Understanding the Genetic Architecture of Schizophrenia in South Asian Populations

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Background & Objectives

Schizophrenia is a highly heritable psychiatric disorder (Hilker et al., 2018), and large genome-wide association studies (GWAS) have identified over a hundred common risk variants (Trubetskoy et al., 2022). However, most genomic studies have focused on European ancestry (Sirugo et al., 2019), limiting the generalisability and reducing the predictive performance of polygenic risk scores (PRS) in non-European populations (Martin et al., 2019). Recent work has begun to include more diverse populations (Lam et al., 2019). Yet South Asians remain markedly underrepresented in psychiatric genomics. In addition, South Asian populations have higher rates of consanguinity, leading to increased genomic autozygosity (Bittles & Black, 2010), which may also influence the distribution and expression of schizophrenia risk alleles. Together, these factors highlight the need for more genetic studies in South Asian populations.

Therefore, the objectives of this study were to: (1) perform a genome-wide association study (GWAS) of schizophrenia in South Asian individuals; **(2)** examine cross-ancestry consistency by comparing association signals between South Asian and European-ancestry GWAS; and **(3)** investigate whether increased genomic autozygosity contributes to schizophrenia risk in South Asians.

Method

Sample

South Asian individuals from the Genes & Health (G&H) cohort were included, comprising British Bangladeshi and Pakistani participants. Schizophrenia cases were defined using ICD-10 codes F20/F25.1 from linked NHS electronic health records. Controls were individuals without psychotic disorder diagnoses (F20–F29, F31).

Genotyping &Quality control

Genotyping was performed using the Illumina GSA v3.0 and imputed to TOPMed (GRCh38). Variant QC included INFO ≥ 0.6, minor allele count (MAC) ≥ 20, and autosome-only filters. Principal component analysis was performed.

Association Analysis

GWAS was performed using Regenie, adjusting for age, sex and 20 PCs.

Cross-Ancestry Comparison

Effect directions and effect sizes from the South Asian GWAS were compared with three PGC schizophrenia GWAS result: multi-ancestry, European-only, and Asian-only. Concordance was evaluated using binomial sign tests and effect size correlations. PRS of schizophrenia were generated based on European GWAS, and its predictive performance for schizophrenia was assessed in the South Asian sample.

Autozygosity Analysis

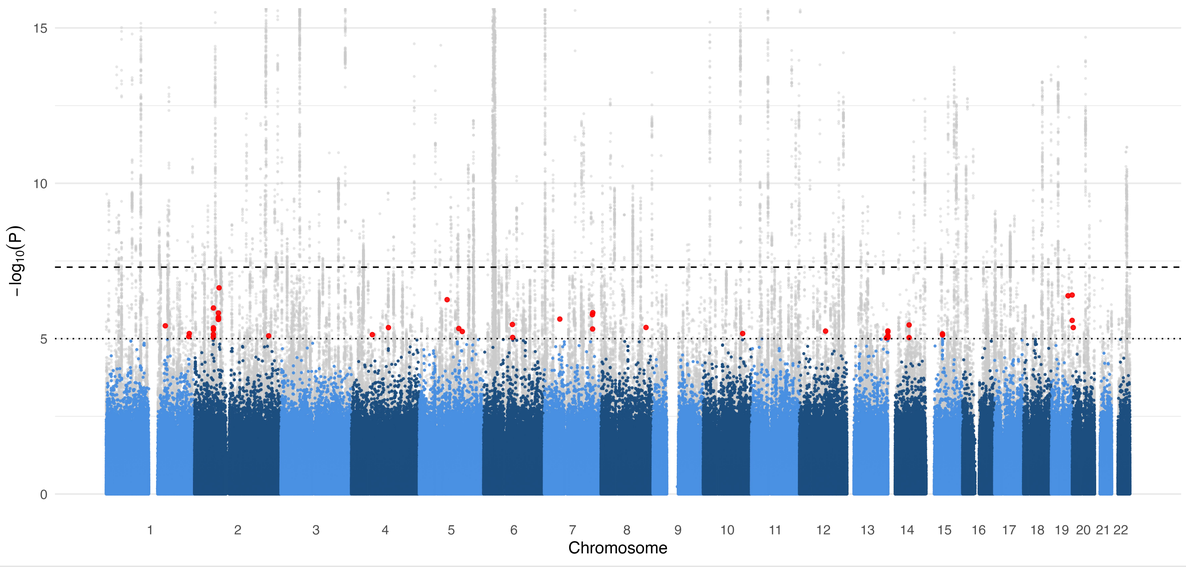
Autozygosity was quantified as the fraction of genome in runs of homozygosity (FROH), calculated using PLINK. Associations between FROH and schizophrenia were evaluated using logistic regression adjusting for age, sex, and principal components.

Result

Genome-wide Association Study

- 415 schizophrenia cases and 42,849 controls were included in the GWAS.
- After standard quality control, ~7.5 million imputed SNPs were retained for analysis.
- No variants reached genome-wide significance ($p < 5\times10^{-8}$)
- 46 SNPs surpassed the suggestive significance threshold ($p < 1\times10^{-5}$).
- FUMA identified **10 independent lead SNPs**, corresponding to 39 candidate SNPs.

