Using Coordinated Epistasis to Investigate Genetic Architecture of Psychiatric Comorbidity

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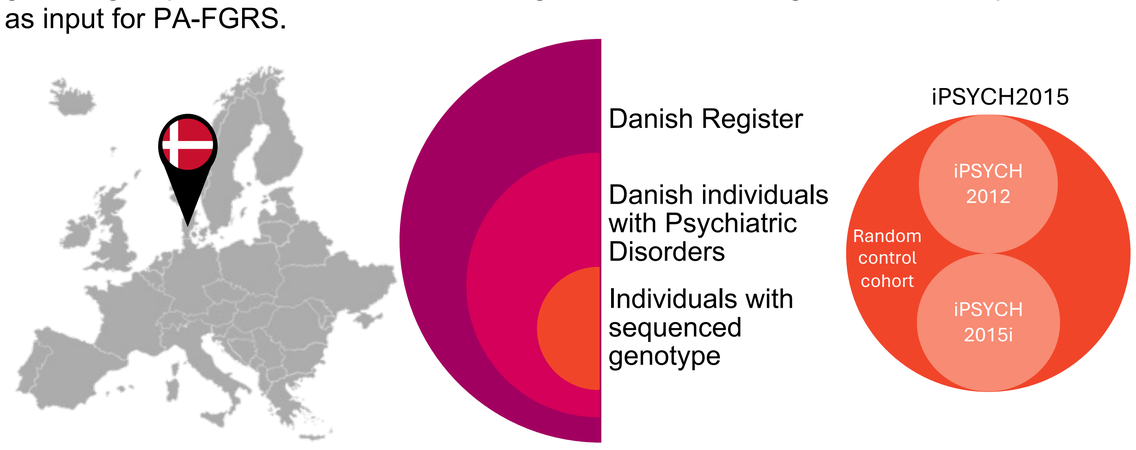
SUMMARY

Our research focuses on the identification of the shared genetic architecture across psychiatric disorders. This has not been previously possible as most genetic cohorts focus on single disorders. We work with data from the iPSYCH[1] dataset, which contains information on psychiatric comorbidity drawn from the Danish Medical Registry. Using this data, we perform the first study on the genetics of psychiatric comorbidity, asking if the genetic liability to each disorder and a variety of comorbid measures are likely on different and interacting pathways. To do this we extend the Coordinated Epistasis[2] (CE) framework using a combination of Polygenic Risk Scores[3] (PRS) and Pearson-Aitken Family Genetic Risk Scores[4] (PA-FGRS). For the first time, we identify coordinated polygenic interactions contributing to cross-disorder genetic sharing and comorbidity among five psychiatric disorders.

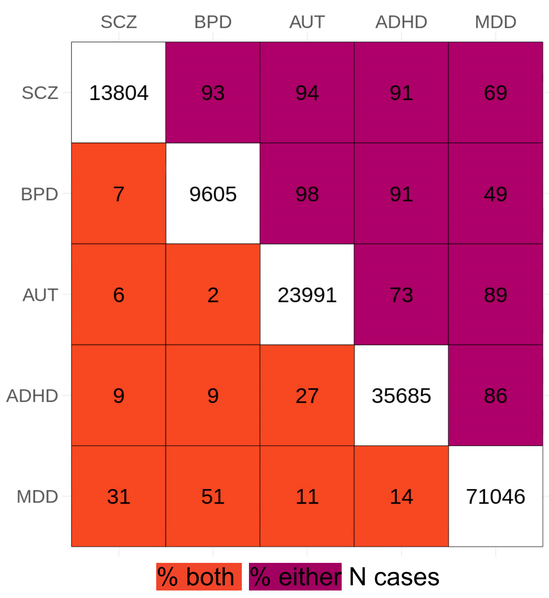
DATA

The iPSYCH dataset

The Lundbeck Foundation initiative for Integrative Psychiatric Research (iPSYCH2015[1]) contains genotype and phenotype information of individuals within the Danish Register that have a psychiatric disorder (cases), and a random sample of their population (controls). The whole of iPSYCH2015 is split into two sub-cohorts: iPSYCH2012[5] (30,000 controls; 57,377 cases) and iPSYCH2015i (19,982 controls; 36,741cases) which were genotyped on different SNP arrays. Besides genotype information, the current study also utilizes the geneologies present within the Danish Register data containing 2,066,657 unique relatives as input for PA-FGRS.



