Polygenic dissection of phenotypic heterogeneity in Alzheimer's disease

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December 2022

Problem and Motivation

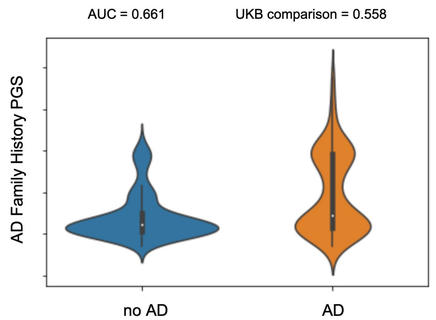
Alzheimer's disease (AD) is complex and multifaceted, with many implicated pathways across diverse cell types. The heterogeneous phenotypic manifestation across cognition, pathology, and treatment response is well-recognized. However, the genetic basis of phenotypic heterogeneity in AD remains unclear, due to limitations in statistical power. Statistical power is in turn limited by the sample size of genotyped individuals with densely profiled pathological and cognitive phenotypes, such as is the case with the Religious Orders Study/Memory Aging Project (ROSMAP).

Proposed Solution

We present an approach for mapping the genetic basis of phenotypic heterogeneity in AD through polygenic scores (PGS). Using PGS models trained on the larger but comparatively sparsely profiled UK Biobank dataset, we compute PGS for the ROSMAP participants and use these PGS as a condensed genotype for downstream analysis. This reduces the number of tested hypotheses and addresses the limitations in statistical power.

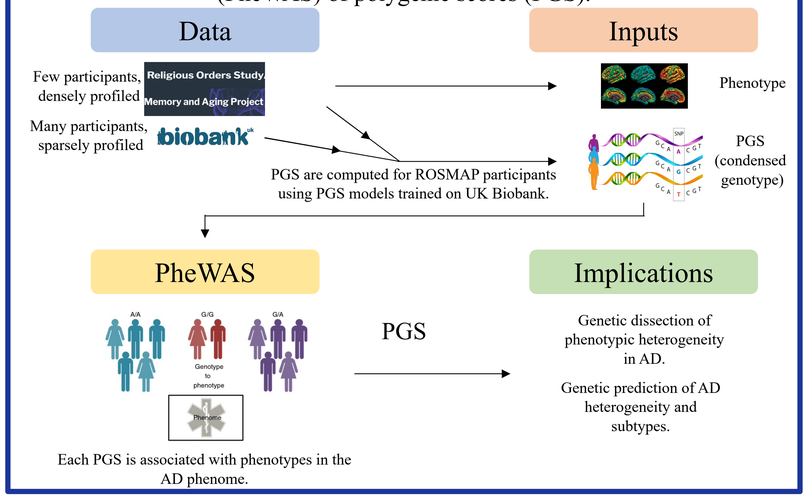
Result I: AD diagnosis prediction

The PGS for AD family history is predictive of AD diagnosis in the ROSMAP cohort (AUC=0.661), providing evidence that PGS translate well from the UK Biobank to ROSMAP.



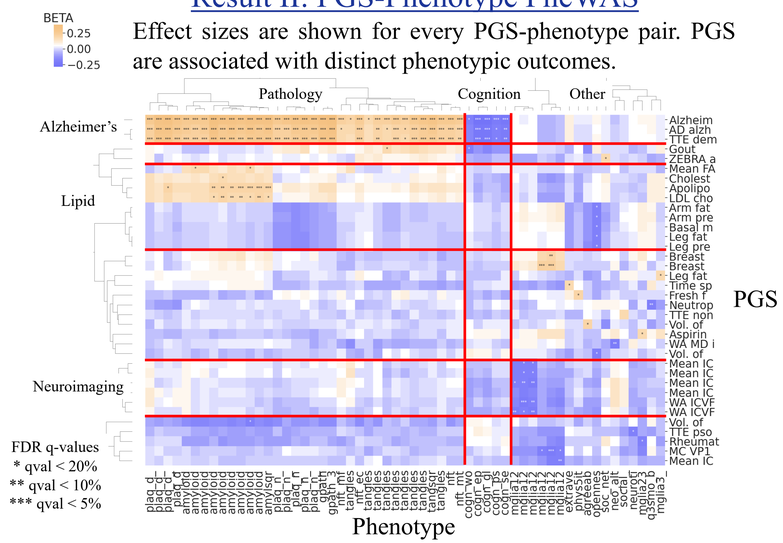
Overview

We map a genetic basis for cognitive and pathological heterogeneity in Alzheimer's disease (AD) by performing a phenome-wide association study (PheWAS) of polygenic scores (PGS).



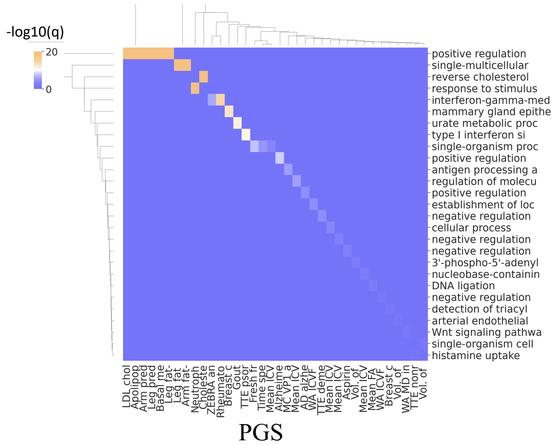
Result II: PGS-Phenotype PheWAS

Effect sizes are shown for every PGS-phenotype pair. PGS are associated with distinct phenotypic outcomes.



Result II: PGS-Phenotype PheWAS

We show the FDR q-values of PGS enrichment for biological processes, evaluated with GREAT on the genomic regions contributing to each PGS.



Implications

Our results pave the way towards mapping genetic basis of pathological and cognitive heterogeneity in AD, and more generally towards genetics-based dissection of phenotypic heterogeneity in complex and heterogeneous traits even in inaccessible tissues.

References

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