Quantifying clinically actionable enrichment of polygenic risk for psychiatric disorders in pharmacologically receptive pathways in individuals with schizophrenia

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Background: Individuals with psychiatric disorders usually have a heritable burden of common genetic variation that can be aggregated and quantified using a polygenic risk score (PRS). While PRS has some predictive utility, it lacks the molecular specificity to be directly informative for clinical interventions. We wanted to develop a new analytic method which captures and scores the polygenic risk for psychiatric disorders in discrete pathways that are receptive to pharmacological manipulation.

Materials and Methods: A metric, we designated the ***Pharmagenic Enrichment Score*** (PES), was established to quantify the impact of common variation in systems that interact with existing drugs and nutrients. The PES framework identifies clinically actionable pathways enriched with common variation, which can be profiled in individual patients.

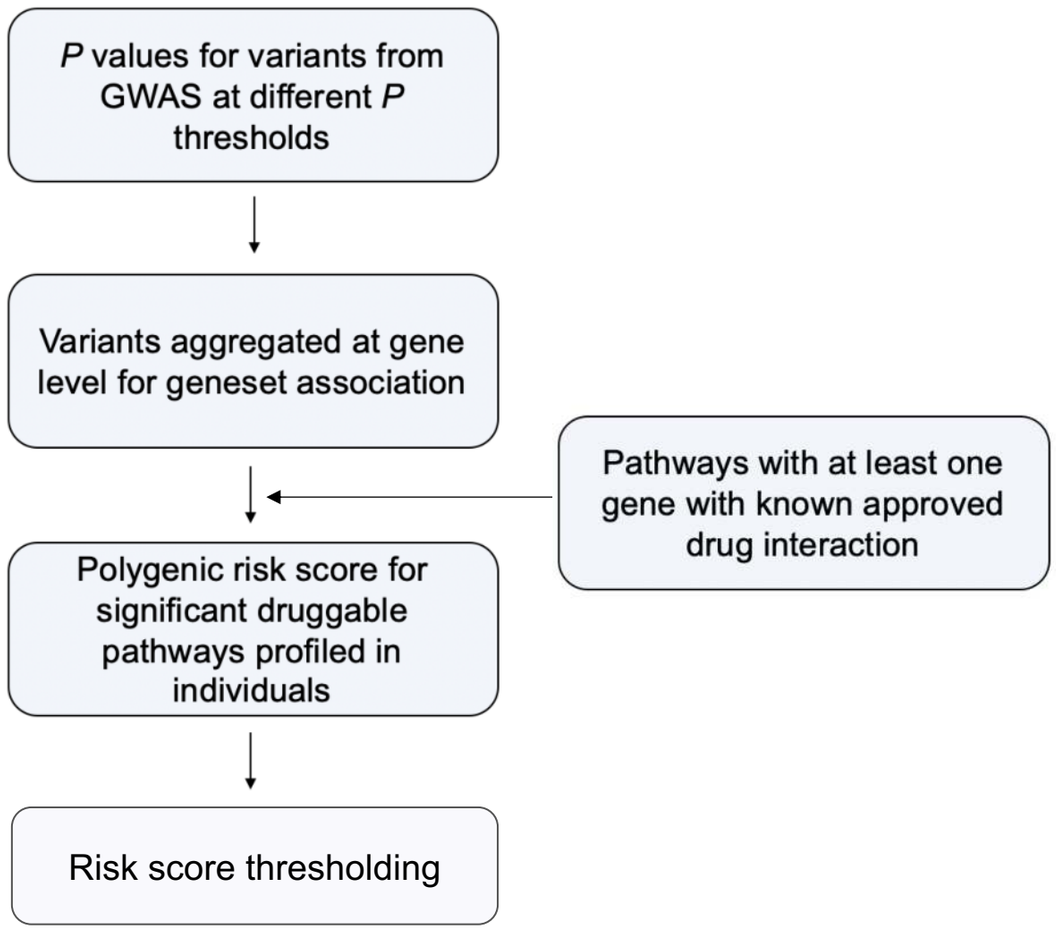

Figure 1: Schematic for PES framework for quantifying enrichment of disease-associated polygenic risk in clinically actionable pathways.

Results: The PES framework was used to identify 8 pharmacologically modifiable pathways enriched with common variation associated with schizophrenia ($P < 1x10^{-3}$) using the 2014 PGC GWAS summary statistics. These pathways were enriched with genes expressed in the brain ($P_{Adj} = 6.45 \times 10^{-13}$).

