Genome-wide association studies in schizophrenia: recent advances, challenges and future perspective

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Abstract

Genome-wide association studies (GWAS) have proved to be a powerful approach for gene discovery in schizophrenia; their findings have profound implications not just for our understanding of the genetic architecture of the disorder, but for the potential applications of personalised medicine through targeted diagnosis and therapies. In this article we review the current status of GWAS literature in schizophrenia including functional annotation methods and polygenic risk scoring, as well as the directions and challenges of future research. We consider recent findings in East Asian populations and the advancements from trans-ancestry analysis, as well as the insights gained from research looking across psychiatric disorders.

Introduction

It has been well established through twin and family studies that schizophrenia has a strong genetic component, with heritability estimates of around 80-85% (Cardno and Gottesman, 2000). Prior to genome-wide association studies (GWAS), research relied on the use of candidate gene and linkage approaches to identify variants associated with the disorder. These methods proved largely unsuccessful for schizophrenia gene discovery, with prime targets such as *DISC1* lacking replication within candidate studies and failing to gain support from subsequent GWAS (Mathieson et al., 2012; Sullivan, 2013). Advances in genotyping technology allowed the field to move away from such methods, enabling genome-wide data-driven approaches and the potential of identifying common variants of individually small effect that, when aggregated, increase predisposition to the disorder. Success in identifying common variants has largely been driven by falling costs of genotyping technology, allowing for efficient processing of much greater sample sizes (van Dijk et al., 2014). However, a sufficiently-powered GWAS in schizophrenia has been proven to require tens of thousands of cases (Sullivan et al., 2018), creating a challenge for individual groups. Hence international collaboration has been integral to the advances secured through GWAS, with research groups working as consortia to meta-analyse their data and reach the necessary sample sizes for high-powered discovery. The most notable and productive of these collaborations in the mental health field has been the Psychiatric Genomics Consortium (PGC), whose Schizophrenia Working Group spans researchers from hundreds of institutions worldwide (Sullivan et al., 2018). The joint efforts of this group have provided key advances in our understanding of the genetic underpinnings of schizophrenia. As we enter the third wave of the PGC (PGC3), greater sample sizes combined with in-depth phenotype data and advanced analytic strategies should further elucidate the genetic nature of schizophrenia.

Current status of GWAS in schizophrenia

Given the polygenic nature of schizophrenia, the vast majority of its common risk alleles will have small effect sizes, conferring genotype relative risks lower than 1.5 (Sullivan et al., 2012). This makes small sample sizes arguably the biggest factor hindering progress in schizophrenia genetics, as a certain threshold of cases and controls is required to achieve adequate power to detect variants of small effect (Sullivan et al., 2018, 2012). Early schizophrenia GWAS failed to identify markers reaching genome-wide significance, primarily due to their lack of power, though when samples were combined genome-wide significant alleles were identified (O'Donovan et al., 2008; Shi et al., 2009; Stefansson et al., 2009; Sullivan et al., 2008). The last decade has seen large-scale international collaboration enabling us to move from the first studies that identified one genome-wide significant locus for

psychosis in just 479 cases (O'Donovan et al., 2008), to the amalgamation of datasets containing upward of 40,000 cases identifying 145 significant loci (Pardiñas et al., 2018). Early partnerships between the International Schizophrenia Consortium (ISC), Molecular Genetics of Schizophrenia (MGS), and SGENE groups unearthed the first major findings of common variants in the major histocompatibility complex (MHC), as well as markers in *TCF4* and *NRGN*, implicating dysfunctional brain development and cognitive functioning as key pathophysiological processes of potential relevance in schizophrenia (Stefansson et al., 2009). These landmark findings illustrated the polygenic nature of schizophrenia, whilst demonstrating the necessity for international collaboration to amass large samples and thus facilitate reliable genomic discovery efforts. Other collaborations have since supported and expanded upon these findings, with the first wave of PGC schizophrenia data (PGC1) identifying single nucleotide polymorphisms (SNPs) across seven loci in a total combined sample of 17,836 cases and 33,859 controls (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). The data from this study was combined with additional samples, mainly from a large Swedish case control cohort, in a meta-analysis with total sample size 21,246 cases and 38,072 controls, and identified 22 loci, 13 of which were novel associations (Ripke et al., 2013). In these initial schizophrenia GWAS consortia studies one of the most consistent findings was strong support for association for the Major Histocompatibility Complex (MHC) region on chromosome 6, although identifying specific causal variants at this locus has been challenging due to the size, complexity, and high linkage disequilibrium (LD) of the region (Irish Schizophrenia Consortium and the Wellcome Trust Case Control Consortium 2, 2012; Lehner, 2012).