Figure 1. *Manhattan plot: South Asian GWAS overlaid on PGC GWAS*

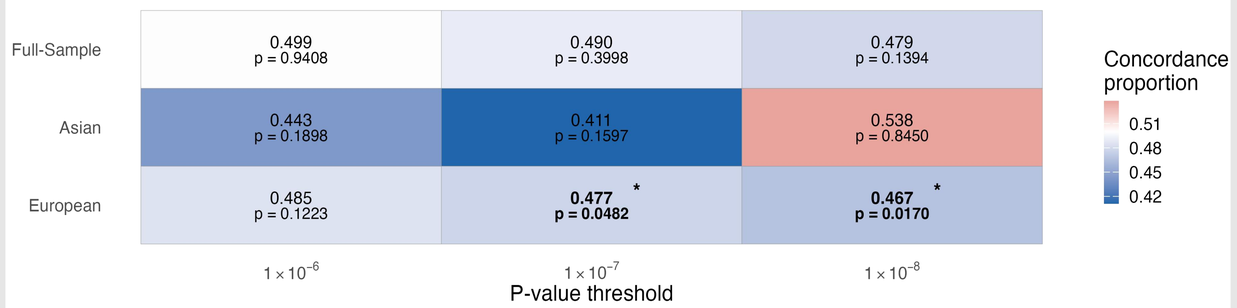


Cross-ancestry Consistency

Binomial Test

- Overall concordance with PGC schizophrenia GWAS was close to chance (~ 0.48-0.50) and not statistically significant.
- Concordance with the Asian reference increased above 0.5 at the strictest p-value threshold, but was not significant.
- Concordance with the European reference was significantly below 0.5 at strict p-value thresholds, indicating modest **directional discordance**.

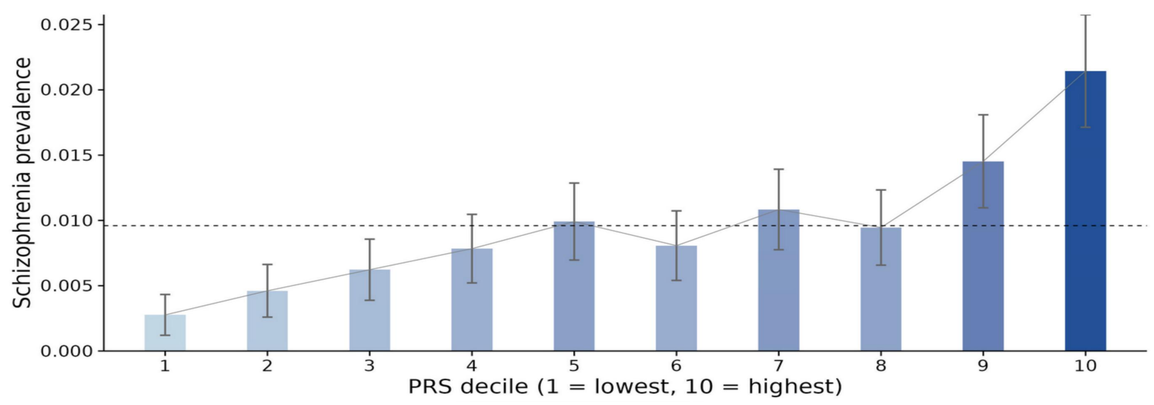
Figure 2. *Effect-direction concordance between South Asian GWAS and other ancestry GWAS across p-value thresholds*



Polygenic Risk Score (PRS) Transferability

- Schizophrenia prevalence increased steadily across PRS deciles.
- Logistic regression showed that European-derived PRS significantly predicted schizophrenia status in South Asians ($\beta = 0.516$, $p < 2\times10^{-16}$). Model fit was modest (Nagelkerke $R^2 = 0.015$).

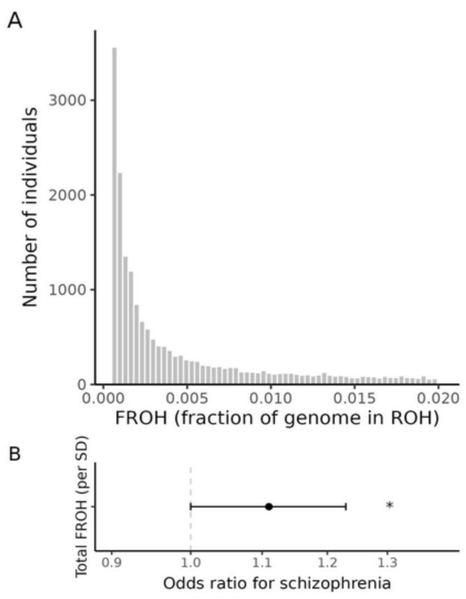
Figure 3. *Schizophrenia PRS across PRS deciles*



Autozygosity

- FROH showed a right-skewed distribution, with most individuals having low autozygosity but a noticeable long tail of higher FROH values
- Total FROH (per SD increase) showed a **modest but significant association** with schizophrenia in logistic regression (OR = 1.11, 95% CI = 1.00–1.23, $p = 0.047$).
- The association was not significant when restricting the analysis to the high-FROH subgroup.

Figure 3. *FROH distribution and its association with schizophrenia*



Conclusions

- South Asian and European schizophrenia GWAS showed limited directional overlap, highlighting **ancestry-related differences** in genetic architecture.
- **Larger South Asian datasets** will be essential to clarify population-specific risk alleles and improve the global representation of psychiatric genomics.

Acknowledgements

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