The polygenic architecture of schizophrenia — rethinking pathogenesis and nosology

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Abstract | Schizophrenia is a severe psychiatric disorder with considerable morbidity and mortality. Although the past two decades have seen limited improvement in the treatment of schizophrenia, research into the genetic causes of this condition has made important advances that offer new insights into the aetiology of schizophrenia. This Review summarizes the evidence for a polygenic architecture of schizophrenia that involves a large number of risk alleles across the whole range of population frequencies. These genetic risk loci implicate biological processes related to neurodevelopment, neuronal excitability, synaptic function and the immune system in the pathogenesis of schizophrenia. Mathematical models also suggest a substantial overlap between schizophrenia and psychiatric, behavioural and cognitive traits, a situation that has implications for understanding its clinical epidemiology, psychiatric nosology and pathobiology. Looking ahead, further genetic discoveries are expected to lead to clinically relevant predictive approaches for identifying high-risk individuals, improved diagnostic accuracy, increased yield from drug development programmes and improved stratification strategies to address the heterogeneous disease course and treatment responses observed among affected patients.

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Schizophrenia is a debilitating psychiatric disorder characterized by disturbances in thought, perception, emotion and behaviour. Although schizophrenia affects <1% of the global population[1], this disorder is a leading cause of morbidity and premature mortality[2]. The life expectancy of individuals with schizophrenia is estimated to be ~15 years shorter than that of the general population owing to a high prevalence of both suicide and comorbid physical illness[3]. Schizophrenia typically begins in adolescence. Its onset is often characterized by social withdrawal and cognitive decline, which might precede the first psychotic episode by many years[4]. Currently, no valid objective biomarkers are available that can aid in its diagnosis, predict the onset, course or severity of the disorder, or predict the response to treatment.

The diagnosis of schizophrenia is based upon a checklist of criteria[5,6] and requires a combination of 'positive' symptoms, such as hallucinations, delusions and disorganized speech, and 'negative' symptoms such as apathy, social withdrawal, loss of motivation and an inability to feel pleasure. Antipsychotic medications, which have been the cornerstone of schizophrenia treatment for the past 60 years, can provide clinically meaningful reductions in positive symptoms and prevent psychotic relapse[7] but should always be combined with psychosocial interventions. In ~20–30% of patients, antipsychotic medications have little or no beneficial effect, and intolerable adverse effects and treatment discontinuation are fairly common[7]. Furthermore, current pharmacotherapy is largely ineffective against negative symptoms of schizophrenia and cognitive impairment[8]. Although patients' outcomes show wide heterogeneity, many individuals with schizophrenia endure poor societal functioning, stigma and a poor quality of life[9]. Additionally, the illness is associated with a high burden of societal costs — both direct costs of hospital and other treatment and indirect costs associated with loss of productivity[10]. Hence, improving the prevention and treatment of schizophrenia is a public health priority[11].

Although schizophrenia has long been recognized to be highly heritable[12], research in the past two decades has made considerable advances in understanding the genetic architecture of schizophrenia. In particular, the introduction of large-scale genome-wide association studies (GWAS) has generated a wealth of genetic data that provide novel insights into the aetiology of this disorder (BOX 1).

This Review presents the evidence for a polygenic architecture of schizophrenia and discusses the advances in molecular genetics that led to the identification of common and rare genetic variants that implicate various biological pathways in schizophrenia. We consider

Key points

- Schizophrenia is characterized by 'positive' psychotic symptoms (including hallucinations and delusions) and 'negative' symptoms (including blunted affect, apathy and social impairment); this disorder is associated with considerable morbidity and mortality.
- In the past decade, important advances have been made in our understanding of the genetics of schizophrenia.
- The polygenic architecture of schizophrenia is accounted for by thousands of common genetic variants with small effect sizes and a few rare variants with large effect sizes.
- These genetic risk variants implicate dysregulation of biological processes linked to neurodevelopment, neuronal excitability, synaptic function and the immune system in schizophrenia.
- Genetic risk factors associated with schizophrenia transcend diagnostic boundaries and form a continuum with normal psychosocial traits, which challenges current psychiatric nosology.
- Although increasingly larger sample sizes will accelerate the discovery of genetic variants, novel statistical methodologies could also improve the efficiency of analyses, render discoveries clinically relevant and facilitate precision medicine approaches.

how these insights have led to a conceptual change in our understanding of schizophrenia and its important implications for disentangling the genetic relationships between schizophrenia and other traits and disorders. We also discuss how understanding of this polygenic architecture might inform psychiatric nosology, guide research into pathophysiological mechanisms and lead to the development of novel prediction and stratification tools for research and clinical purposes.