Arguably the most ground-breaking discovery in schizophrenia genetics came from the second wave of data from the PGC schizophrenia working group (PGC2). A total of 34,241 cases and 45,604 controls were analysed, which, together with 1,235 parent-offspring samples and a replication sample of 1,513 cases and 66,236 controls, led to the identification of 128 genome-wide significant SNPs, spanning 108 independent loci, associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). As well as a further demonstration of the importance of technological and analytic advances, the PGC2 study identified multiple novel candidate genes and pathways of potential therapeutic relevance. For the first time the PGC2 study found genome-wide significant association with a polymorphism implicating the *DRD2* gene, encoding the Dopamine D2 receptor, which is the therapeutic target of all currently licensed antipsychotic medications, thus providing a validation of the GWAS approach in schizophrenia. Moreover, the group reported 82 novel associations, including SNPs implicating genes enriched for glutamatergic neurotransmission and synaptic plasticity. Building on this work with the addition of new schizophrenia samples in the CLOZUK sample, Pardiñas and colleagues extended the PGC2 findings using up-to-date gene set

analyses to demonstrate an enrichment of variants in genes that are intolerant to rare loss-of-function mutations, as well as in gene sets involved in synaptic and neuronal functioning and also highlighted the strong enrichment of SNPs in regions under strong background selection (Pardiñas et al., 2018).

Despite the many successes of these studies, GWAS have so far been unable to explain the majority of schizophrenia heritability, with only 22.5% of variance currently explained in common variant studies and much less in rare variant analyses (Pardiñas et al., 2018). Missing heritability poses a significant challenge to future research, which may in part be overcome through further study of rare variants, environmental modifiers, and epigenetic effects (Eichler et al., 2010; Manolio et al., 2009). Furthermore, schizophrenia GWAS have predominantly been undertaken in populations of European ancestry. Restricting a sample to individuals of the same ancestry allows better control of population stratification, thereby limiting the rate of false positives arising from systematic differences between cases and controls (Wu et al., 2011). However, meta-analysis of ancestry-specific results can successfully address confounding effects (Wang et al., 2013), indicating that excluding non-European samples from studies limits our ability to generalise GWAS results and underestimates the genetic burden carried by individuals in these populations (Martin et al., 2017). As an example, polygenic risk scores (PRS) calculated from a European population explained substantially less of the variance in an African-American sample compared to two independent European samples (The International Schizophrenia Consortium, 2009). The evolutionary history of the human species and its rapid demographic expansion makes it likely that some degree of population-specific risk exists, and by limiting ourselves to one population we are potentially missing important contributors to schizophrenia heritability. More substantial GWAS in Asian populations have gradually emerged over the past decade, with discovery sample sizes progressing from less than a thousand cases in some of the earliest studies (Ikeda et al., 2011; Yue et al., 2011) to over 13,000 in the most recent PGC analysis (Lam et al., 2018). The findings from schizophrenia GWAS in Asian populations have been broadly consistent with those of European populations (Yue et al., 2017). A recent study meta-analysed results from 8723 cases of Han Chinese ancestry and found associations at three loci, all of which had previously been found in European samples (Yu et al., 2017). Research by Li et al. (2017) found seven genome-wide significant loci in an analysis of those with Chinese ancestry, three of which had previously been found in schizophrenia GWAS restricted to those of European ancestry. The remaining four loci were only associated with schizophrenia in the Chinese sample and were not significant in a trans-ancestry analysis with PGC2 data. Additionally, they found 26 novel loci amongst 106 significant loci through trans-ancestry analysis, owing to the greater power of the larger combined sample. Notably, GWAS of Asian populations often fail to find associations in the MHC (Corvin and Morris, 2014; Lam et al., 2018), despite strong evidence in European populations. It has been suggested that

this may be due to ancestry-specific patterns of LD combined with higher minor allele frequency (MAF) of key SNPs in this region in European samples compared to Asian samples (Lam et al., 2018), resembling observations in some immune phenotypes (Matzaraki et al., 2017).

