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The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review

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ABSTRACT

Studying the phenotypic manifestations of increased genetic liability for schizophrenia can increase our understanding of this disorder. Specifically, information from alleles identified in genome-wide association studies can be collapsed into a polygenic risk score (PRS) to explore how genetic risk is manifest within different samples. In this systematic review, we provide a comprehensive assessment of studies examining associations between schizophrenia PRS (SZ-PRS) and several phenotypic measures. We searched EMBASE, Medline and PsycINFO (from August 2009–14th March 2016) plus references of included studies, following PRISMA guidelines. Study inclusion was based on predetermined criteria and data were extracted independently and in duplicate. Overall, SZ-PRS was associated with increased risk for psychiatric disorders such as depression and bipolar disorder, lower performance IQ and negative symptoms. SZ-PRS explained up to 6% of genetic variation in psychiatric phenotypes, compared to <0.7% in measures of cognition. Future gains from using the PRS approach may be greater if used for examining phenotypes that are more closely related to biological substrates, for scores based on gene-pathways, and where PRSs are used to stratify individuals for study of treatment response. As it was difficult to interpret findings across studies due to insufficient information provided by many studies, we propose a framework to guide robust reporting of PRS associations in the future.

1. Introduction

Schizophrenia (SZ) is highly heritable (Sullivan et al., 2003). The importance of studying the phenotypic manifestations of increased schizophrenia liability has long been recognized as a way to increase our understanding of this disorder. However, until recently, such research has been limited to small studies of individuals at high risk as indexed by having a family history (Niemi et al., 2003).

Genome-wide association studies (GWAS) of schizophrenia have now identified multiple risk variants (Purcell et al., 2009; Ripke et al., 2014), and although individual loci have small effects on risk, information from even moderately associated alleles can be collapsed into a single polygenic risk score (PRS) to explore how genetic risk is manifest across different populations or stages of development (Fig. 1) (Wray et al., 2014).

Since this approach was first described, many studies have examined whether SZ-PRS is associated with a diverse range of phenotypes. To summarise this literature, we conducted a systematic review to identify studies that have used a PRS approach to examine phenotypes associated with genetic risk for schizophrenia.

2. Methods

We undertook a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) (Supplementary Table 1).

2.1. Search strategy

2.1.1. Inclusion/exclusion criteria

We included articles that examined associations between a PRS (derived from GWAS data of participants with schizophrenia) and a measurable phenotype (excluding neuroimaging outcomes). Articles reporting associations with a diagnosis of schizophrenia as an outcome were not included. Articles were required to be published in peer-reviewed journals in English (see Supplementary Table 2 for inclusion/exclusion criteria).

