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 less than 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.

Key words: polygenic risk score, schizophrenia, genetic, phenotypes

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 (Figure 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).

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 (Figure 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=5x10^{-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 =3.1x10^{-5}), schizoaffective disorder (p=7.4x10^{-3}), and psychosis-NOS (p= 0.016) compared to controls without SZ, BD or MDD (Tesli et al. 2014).

In another study, the SZ-PRS was reported as not associated with psychosis history in individuals with BD, though no statistics were provided (Ruderfer et al. 2014).

3.2 Schizophrenia symptoms/severity

In the Netherlands case-control study of schizophrenia, SZ-PRS was associated with five symptom dimensions (strongest P_T<0.5): positive (p=<0.01), negative (p= <0.001), mania (p= <0.01), depression (p= <0.001) and disorganisation (p=0.04) within the combined case-control sample, but not with these dimensions in cases and controls examined separately (Derks et al. 2012).

In data from the Molecular Genetics of Schizophrenia sample, SZ-PRS was associated with the negative/disorganized factor (strongest P_T<0.5, p=0.006), but not with the positive symptoms or mood factors (Fanous et al. 2012).

The population-based Longitudinal Experiences and Perceptions (LEAP) study found that SZ-PRS was associated with decreased anhedonia (strongest P_T<0.5; one-tailed p=0.003) and parent-rated negative symptoms in adolescence (one-tailed p=0.029) (Sieradzka et al. 2014).

In another population cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC), there was weak evidence that SZ-PRS was associated with increased adolescent psychotic experiences (strongest P_T<0.3; p=0.134). However, a PRS derived from the 17 genome-wide significant single nucleotide polymorphisms (SNPs) published at the time was associated with reduced odds of psychotic experiences (p=0.024) (Zammit et al. 2014).

A further ALSPAC study used the larger PGC-2-SZ discovery sample and reported that SZ-PRS (P_T<0.05) was associated with adolescent negative symptoms (p=0.001) and anxiety disorder (p=0.002), but not with depression (p=0.77) or psychotic experiences (p=0.14) (Jones et al. 2016).

A study from the Centre for Addiction and Mental Health found no evidence of association between SZ-PRS and antipsychotic dosage (e.g. defined daily dosage: P_T<0.01; p=0.512) or global assessment of functioning (p=0.550) (Hettige et al. 2016).

One study reported higher SZ-PRS in individuals with schizophrenia with a history of clozapine treatment, compared to those without (strongest P_T<0.5; 1-tailed p=0.02), as well as in those who responded to clozapine compared to those who did not (1-tailed p=0.06) (Frank et al. 2015).

3.3 Other psychiatric disorders

A study using data from the PGC reported the SZ-PRS was associated with BD (strongest P_T<0.3; p=$1x10^{-16}$), depression (p=$1x10^{-16}$), and Autism Spectrum Disorder (ASD) (strongest P_T<0.001; reported as p= <0.05), but not with ADHD at any P_T (Cross-Disorder Group of the Psychiatric Genomics 2013). There was also weak evidence supporting an association with ASD in the Autism Genome Project (strongest P_T<0.01; p=0.08) (Vorstman et al. 2013), and

strong evidence of association with depression (strongest P_T<0.1; p=8.3x10^{-12}), severe atypical (p=7.8x10^{-5}) and typical (strongest P_T<0.5; p=7.8x10^{-9}) depression in combined data from two Netherlands-based samples (Milaneschi et al. 2016).

SZ-PRS was also associated with BD in two other studies: one using data from the STEP-BD and WTCCC-BD samples (strongest P_T<0.5; p=7x10^{-9} and p=1x10^{-12} respectively) (Purcell et al. 2009), and another also using data from the WTCCC but using the larger PGC-2-SZ discovery sample (P_T<1; p=3.7x10^{-47}) (Stringer et al. 2014).

Inconsistent with the results from the PGC described above, a study using data from adolescents in Dublin, UK, reported a higher SZ-PRS in ADHD cases compared to controls (P_T<0.5; p=1.04x10^{-4}) (Hamshere et al. 2013).

SZ-PRS was not associated with post-traumatic stress disorder (PTSD) across any P_T in the Marine Resiliency Studies (Nievergelt et al. 2015).