Sampling different ancestries can provide insights into SNPs with MAF that are too rare to be studied in any single population. In a sample of Han Chinese ancestry, Yu et al. (2017) identified a significant SNP within the *GABBR1* gene with a MAF of 0.13 in an Asian sample, compared to 0.01 a European sample. Dysfunction in the GABA system has been implicated in schizophrenia (Wassef et al., 2003), suggesting that variation within this gene could play a role in both European and Asian populations. In recent work by the PGC, 21 variants spanning 19 loci were found to be significant in an East Asian sample (Lam et al., 2018). Of these, 15 loci had a higher MAF in the Asian sample compared to European samples. The locus containing *CACNA2D2* was significant in the Asian sample only, likely owing to vastly different MAF in the index SNP; 45% in Asian and 0.07% in European samples, respectively. The association with this variant suggests that whilst different patterns of LD and MAF may implicate different causal SNPs and/or haplotypes, the underlying genes and pathways implicated are shared across populations. Consistent with this idea is the finding of a genetic correlation of 0.98 between European and Asian samples, indicating that the genetic architecture of schizophrenia is largely consistent across populations (Lam et al., 2018). The study's findings confirm that, in the particular case of schizophrenia, meta-analysing samples of different ancestries is not only a valid approach but is advantageous compared to analyses restricted to ancestrally-homogenous samples.

Fine-mapping and functional annotation

With increasing sample sizes, as well as technical developments such as improved imputation, many more associated loci have been identified by schizophrenia GWAS. In order to move from these implicated genomic regions of association to identifying putatively causal variants and genes (Zondervan and Cardon, 2004), statistical fine-mapping and functional annotation techniques have been developed and implemented in recent years. Statistical fine-mapping is a commonly used technique that aims to overcome this problem by assigning each candidate variant a probability of being the causal variant at that locus (Spain and Barrett, 2015). High LD in many associated regions complicates this process, but again the use of data from multiple ancestries is starting to overcome this issue by exploiting the differences in patterns of LD between populations. Li et al. (2017) found that 80% of SNP sets spanned smaller regions when using trans-ancestry data compared to European or Chinese samples alone. Of 62 variants reaching the threshold for high causal probability, 38 had a higher probability in trans-ancestry analyses, including 16 that did not reach the threshold in single-

ancestry analysis. In trans-ancestry work by the PGC, the number of credible SNPs was refined in 93 loci, 20 loci were associated with a single variant, compared to 16 in previous work, an additional seven loci were refined to less than five candidate variants, and the overall median size of the mapped loci was reduced by over half (Lam et al., 2018).

Functional annotation of significant variants allows for analysis across pathways and gene sets, marking an important next step toward understanding the biological role of these variants. Additionally, grouping SNPs by function may better identify SNPs and genes to create an easier target for therapy development in the near future (O'Donovan and Owen, 2016). Pardiñas et al. (2018) assessed central nervous system-related gene sets and found six associated with schizophrenia, including targets of Fragile X mental retardation protein (FMRP), voltage-gated calcium ion channel complexes, and abnormal long-term potentiation. Voltage-gated calcium ion channels have been robustly implicated in schizophrenia, GWAS and gene set analysis reporting associations in European and Asian populations (Green et al., 2010; Jiang et al., 2015; Li et al., 2017; Ripke et al., 2013). Furthermore, variants in this gene set have been consistently implicated in other psychiatric disorders, notably bipolar disorder, suggesting a mechanism through which phenotypic and genotypic overlap may occur (Ferreira et al., 2008; Psychiatric GWAS Consortium Bipolar Disorder Working Group., 2011). The findings of Pardiñas et al. (2018) provide evidence of a potential shared aetiology with autism spectrum disorders, which have also been associated with variation in FMRP and its targets (Iossifov et al., 2012; Steinberg and Webber, 2013). Schizophrenia and autism are known to share both common and rare genetic risk (Carroll and Owen, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019) and more detailed exploration of SNPs within the FMRP gene set may further elucidate their common and pleiotropic effects.

Gene sets implicated by common variant studies overlap with those discovered through CNV and rare variant analyses. De novo mutations have been shown to be enriched in genes involved in calcium ion channels, synaptic plasticity, and FMRP targets (Fromer et al., 2014; Purcell et al., 2014). However, several studies report an enrichment of rare mutations in ARC and NMDAR gene sets (Fromer et al., 2014; Kirov et al., 2012; Pocklington et al., 2015; Purcell et al., 2014), which has not been reported robustly in common variant analysis. It remains possible that sampling of non-European populations may reveal common variants in these pathways that are too rare to detect within European populations.