PES pathway	Drug*	ATC Code Level 4
NOS1	Glycine	Other irrigating solutions
GABA	Baclofen	Other centrally acting agents#
CRMPs Sema3A	Dasatinib	Protein kinase inhibitors
HIF-2	Sunitinib	Protein kinase inhibitors
Acetylcholine	Varenicline	Drugs used in nicotine dependence
Hedgehog	Tacrine	Anticholinesterases
Folate	Trifluridine	Antivirals
Insulin	Exenatide	Glucagon-like-peptide-1 analogue

Table 1: Clinical actionable pathways enriched with common variation associated with schizophrenia. Actionable pathways were designated by virtue of having targets for existing drugs including those exemplified in the drug column.

The PES analysis for schizophrenia was performed on participants in the Australian Schizophrenia Research Bank (ASRB) cohort genotyped with the illumina 610K SNP array. More than 50% of cases had top percentile PES and 50% of these had relatively low total PRS for schizophrenia (Fig. 2).

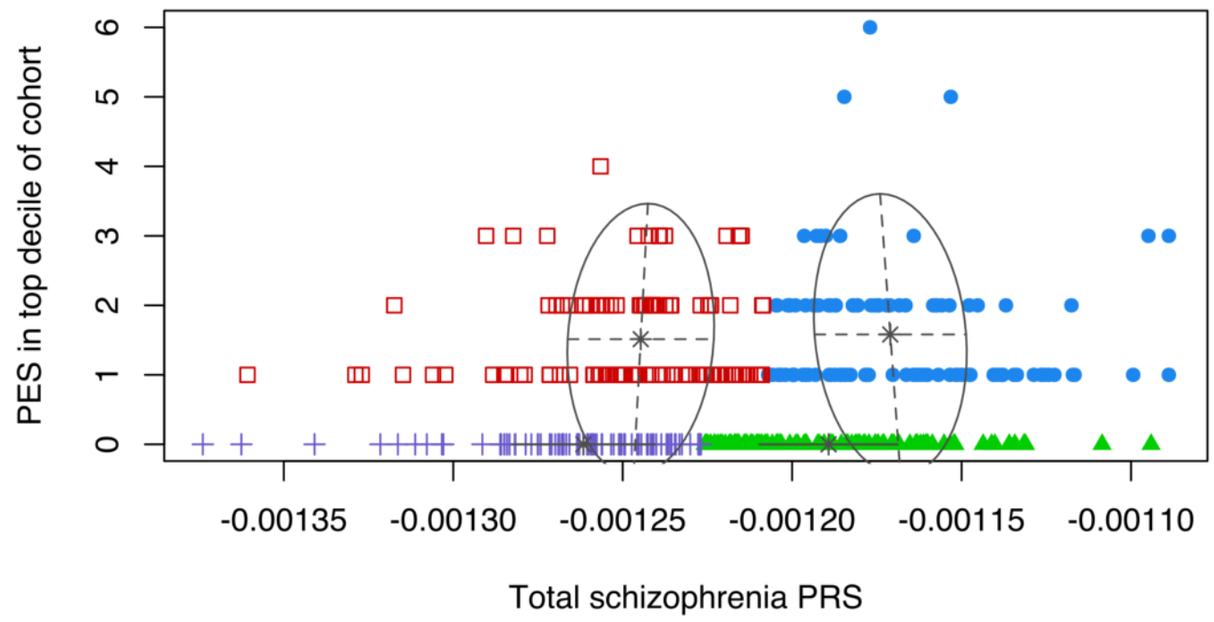

Figure 2: Clustering of genome wide **PRS** and the individual count of elevated **PES** using finite Gaussian mixture modelling.

The effect of PES on the expression of genes within each pathway was examined in PBMCs from the same cohort. All but one pathway had nominally significant relationships with expression (14 genes) including 3, such as *Regulation of insulin secretion*, that survived correction for multiple testing (FDR<10%) (Fig 3).