3.4 Cognition

Higher SZ-PRS was associated with lower total IQ in a combined schizophrenia case–control sample (strongest P_T<0.3, p=8x10^{-4}), but this was attenuated when analysing cases only (p=0.067), with no association in controls (van Scheltinga et al. 2013). Higher SZ-PRS was also associated with worse cognitive ability in people with schizophrenia within the Cognitive Genomics Consortium (strongest P_T< 0.5, p=1.4x10^{-4}) (Lencz et al. 2014).

Higher SZ-PRS was also associated with poorer cognitive ability in two population-based samples: i) the Lothian birth cohort (Moray House Test (MHT) of cognitive ability at age 70, strongest P_T <0.1, p=0.08; Wechsler non-verbal subtests, strongest P_T <0.5, p=0.005), and ii) the ALSPAC birth cohort (performance IQ, strongest P_T <0.1, p=6.07x10^{-4}; total IQ, p=0.008) (Hubbard et al. 2016).

Furthermore, higher SZ-PRS was also associated with greater decline in IQ with age in the Lothian birth cohort (MHT, strongest P_T<0.01, p=0.03; Wechsler non-verbal subtests, p=0.003) (McIntosh et al. 2013).

However, it is notable that not all findings were consistent across different samples, ages or measures. In the Lothian birth cohort, there was no evidence of association between SZ-PRS and IQ at age 11 years (strongest P_T<0.5, p=0.22) (McIntosh et al. 2013), whilst in the ALSPAC study, there was very weak evidence of association with verbal IQ (strongest P_T<0.0001, p=0.119) (Hubbard et al. 2016). Furthermore, in the Athens Study of Psychosis Proneness, there was no association between SZ-PRS and non-verbal IQ or the verbal n-back test (no statistics reported) and weak evidence of association with shorter sustained attention (strongest P_T <0.5; 1-tailed p=0.045) and poorer spatial working memory accuracy (1-tailed p=0.044) (Hatzimanolis et al. 2015).

Higher SZ-PRS in individuals with schizophrenia was associated with lower pre-pulse inhibition (PPI) in the Learning on Genetics of Schizophrenia study (strongest P_T<0.05, p=0.005) (Roussos et al. 2015), and with lower auditory steady-state response (ASSR) gamma oscillation (strongest P_T<1x10^{-5}, p=0.003), but not with other event-related potential phenotypes (P3 latency, P3 amplitude or P50 ratio) across any P_T in another study (Hall et al. 2015).

3.5 Other phenotypes

For other phenotypes, higher SZ-PRS was associated with: i) increased creativity (strongest at P_T<0.2, p=5.2x10^{-6}), years in school (p=1.2x10^{-4}) and obtaining a university degree (p=0.014) within an Icelandic general population study (Power et al. 2015); ii) higher seasonality score, indexing risk for seasonal affective disorder (strongest at P_T<0.5, p=1.61x10^{-15}) within the Australian Twin Registry (ATR) and Midwest Alcohol Research Centre data (Byrne et al. 2015); iii) lifetime cannabis use (strongest P_T< 0.01, p=2.6x10^{-4}) also using ATR data (Power et al. 2014); iv) family history of psychotic illness in individuals with SZ using PGC data (strongest P_T<0.4 (1-tailed-p=0.003) (Bigdeli et al. 2015); v) in individuals

with BD with psychosis compared to without psychosis in the WTCCC (P_T<0.5; p=0.092), but not in the UCL-BD sample (p=0.232) (Hamshere et al. 2011); and vi) with reduced risk of suicide attempts in individuals with depression from four independent samples (strongest P_T<0.05, p=0.05) (Mullins et al. 2014).

3.6 Non-psychiatric disorders

Higher SZ-PRS was not (or only very weakly associated with physical health disorders in a study using WTCCC data (strongest P_T<0.5: coronary artery disease p=0.71; Crohn's disease (CD) p=0.05; hypertension p=0.3; rheumatoid arthritis (RA) p=0.65; type I diabetes (T1D) 0.23; type II diabetes (T2D) p=0.06 (Purcell et al. 2009). Another study also using the WTCCC RA sample reported only weak evidence of association with RA (strongest P_T<0.01, p=0.085) (Euesden et al. 2015).