The gene sets discussed provide evidence that risk variants for schizophrenia act by disrupting the functioning of the synapse through multiple inter-related mechanisms (Hall et al., 2015; Owen, 2012). Analysis of transcriptomic data in PGC2 provides further support for this hypothesis by

demonstrating that common variants identified are enriched for expression in the brain, and not in tissues thought to be unrelated to schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Further analyses also found an enrichment of variants expressed in tissues and pathways associated with immune function, suggesting a role of immunity in schizophrenia (The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium, 2015). While this might not necessarily implicate large numbers of immune genes (Pouget, 2018), consistent findings in the MHC do support this hypothesis, with variation in complement component 4 (C4) in particular showing strong evidence of association with schizophrenia (Sekar et al., 2016). In addition to the above fine mapping and functional gene set annotations, which rely on LD and genomic location, functional annotation is also possible using experimentally derived data. These include expression quantitative trait locus data (eQTL), methylomic and open chromatin data, and functional data derived from the 3D conformation of chromatin, such as Hi-C. Such approaches have been investigated in schizophrenia (Huckins et al., 2019; Pardiñas et al., 2018)and are described elsewhere in this special issue.

Application of GWAS results

Polygenic risk scoring has rapidly emerged as a powerful and potentially clinically useful application of GWAS results. SNPs identified through GWAS as being significant at a given threshold are weighted by their association odds ratios and summed for each individual to create a risk score in an independent dataset, with higher scores indicating greater genetic liability to the disorder. The ISC (2009) were the first to use this method to predict schizophrenia case-control status, finding that schizophrenia PRS was a highly significant predictor of the disorder in European samples. Moreover, schizophrenia PRS significantly predicted bipolar disorder case status, adding further weight to evidence from GWAS that the two disorders share a common genetic architecture, which was later further quantified through genetic correlation (r_g=0.70) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019, 2013). Such powerful genetic prediction has the potential to be clinically useful although the situations in which such information may be clinically employed require careful consideration including the limitations in the application of PRS across populations (Martin et al., 2019) and hence there is an ongoing debate about whether PRS can safely and effectively be implemented in medical genetic settings (Torkamani et al., 2018). At the moment, PRS is only weakly able to predict schizophrenia status, with an area under the curve (AUC) of 0.65 (Ripke et al., 2013). Consequently, current scores are unreliable for diagnostic purposes, though they have showed some encouraging performance in first-episode psychosis samples (Vassos et al., 2017). For research purposes, however, some study designs might benefit from sampling cases at the extreme of the PRS distribution, in a manner similar to CNV studies that compare deletion with duplication cases (Niarchou et al., 2019). Power of this

design depends on the difference between the risk profiles of the two studied groups (Risch and Zhang, 1995), which is related, but not analogous, to the predictive accuracy of the risk factor that has been used to select them (Wald et al., 1999). To illustrate this point, a recent study assessed the CLOZUK sample, a UK-wide study of 11,260 schizophrenia cases and 24,542 controls (Pardiñas et al., 2018). PRS analysis of CLOZUK showed an AUC=0.67 to predict schizophrenia case status, with a 5.7% variance explained, values similar to most PGC2 cohorts. In presenting previously unpublished data we show that when CLOZUK case control sample was stratified into PRS percentiles, the difference between the top and the bottom percentile conferred an OR≈40 (Figure 1), larger than that conferred by several highly penetrant CNVs (Rees et al., 2014). This shows that PRS might be an effective way of screening and prioritising population samples for functional and post-GWAS studies.

Increasing sample sizes and diversity can also improve PRS-based prediction, with Li et al. (2017) reporting up to 8% of variance in schizophrenia status within their sample explained by PRS derived from the PGC2 plus the Chinese ancestry data, an improvement of 5% from PGC2 alone. Although these improvements are relatively small, they indicate that missing heritability may in part be explained by the under-representation of non-European populations within GWAS cohorts. Further sampling of individuals from multiple ancestries will improve schizophrenia prediction across worldwide populations.

