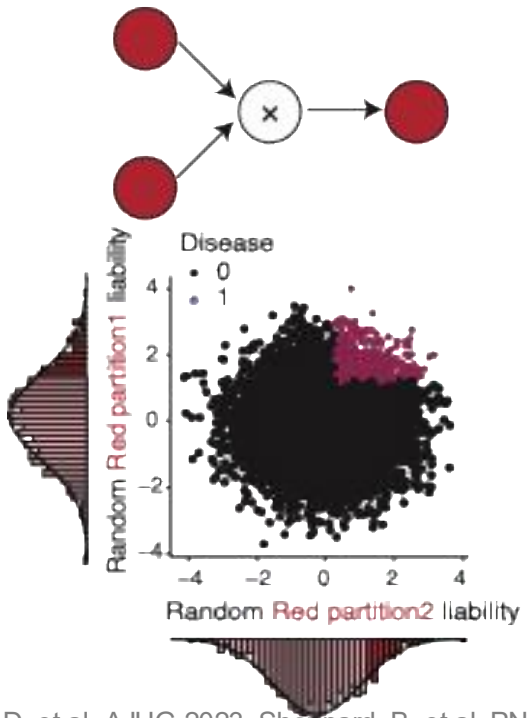
additive



antagonistic



synergistic



Tang D, et al. AJHG 2023, Sheppard, B. et al. PNAS 2022