Psychiatric disorders and measures of their comorbidity



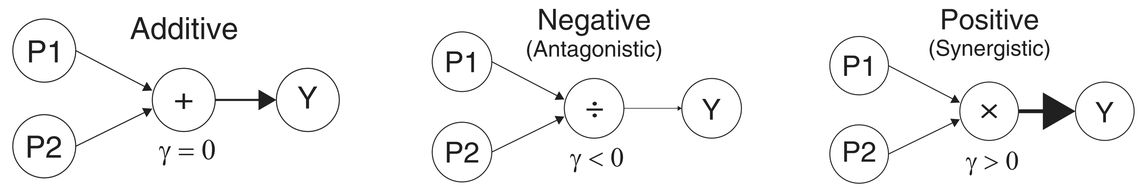
Within iPSYCH2015 we work with cases of schizophrenia (SCZ), major depressive disorder (MDD), bipolar disorder (BPD), attention-deficit hyperactivity disorder (ADHD) and autism (AUT). We derive the following **comorbidity measures** from them:

Comorbidity phenotype	Cases	Controls
Both	Having both disorders	Having neither
Either	Having either but not both disorders	Having neither
Both vs ether	Having both disorders	Having either but not both

METHODS

Coordinated Epistasis (CE)

The CE framework utilizes genetic liability scores (GS) to obtain representations of genetic pathways.[2] Then, using shown regression models, it shows us the direction of the interaction effect (γ) and we test for significance through log-likelihood test.

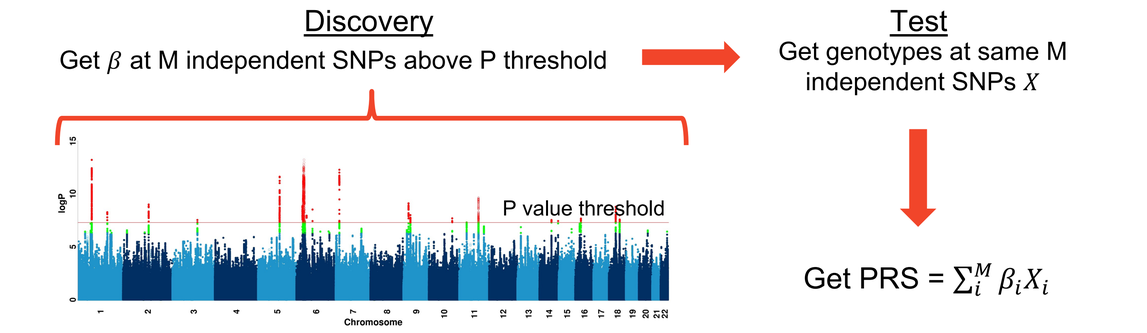


Single - pheno $A \sim covariates + \alpha_{A1} GS_{A1} + \alpha_{A2} GS_{A2} + \gamma_{A1,A2} GS_{A1} * GS_{A2}$

Cross - pheno $A \,\&\, B \sim covariates + \alpha_A GS_A + \alpha_B GS_B + \gamma_{A,B} GS_A * GS_B$

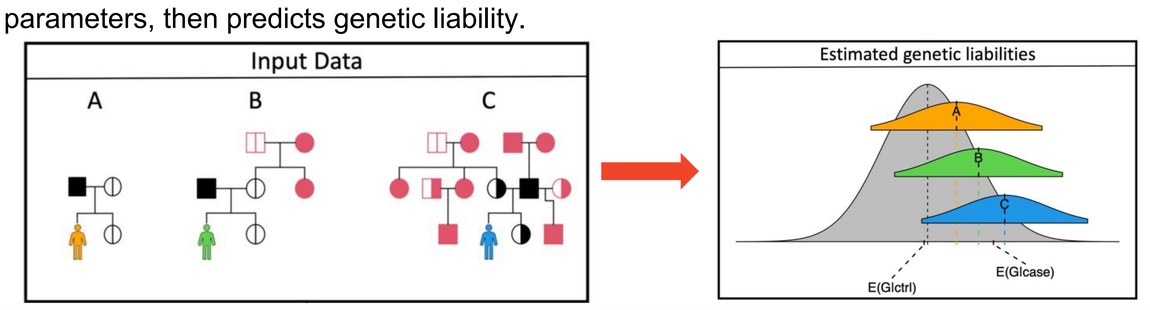
Polygenic risk scores (PRS)