Given the explanatory power of PRS for susceptibility to schizophrenia, studies have investigated whether these scores can be informative regarding clinical heterogeneity within the disorder. Chronicity of illness, indexed by number and length of hospital admissions, is associated with schizophrenia PRS (Meier et al., 2016). Conversely, treatment-resistance to medication does not appear to be predicted by PRS, despite being associated with number of hospitalisations (Legge et al., in press; Martin and Mowry, 2016; Wimberley et al., 2017). These findings suggest a complex relationship between polygenic risk scores and outcomes which is in part dependent on the constitution of the schizophrenia training dataset used for the polygenic risk score derivation (i.e. the mixture of poor and good outcome cases). Attempts to predict cognitive ability have also provided conflicting results, with schizophrenia PRS significantly predicting cognition in healthy adults and children but not in schizophrenia cases (Germine et al., 2016; Shafee et al., 2018). Limited research has currently been conducted on genetic influences of specific symptoms in schizophrenia, with available evidence indicating that schizophrenia PRS predicts symptoms within a negative/disorganised domain, but not positive psychotic symptoms (Fanous et al., 2012). Consistent with this are findings that schizophrenia PRS does not predict psychotic experiences in adolescence but in contrast does predict negative symptoms at age 16 (Jones et al., 2016). These associations suggest that genetic liability for schizophrenia may manifest as negative symptoms (Mistry et al.,

2018), and that further exploration of positive symptoms is required in order to understand the aetiology of this phenotype.

Cross-disorder risk

The validity of existing diagnostic categories for psychotic and mood disorders has often been questioned (Allardyce et al., 2007), particularly given the evidence of a spectrum of illness and the existence of intermediary categories that fit neatly on neither side of the dichotomy, such as schizoaffective disorder bipolar subtype. Subsequently, additional insights have been gained by cross disorder analyses, particularly between schizophrenia and bipolar disorder. Several studies have employed this method, with the most recent findings identifying 32 loci associated with schizophrenia and bipolar disorder and eight significant pathways, of which seven are involved in synaptic and neuronal functioning (Ruderfer et al., 2018). These findings suggest that disrupted neuronal signalling plays a key role across both disorders, and is consistent with previous findings within each disorder (Nurnberger et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The cross-disorder group of the PGC has looked across eight psychiatric disorders, including schizophrenia and bipolar disorder, to identify pleiotropic loci and their role in shared aetiology. They found 136 loci reaching genome-wide significance, including 23 associated with at least four disorders. Consistent with pleiotropic effects, significant SNPs were enriched for genes known to be expressed in multiple brain tissues. One SNP, located in the gene *DCC*, was associated with all eight disorders and is involved in axonal growth during prenatal development. Gene set analysis implicated neurogenesis and neuron differentiation, as well as synaptic signalling sets, including voltage gated calcium channels. Eleven loci were shown to have opposite effects on risk between disorders, including two with opposite effects on schizophrenia and ASD. Notably, no loci had opposite effects on schizophrenia and bipolar disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019).

Other research has utilised PRS and genetic correlation analyses to measure the overlap between psychiatric disorders. Allardyce et al. (2018) report schizophrenia PRS predicting bipolar sub-types along a spectrum, with the strongest prediction for schizoaffective bipolar and the weakest for bipolar II disorder. Furthermore, individuals with Bipolar I disorder and psychosis showed greater enrichment of schizophrenia PRS than individuals with bipolar I disorder who had not experienced psychosis, suggesting that schizophrenia PRS may predict more severe illness course in bipolar disorder. The findings demonstrate that genetic overlap between schizophrenia and bipolar disorder can be seen at a phenotypic level, and provide further weight to the suggestion of a spectrum of psychotic illness that

includes bipolar disorder as has been shown in studies of cognition (Lynham et al., 2018; O'Donovan and Owen, 2016). Research by the Brainstorm Consortium measured genetic correlations between 25 neurological and psychiatric disorders, as well as several behavioural and cognitive phenotypes. They found positive associations between schizophrenia and most other psychiatric disorders, as well as with years in education and neuroticism. Significant negative associations were observed between schizophrenia and intelligence, subjective well-being, and BMI (The Brainstorm Consortium, 2018). The authors suggest this may reflect a general psychopathology factor on which other genetic and environmental factors influence illness presentation, as previously proposed (Caspi et al., 2014). Alternatively, it may also be due to endophenotypes or symptom dimensions that traverse disorders. Whatever the explanation these results indicate the complexity of cross disorder relationships and the heterogeneity of schizophrenia, but also highlight the fact that cross disorder analytic approaches may offer insights into aetiology and classification of schizophrenia and related disorders.