Aetiology and pathophysiology

The underlying pathophysiology of schizophrenia has proven challenging to identify, and this difficulty has impeded the development of effective treatments. The most influential hypotheses have focused on dysregulation of the neurotransmitters dopamine[13], glutamate[14] and GABA[15], which is thought to affect neural pathways in the striatum, hippocampus, prefrontal cortex and midbrain, and thereby lead to psychosis[16]. The discovery that the beneficial effects of most antipsychotic drugs are largely mediated by blocking or partially inhibiting dopamine D2 receptors laid the foundation for the dopamine hypothesis of schizophrenia[17,18]. The latest revision of this hypothesis proposes that multiple neural pathways are disrupted in schizophrenia and that psychosis results from excess synaptic levels of dopamine in the striatum[13], a notion empirically supported by the results of in vivo imaging studies[19]. Support for the glutamate hypothesis of schizophrenia comes from studies of the effects of NMDA receptor (NMDAR) antagonists and glutamate receptor antagonists, including ketamine and phencyclidine, which induce schizophrenia-like symptoms in healthy persons and aggravate schizophrenia symptoms in patients with the disorder[20–22]. Moreover, anti-NMDAR encephalitis, which is associated with antibodies targeting the NR1 (also known as GluN1) subunit of NMDARs, can mimic the psychotic symptoms of schizophrenia[23]. However, the rapid progression of anti-NMDAR encephalitis and its typical neurological features (such as autonomic dysfunction and seizures) aid in the differential diagnosis of these two conditions. Studies of post-mortem brain tissue from individuals with schizophrenia have not revealed consistent deficits in either the dopamine or glutamate systems[19]. By contrast, multiple studies have reported decreased mRNA expression of *GAD1* (encoding the GABA-synthesizing enzyme glutamate acid decarboxylase 1)[24,25] as well as other abnormalities in GABAergic signalling[15], suggesting that GABA dysfunction could have a role in schizophrenia. Additionally, molecular alterations in parvalbumin-positive GABAergic interneurons, which regulate gamma oscillations and synchronize cortical activity, are reported in the prefrontal cortex of patients with schizophrenia[26]. However, these models are not mutually exclusive. Current pathophysiological models of schizophrenia propose that multiple neurotransmitter pathways are altered in schizophrenia and affect the balance between inhibitory and excitatory states in multiple neural systems[16], but considerable heterogeneity is likely among affected patients[27].

The prevailing hypothesis for the aetiology of schizophrenia is the neurodevelopmental model[28,29], in which complex interactions between multiple genetic and environmental factors are postulated to interfere with normal brain development, specifically synaptic formation and connectivity. These changes ultimately result in aberrant information processing and in an increased susceptibility to schizophrenia[30,31] (FIG. 1). Post-mortem studies have found a decreased density of dendritic spines on cortical neurons from patients with schizophrenia[32,33], possibly as a result of excessive spine pruning during late childhood and adolescence, which is coincident with the clinical onset of schizophrenia.

Further support for the neurodevelopmental model is provided by evidence from genetic studies that implicates immune system components, such as the classical complement cascade, in the aetiology of schizophrenia[34–36]. As well as the recognition and removal of pathogens, the complement system contributes to healthy brain development by eliminating immature synapses[37,38]. Further, many patients with schizophrenia have abnormal circulating levels of inflammatory cytokines[39]. Some of