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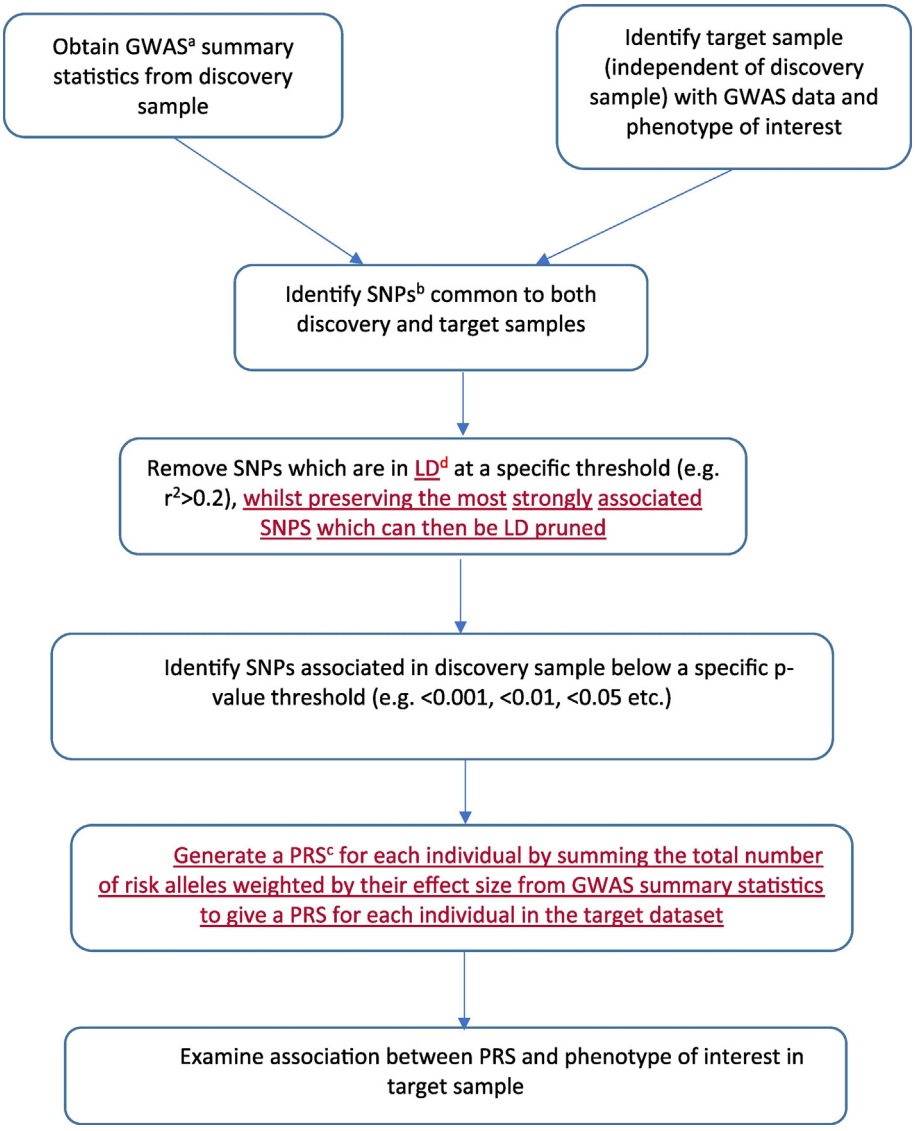

Fig. 1. Basic steps for constructing a polygenic risk score based on discovery sample p-thresholds. a. GWAS; Genome Wide Association Studies, b. SNPs; Single Nucleotide Polymorphisms, c. PRS; Polygenic Risk Score d. LD; Linkage Disequilibrium.

2.1.2. Data sources

We searched EMBASE, Medline and PsychINFO from 06/08/2009 to 14/03/2016, and hand-searched references of included articles.

2.1.3. Search terms and delimiters

We searched for articles using the terms "schizophrenia (or variations of)" AND "polygenic (or variations of)". Full search strategy terms are listed in Supplementary List 1.

2.1.4. Data collection and analysis

2.1.4.1. Selection of studies. There were 1043 articles after de-duplication (Fig. 2). Titles and abstracts were initially screened by one author (S.M.). If it was unclear whether the paper contained relevant data, or the abstract was not available, the full-text article was retrieved. Full-text articles were reviewed and checked against inclusion criteria by two authors independently. Disagreements were resolved by a third author. Relevant data were extracted using a data extraction form (Supplementary Table 3). Results were summarised using a narrative approach because most studies did not report results in a format comparable with other studies.

3. Results

Thirty-one articles examined the association between SZ-PRS and a measurable phenotype. Most studies used the Psychiatric Genetics Consortium-1 SZ (PGC-1-SZ) discovery sample and reported associations at different P_T values (Supplementary Tables 4a-4e).

3.1. Non-schizophrenia psychosis diagnoses

A higher SZ-PRS was found in schizoaffective compared to non-schizoaffective bipolar disorder within the Wellcome Trust Case-Control Consortia (WTCCC) ($P_T < 0.5$; one-tailed $p = 5 \times 10^{-4}$), and replicated using University College London Bipolar Disorder (UCL-BD) sample data (one-tailed $p = 0.007$) (Hamshere et al., 2011).

In a Norwegian sample, the SZ-PRS was higher in those with bipolar I disorder (strongest $P_T < 0.05$; $p = 3.1 \times 10^{-5}$), schizoaffective disorder ($p = 7.4 \times 10^{-3}$), and psychosis-NOS ($p = 0.016$) compared to controls without SZ, BD or MDD (Tesli et al., 2014).

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