Future directions

Over the past decade our understanding of the genetic architecture of schizophrenia, and the nature of the condition itself, has developed substantially due to large genomic studies made possible by technological advances and internal collaboration. A picture has emerged of a complex polygenic disorder, with over 150 common genetic loci associated with the disorder implicating synaptic protein dysfunction and disruption of neurodevelopment and function. Moreover, we now know that these common variants are enriched in loss of function-intolerant genes, suggesting that schizophrenia in part arises from an excess burden of deleterious variation in highly conserved regions that underpin important biological functions. We also know the prevalence of common risk variants in the population is not necessarily due to ancient advantageous effects (Keller, 2018), but that the persistence of mildly deleterious common variants is made possible through the evolutionary processes of background selection and genetic drift, which recurrently remove mutations of large deleterious effect, allowing those of small effect to rise in frequency (Pardiñas et al., 2018).

Despite these substantial advances, many challenges still face the field of schizophrenia genomics. Whilst sample sizes in schizophrenia are increasing, they remain substantially smaller than GWAS of non-psychiatric illnesses and phenotypes such as blood pressure and educational attainment, which have combined discovery and replication sample sizes of over 750,000 and 1 million, respectively (Giri et al., 2019; Lee et al., 2018). The availability of large population-based cohorts, such as UK Biobank and 23andMe, is unlikely to address this problem, as they show low rates of participation for severe psychiatric conditions and those that do participate in such studies are poorly representative of those

with the condition under clinical care (Kendall et al., 2017). The PGC is making considerable strides in enhancing recruitment in this area, with ongoing waves of data aiming to recruit over 100,000 cases using novel high throughput recruitment strategies which have been shown to be effective (Pardiñas et al., 2018). A sample of this size will allow for greater predictive accuracy of PRS, which may be used to assess environmental interactions, phenotypic relationships, and developmental effects (Sullivan et al., 2018). Moreover, the sample can be used to measure genetic correlations across psychiatric and neurological disorders, as well as assess potential causation through methods such as Mendelian randomisation (Sullivan et al., 2018).

Furthermore, we are limited in our ability to assign causal SNPs at each identified locus, with recent work identifying only 27 confidently assigned causal SNPs out of a possible 145 genome-wide significant loci (Pardiñas et al., 2018), a result which is consistent with other complex disorders assessed using related methods (Huang et al., 2017). The use of trans-ancestry data is beginning to improve our ability to fine-map associated loci (Lam et al., 2018), therefore future research will need to sample individuals from diverse backgrounds in order to identify the causal SNPs. GWAS of Asian populations are becoming more prominent in the literature, yet African ancestries still remain vastly under-represented. Sampling a diverse range of ancestries will also aid our ability to detect rarer variants, as well as address a major barrier to any clinical application of polygenic risk score prediction, alongside advances in imputation panels allowing variants with much smaller MAF to be imputed and tested (Corvin and Sullivan, 2016).

Other work by the PGC and other groups is utilising GWAS to further our understanding of the clinical dimensions of schizophrenia. By analysing genetic risk at a symptom or endophenotype level, the issue of clinical heterogeneity may be addressed leading to improvements in classification based more on aetiology than symptomatic presentation. However, advances of this type will be reliant on the availability of deep phenotype data at scale and will require significant investment of research resources to produce replicable findings alongside renewed investment in international collaboration. Data linkage to anonymised electronic health records may help to facilitate this process by providing a wealth of longitudinal data that cannot be achieved accurately through participant interview. For instance, use of the Danish National Registry has produced research showing associations between increased risk of schizophrenia and both maternal C-reactive protein and maternal exposure to stress during pregnancy (Canetta et al., 2014; Khashan et al., 2008). Further advancements in genomic technologies also present a challenge to future schizophrenia GWAS research. Whilst next-generation sequencing technology is advancing rapidly and costs are falling, the regulatory environment is changing and secure storage and access to this data remains a challenge. Similarly whilst international efforts are underway to realise the potential of electronic health data, streamlined linkage of genomic

data to these datasets is far from simple even in well-funded research fields such as oncology (Agarwala et al., 2018). As we move toward whole-genome sequencing in much larger samples, these issues will only become more apparent hence equivalent advances are required in study design, regulatory environments and funding streams to fully realise the potential of this data.