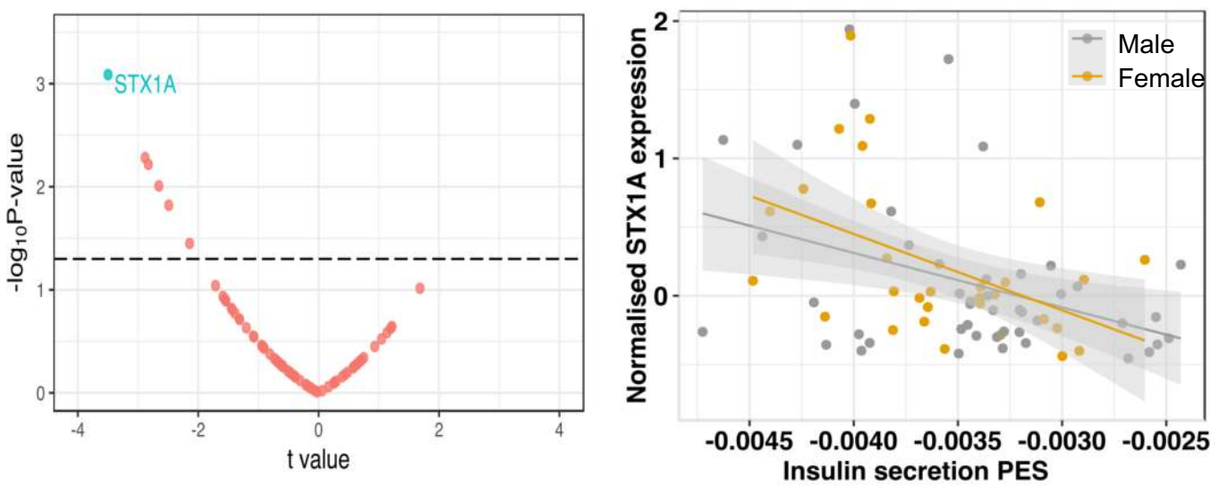

Figure 3: The relationship between PES for ***regulation of insulin secretion*** and the expression of the member gene ***STX1A*** in peripheral blood mononuclear cells.

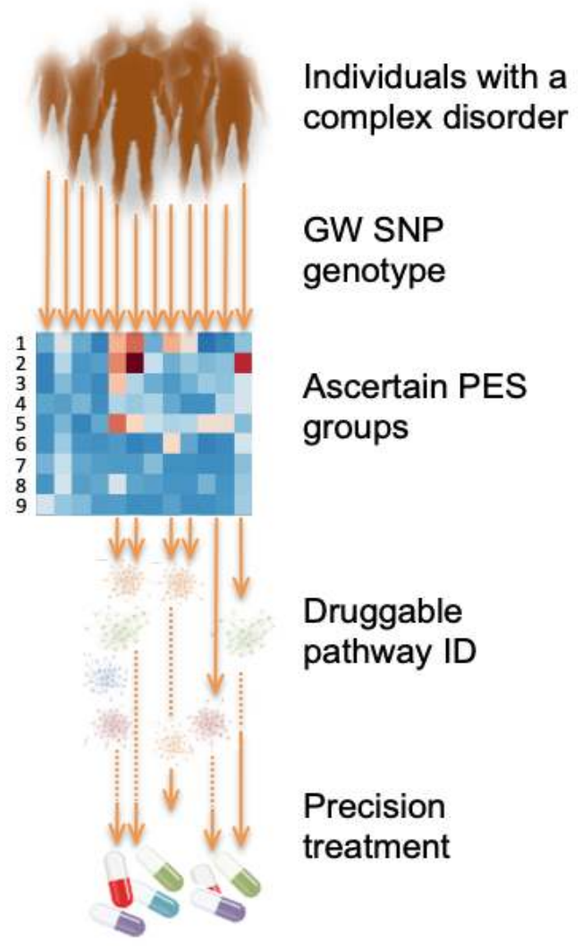

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Figure 4: Implementation of PES in precision treatment of complex disorders. Individuals provide DNA for common variant SNP genotyping. These are used to ascertain related PES. High scores relative to a reference population would then be used to direct treatment with compounds that act in the associated pathways.

Conclusions: A large proportion of schizophrenia cases had elevated PES in one or more of eight clinically actionable genesets enriched with schizophrenia associated common variation, including many with low total PRS for the disorder. While some compounds implicated have been used in schizophrenia, many are approved for other conditions and have not been previously considered for psychiatric treatment. This approach has the potential to provide a mechanism for precision medicine in psychiatric disorders, particularly for difficult treatment resistant cases.