Another study reported much stronger evidence of association between the SZ-PRS and physical disorders using WTCCC data, but using the larger PGC-2-SZ discovery sample: T1D ($p=2.8x10^{-11}$), CD ($p=1.4x10^{-9}$), RA ($p=1.8x10^{-11}$) and T2D ($p=5.7x10^{-5}$), all compared to controls at P_T<1. The SZ-PRS also differed between immune cases (T1D, CD and RA combined), BD cases and T2D cases (p= <0.05); between immune cases and BD cases (p= <0.05); and between immune cases and T2D cases (p= <0.05), though how these groups differed was not specified (Stringer et al. 2014).

Finally, a USA-based study reported no association between the SZ-PRS and Parkinson's disease, although no statistics were reported (Schulze et al. 2014).

4. Discussion

To the best of our knowledge, this is the first paper to systematically review how SZ-PRS is associated with a wide range of phenotypic outcomes, although other reviews have covered PRS methodology and some have included studies of SZ-PRS (Wray et al. 2014).

Higher SZ-PRS was associated with increased risk of several different psychopathologies. Typically, R^2 values for other psychiatric disorders was greatest (1%-6%), whereas values for schizophrenia symptoms and cognitive phenotypes were smaller (<0.7%).

4.1 Psychiatric disorders

There was consistent evidence in at least two studies of higher SZ-PRS in individuals with BD, schizoaffective bipolar disorder, (Hamshere et al. 2011; Tesli et al. 2014) and depression (Cross-Disorder Group of the Psychiatric Genomics 2013; Milaneschi et al. 2016). This is consistent with epidemiological evidence of substantial comorbidity across these disorders in population-based registers (Laursen et al. 2009), as well as genetic overlap (Craddock et al. 2006; Cardno and Owen 2014). Elevated genetic risk for schizophrenia in those with depression has been documented more recently (Power et al. 2017; Verduijn et al. 2017), plus greater suicide attempts in individuals with depression (Sokolowski et al. 2016), contrary to the findings by Mullins et al. (2014) reported here.

One study in our review reported an association between genetic risk for schizophrenia and anxiety disorder, consistent with reports of comorbidity between schizophrenia and anxiety (Braga et al. 2013; Young et al. 2013).

In our review, the SZ-PRS was not consistently associated with ADHD, and although epidemiological evidence suggests that the risk of developing schizophrenia is elevated in individuals with ADHD (Keshavan et al. 2005; Keshavan et al. 2008; Pallanti and Salerno 2015), the SZ-PRS only captures common genetic variation (Thapar et al. 2016).

4.2 Schizophrenia symptoms

One of the main advantages of the PRS approach is the ability to study how genetic risk for schizophrenia is manifest across the general population, and during different stages of development. This is best exemplified by studies that have examined schizophrenia-related psychopathology and cognition as phenotypes.

In two independent population-based samples there was a lack of evidence to support the presence of a higher SZ-PRS in individuals who had experienced positive psychotic symptoms (Sieradzka et al. 2014; Zammit et al. 2014; Jones et al. 2016). This suggests that genetic risk for schizophrenia might be manifest more strongly by other psychopathology during adolescence, with positive psychotic experiences only becoming manifest at a later age. Perhaps SNPs identified in GWAS of schizophrenia more strongly index other characteristics of schizophrenia, such as negative symptoms, that might be selected for in clinical samples, as opposed to population-based samples.

Evidence for association with negative symptoms was inconsistent: studies reported both an increase (Jones et al. 2016) and a decrease (Sieradzka et al. 2014) in negative symptoms in those with higher SZ-PRSs in two population-based cohorts. However, it is difficult to define and measure negative symptoms in general population samples. This makes it difficult to know to what extent these studies reflect negative symptoms as assessed in clinical samples of individuals with schizophrenia. Studies of clinical samples have been more consistent, with two studies reporting more negative symptoms in those with a higher SZ-PRS (Derks et al. 2012; Fanous et al. 2012; Jones et al. 2016).

4.3 Cognition

The SZ-PRS was consistently associated with poorer cognition in population-based studies and from childhood through to older age (McIntosh et al. 2013; Hubbard et al. 2016). There was some inconsistency as to which aspects of cognition were most strongly related to schizophrenia genetic risk, though more recently published studies support an association with general cognitive deficits e.g. IQ (Liebers et al. 2016; Benca et al. 2017). However, in a

study of the Icelandic general population, a higher SZ-PRS was associated with greater number of years in education and having a university degree (Power et al. 2015), which seems, at face value to be contrary to the findings for measures of cognition, and to epidemiological studies that show consistent evidence that individuals with lower IQ have an increased risk of developing SZ (Zammit et al. 2004; Khandaker et al. 2011).