Overall, the past decade has seen tremendous progress in our ability to rapidly analyse tens of thousands of samples and identify common loci contributing to risk of developing schizophrenia. These loci cluster in genes with important neurological functions, with many contributing not just to schizophrenia, but also to a host of related neuropsychiatric conditions and traits. GWAS have led to the development of a number of experimental analyses that aim to determine through which variants and genes these loci act to confer risk of schizophrenia, to elucidate the actions of such variants across disorders, and their potential use in predicting outcomes in patients. Continued investment in GWAS seems warranted given the insights they have provided that have established GWAS as a valid, valuable and widely employed methodology. Ongoing collaboration and the engagement and support of patients is crucial in order to continue to build the required sample sizes that are needed to fully realise the clinical potential of GWAS findings.

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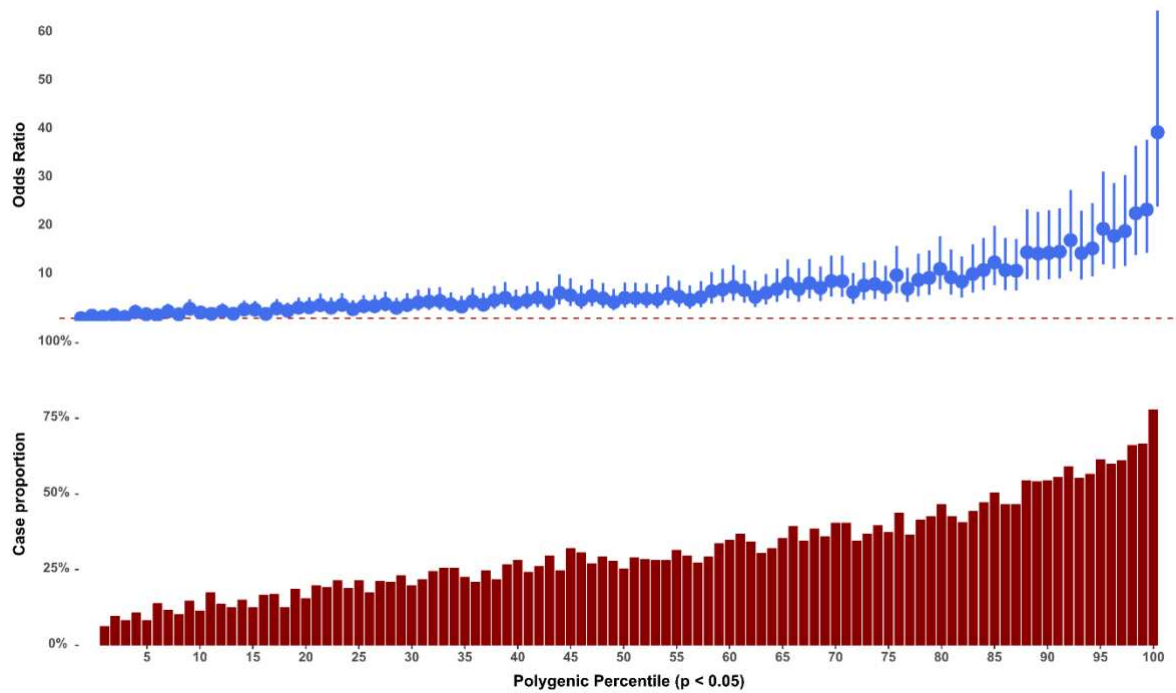Zondervan, K.T., Cardon, L.R., 2004. Erratum: The complex interplay among factors that influence allelic association. Nat. Rev. Genet. 5, 89–100. https://doi.org/10.1038/nrg1270

Figure 1: PRS-based stratification of the CLOZUK sample (Pardiñas et al., 2018), showing proportion of schizophrenia cases within each percentile and the OR conferred by comparing it with the 1st percentile. PRS p-value threshold used was 0.05, as it produced the largest AUC and r^2 for case discrimination. PRS were calculated using 'Independent PGC' as a training set (29,415 cases and 40,101 controls) and 'CLOZUK' as a target set (11,260 cases and 24,542 controls), as detailed in Pardiñas et al. (2018).