The PRS is a GS that sums the product of genotypes in a test dataset with effect sizes β at independent significant SNPs from a Genome-Wide Association Studies (GWAS) performed on a discovery cohort. We apply the Clumping and Thresholding (C+T) using PRSice[6] to find optimal PRS that best predicts our phenotypes of interest.



Pearson-Aitken Family Genetic Risk Scores (PA-FGRS)

Under a mixture model, PA-FGRS[4] uses data from up to 20 relatives, estimates population parameters, then predicts genetic liability.

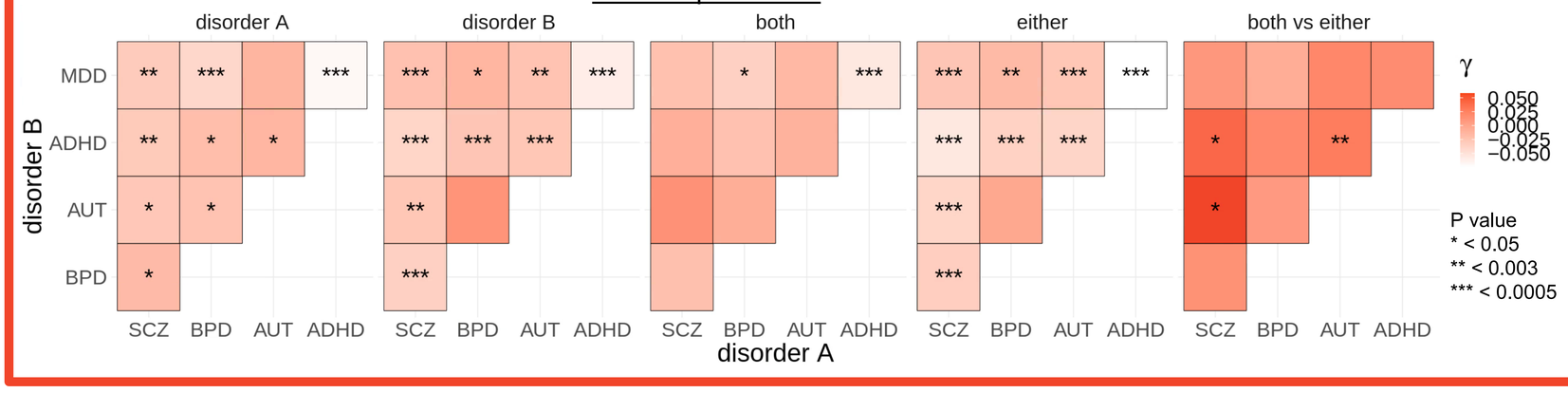


RESULTS

Interactions between psychiatric disorders

Our proof-of-concept analyses takes the pathway representations (PRS/PA-FGRS) of two disorders and asks if they interact in predicting either disorders, or their comorbidity measures. We first perform cross-pheno CE tests using PRS and PA-FGRS derived from single disorders. We find that while all significant interaction tests for individual disorders or the "both" and "either" comorbidity measures are negative, the significant interactions for the "both vs either" comorbidity measure are always positive. We then perform single-pheno CE tests using PRS and PA-FGRS derived from comorbidity measures. We highlight the "both vs either" hit of AUT-ADHD, which shows consistent positive interaction effects in both PRS and PA-FGRS in both the iPSYCH2012 and iPSYCH2015i cohorts.

Cross – pheno CE



Single – pheno CE

Discovery data	Prediction data	Liability estimator	γ	P value
iPSYCH2012	iPSYCH2015i	PRS	5.7E-02	1.3E-02
iPSYCH2015i	iPSYCH2012	PRS	3.0E-02	2.9E-02
Registry Data	iPSYCH2015	PA-FGRS	1.4E-02	1.1E-05

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4. Krebs et al. *MedRxiv* (pre-print)
5. Pedersen et al. *Mol Psychiatry* (2018)
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