Box 1 | **An introduction to GWAS**

Genome-wide association studies (GWAS) led to a breakthrough in the understanding of schizophrenia genetics. GWAS simultaneously investigate the association of millions of genetic variants, typically SNPs or copy number variants (CNVs), with a given phenotype by comparing the genotype frequency between case patients and controls, or using a continuous-trait design. GWAS can capture most of the common genetic variation in the population of interest owing to linkage disequilibrium. Alleles that are in high linkage disequilibrium with each other are commonly inherited together. Thus, tag SNPs that are in linkage disequilibrium with multiple nearby SNPs can be used to extract information for millions of SNPs that are not directly targeted by the genotyping array. The large number of genetic variants investigated by GWAS present a considerable statistical challenge. As each association between a given SNP and the phenotype of interest is treated as a separate statistical test, the millions of such tests performed in a GWAS substantially increase the risk of false positive findings (Type 1 errors). Hence, a correction for multiple comparisons is necessary, which is commonly achieved by applying a statistical significance threshold of $P < 5 \times 10^{-8}$. As this correction inevitably reduces the power of these studies to detect variants with small effect sizes, a key strategy for improving GWAS discovery has been to improve the statistical power of these studies by increasing the number of genotyped individuals and reducing the emphasis on strict phenotypic criteria.

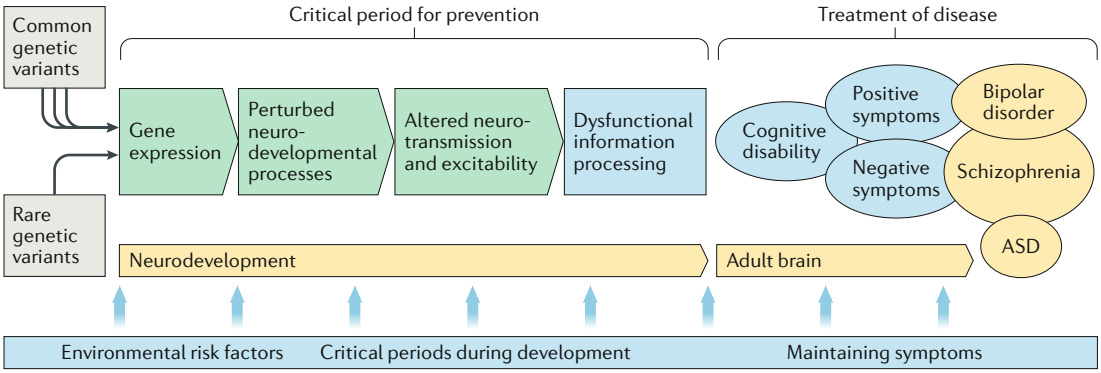

Fig. 1 | **The aetiology of schizophrenia and its relationship to other psychiatric disorders.** Multiple common and rare genetic variants are postulated to interfere with neurodevelopmental programmes that determine synaptic formation and connectivity. In concert with environmental factors, these genetic changes result in aberrant information processing, which confers an increased susceptibility to schizophrenia. However, substantial clinical heterogeneity is evident among patients with schizophrenia, and both its clinical characteristics and the risk factors for this condition transcend the diagnostic boundaries of psychiatric disorders. These shared features indicate that the aetiology of schizophrenia overlaps with that of other psychiatric disorders such as bipolar disorder and autism spectrum disorder (ASD)[159].

these observations might be secondary to physiological or environmental confounding variables, such as treatment with antipsychotic agents, smoking or a high BMI. However, a meta-analysis of data on antipsychotic-naive individuals with a first episode of psychosis reported that cytokine levels in these individuals were still elevated even after accounting for such confounders[40]. These inflammatory and/or immune system abnormalities could also represent features of the pathophysiology of schizophrenia.

Altered brain structures are thought to reflect aberrant neurodevelopment. At the group level, schizophrenia is associated with subtle anatomical abnormalities in cortical and subcortical regions, such as larger lateral ventricles and a smaller intracranial volume[41–43], but these parameters show considerable heterogeneity between individual patients[44]. Schizophrenia is associated with loss of grey matter in several regions, and these losses seem to emerge before the onset of illness and to progress after exposure to antipsychotics[45,46]. Whether or not the grey matter loss results from primary pathophysiological processes or is secondary to illness-related factors, such as medication use, remains an open question[45,47].

The neurodevelopmental hypothesis is further supported by the observation that a wide spectrum of adverse experiences early in life are associated with increased schizophrenia risk, including pregnancy-related complications[48], such as maternal infection or malnutrition, obstetric complications[49], childhood infections[50] and psychosocial adversity[51,52]. Other environmental risk factors that are consistently associated with schizophrenia include cannabis use, an urban environment, minority ethnicity and migrant status[51].