The associations between SZ genetic risk and some event-related potential measures lends support to the body of evidence proposing these as endophenotypes for SZ (Shin et al. 2011; Onitsuka et al. 2013). However, whilst GWASs of endophenotypes could theoretically inform schizophrenia gene-discovery, similarly large samples as those in current schizophrenia GWAS consortia are likely to be required (Hall and Smoller 2010).

4.4 Non-psychiatric disorders

The SZ-PRS was also associated with a number of other, non-psychiatric outcomes, including diabetes, RA and CD (Stringer et al. 2014), though results were not consistent across studies. This is likely to be due to the larger PGC-2-SZ discovery sample used by Stringer et al. (2014). These associations are consistent with increasing evidence that inflammation plays a causal role in the aetiology of SZ (Jones et al. 2005), and with epidemiological evidence of increased incidence of immune disorders in people with schizophrenia (Eaton et al. 2006; Eaton et al. 2010), although this evidence is also not entirely consistent (Chen et al. 2012).

4.5 Implications

Overall our results support other approaches that show pleiotropy between schizophrenia and other disorders, and suggest there is less common-variant genetic overlap between schizophrenia and cognition than with other psychopathology, consistent with other evidence (Bulik-Sullivan et al. 2015). Whilst the variance explained for all phenotypes was small, this will likely increase as discovery sample sizes increase (Dudbridge 2013), though will be limited as the PRS does not capture CNV or rare SNP contributions to variance.

Our review also shows that genetic risk for schizophrenia is manifest in the population from early during development as a broad range of psychopathology, and that biological pathways identified from GWAS may have greater relevance for understanding negative-symptom or other psychopathology rather than positive psychotic experiences as might be expected.

Future gains from using the PRS approach may be greater if used for examining phenotypes that are more closely related to biological substrates (e.g. inflammatory markers or functional brain imaging), if scores are based on gene-pathways rather than the whole genome to enable the study of more specific biological effects, and if used to stratify individuals for study of treatment response. Future increases in size of discovery samples may also enable PRSs to make a meaningful contribution to risk prediction models, as has been shown for some non-psychiatric disorders (Chatterjee et al. 2016).

4.5 Strengths and limitations

We used a comprehensive search strategy to minimise missing eligible studies; however, studies not published in English-language journals will have been missed. We also included a broad range of outcomes, but our exclusion of studies reporting neuro-imaging results, based on the added complexity of summarizing these results means that we are not able to comment on how schizophrenia genetic risk relates to imaging phenotypes. Another strength is that studies were not limited to a specific sampling framework or research design (e.g. clinical samples or longitudinal studies), and this, along with the broad range of outcomes, enhanced our ability to inform how schizophrenia genetic risk is manifest. However, the inconsistency of reporting of results across studies meant that only a narrative approach to this review was feasible, and assessment of publication bias was not possible.

There were several limitations identified in the studies included in this review, which made it problematic to place their findings within the context of other literature in the field. In particular, studies often failed to give a clear description of sample ascertainment, provided insufficient information to determine which comparison groups had a higher PRS,

inappropriately reported one-sided p-values, and did not provide standardised effect estimates or confidence intervals to enable comparison of effect sizes across studies. We therefore propose a reporting framework for future studies to employ which we believe would greatly assist researches synthesising data across such studies in the future (Table 1 and Supplementary Table 5).

4.6 Conclusions

The PRS approach is an important approach used for capturing the contribution of genome wide common variation of complex diseases. To the best of our knowledge, this is the first review attempting to collate information on how the use of the PRS approach has informed our understanding of a variety of phenotypes associated with schizophrenia genetic risk. Our attempt to compare findings across studies leads us to propose a framework that can guide robust reporting of PRS associations.

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Contributors

Author S.M carried out the literature search, writing of the first draft of the manuscript and authors S.M., J.R.H., D.S. and S.Z. checked studies to be included against inclusion criteria. Authors S.M. and J.R.H. extracted data from included studies and all authors checked the final manuscript.

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