Early genetic studies of schizophrenia

At the end of the nineteenth century, Emil Kraepelin not only proposed the classical dichotomy of mental illness into dementia praecox (later termed schizophrenia) and manic-depressive illness (later termed bipolar disorder), but also described the aggregation of dementia praecox within families[53]. A number of twin, family and adoption studies of steadily increasing quality have since confirmed that genetic factors account for a substantial proportion of the propensity to develop schizophrenia[12]. A meta-analysis of data from 12 twin studies estimated the heritability of schizophrenia to be 81%, whereas exposure to shared environmental factors explained 11% of the risk of developing schizophrenia[54]. In 2018, a study of 31,524 pairs of Danish twins with psychiatric register diagnoses reported a similar heritability estimate of 79% for schizophrenia[55]. When these researchers applied a broader definition of schizophrenia that included related psychotic disorders, the heritability estimate was only slightly lower, at 73%, which suggests that genetic risk factors are of comparable importance across the whole spectrum of schizophrenia-related disorders[55]. A population-based study of Swedish registry data on more than nine million individuals of known parentage, of whom 35,985 individuals met the criteria for schizophrenia, reported that the risk of schizophrenia was approximately ten times higher in first-degree relatives of patients with schizophrenia than in the background population[56]. This study yielded a heritability estimate of 64%, which is slightly lower than that seen in the twin studies. This disparity might result from methodological differences such as in the way that shared environmental factors or non-additive genetic effects were addressed.

These observations motivated a series of efforts to elucidate the underlying genetic architecture of schizophrenia. Initial gene mapping efforts during the second half of the twentieth century focused on linkage analysis, a genome-wide method based on the identification of segments of DNA that cosegregate with the phenotype of interest within a family. Although linkage analysis has had notable successes in identifying genes with a large role in disease (such as *BRCA1* in breast cancer)[57], this technique has low power to detect loci with modest effect sizes that are spread across many regions[58]. Accordingly, the lack of robust and replicable findings from linkage analyses of schizophrenia[59,60] suggested

Polygenic risk score
(PRS). An estimate of overall genetic propensity to develop a given phenotype, derived from the sum of a given individual's risk alleles weighted by their effect sizes.

SNP-based heritability
The fraction of phenotypic variation attributable to common genetic variants detected in genome-wide association studies. Heritability of continuous traits (such as height) is estimated by comparison with the observed range (observed scale), whereas heritability of binary traits (such as schizophrenia) is estimated as a propensity score that takes into account population prevalence (liability scale).

Linkage disequilibrium
The tendency for genes, alleles or other genetic markers to be non-randomly inherited in association with each other owing to physical proximity to one another on the same chromosome.

that the genetic architecture of schizophrenia could not be accounted for by a few rare variants with large effect sizes. Candidate-gene studies, which investigate only selected genes that might be plausibly involved in the pathophysiology of schizophrenia (such as those linked to dopaminergic function), have similarly reported successes in other diseases (notably confirming the involvement of *APOE* in Alzheimer disease)[61]. However, candidate-gene studies in patients with schizophrenia were severely underpowered to detect variants with small to modest effect sizes and yielded results of low reproducibility and validity[62].

Evidence of a polygenic architecture

The discovery of common genetic variants associated with schizophrenia lagged behind that of other complex phenotypes for many years. However, international collaborations, in particular the Psychiatric Genomics Consortium (PGC)[63], have conducted a series of increasingly productive GWAS in schizophrenia[34,64–68]. These collaborative efforts were motivated by initial GWAS findings demonstrating that multiple common genetic variants with very small individual effect sizes contribute to the risk of schizophrenia[69–72]. This genetic architecture implied that much larger GWAS samples would be needed to uncover the genomic loci linked to schizophrenia than had been used to investigate other human disorders[71] (BOX 2). In a seminal study published in 2009, the International Schizophrenia Consortium constructed a polygenic risk score (PRS) for schizophrenia, which summarized the effects of a large number of genetic variants identified in a GWAS[71]. In an independent population sample, individuals with schizophrenia had (on average) higher PRSs than controls without schizophrenia, indicating that part of the propensity to develop schizophrenia is due to such polygenic effects[71].

Subsequent GWAS validated the ability of PRSs to predict schizophrenia case or control status at the group level[34,66], which provides a measure of how well common genetic variants explain the variation in schizophrenia risk. Linear regression analyses published in 2014 (REF.[34]) and 2018 (REF.[66]) estimated that PRSs account for up to 12% of the variation in schizophrenia risk in independent populations of patients, whereas variants with genome-wide significance explain up to 2.4% of the variation in schizophrenia risk[66]. However, poor sensitivity and specificity still limit the clinical utility of PRSs to assess the risk of schizophrenia in individual patients[71].

Subsequently, SNP-based analyses firmly established that a substantial proportion of the 'missing' heritability[73] of schizophrenia risk could be accounted for by the additive effects of all common risk variants rather than of just the few above the genome-wide significance threshold. These SNP-based methods can be used to calculate the heritability of schizophrenia (estimated to range from 20% to 40%)[64,66,74–76] from individual-level genotype data[77,78] or summary-level data from GWAS[75,76,79]. Thus, SNP-based heritability estimates account for approximately 50% of the heritability of schizophrenia demonstrated in twin and family studies[54–56]. The discrepancy can be explained by many factors, including poor assessment of rare variants and variants in low linkage disequilibrium with tag SNPs, non-additive genetic effects (including gene–gene interactions (epistasis) and gene–environment interactions), and overestimation of heritability in twin and family studies[73]. Generally, SNP-based heritability estimates are considered to reflect the lower boundary of values that can be explained by common genetic variants.

Pathobiological insights from GWAS

The latest schizophrenia GWAS by the PGC, published in 2014, included 36,989 case patients and 113,075 matched controls of primarily European ancestry and reported 108 loci with genome-wide significance, 83 of which were novel[34]. Each of these loci is associated with a very small increase in the risk of schizophrenia (ORs <1.3) and differences in the allele frequency between cases and controls are subtle (mostly <2%). Among the 108 loci identified, 75% included protein-coding genes, many of which were expressed in the brain[34]. Several of the implicated genes encode proteins involved in neuronal signalling and synaptic function, including *DRD2* (encoding the dopamine D2 receptor), *CACNA1C*, *CACNB2* and *CACNA1I* (encoding voltage-gated calcium channel subunits), *GRIA1* (encoding glutamate receptor 1), *GRM3* (encoding metabotropic glutamate receptor 3), *GRIN2A* (encoding glutamate receptor ionotropic, NMDA 2A), *SRR* (encoding serine racemase), *CLCN3* (encoding H^+/Cl^- exchange transporter 3), and *SLC38A7* (encoding putative sodium-coupled neutral amino acid transporter 7). Subsequent analyses of the full common-variant dataset of schizophrenia revealed substantial enrichment of genes expressed in CNS tissue[80,81], particularly in glutamatergic neurons[80], as well as of genes related to synaptic transmission and neuronal excitability[82,83]. Statistical enrichment tools[84] (BOX 3) have implicated genes encoding transporters of all the main ions determining neuronal membrane potential (Na^+, K^+, Ca^{2+} and Cl^-) and multiple neurotransmitter systems

Box 2 | **Statistical power of schizophrenia GWAS**

The statistical power of genome-wide association studies (GWAS) to identify a trait-associated locus depends not only on the sample size, but also on the magnitude of the genetic effects at that locus. Even though two phenotypes can have similar SNP-based heritability, a phenotype derived from a large number of underlying causal variants will inevitably have a lower average effect size for each individual variant, and, therefore, these variants will have lower discoverability than those associated with a phenotype derived from fewer causal variants. Accordingly, knowledge of the unique genetic architecture (including SNP-based heritability, polygenicity and discoverability) underlying a given phenotype facilitates the calculation of the sample sizes required to establish a given level of statistical power of future GWAS[76,125,177–179].

In schizophrenia, a GWAS sample size of ~860,000 participants is estimated to be needed to identify the number of variants that explain ~50% of its SNP-based heritability[125] (FIG. 4). By contrast, the same sample size is estimated to capture ~80% of the SNP-based heritability of height. All currently available GWAS of schizophrenia have a fairly low statistical power, similar to that of GWAS of other psychiatric disorders (FIG. 4). This low statistical power is mainly a consequence of the highly polygenic architectures of these disorders[180]. These predictions of GWAS sample size and power estimates emphasize the need for continued collaborative efforts to genotype more patients with psychiatric disorders so that future GWAS will be able to uncover a large fraction of their genetic architectures.

Box 3 | **Improving discovery in schizophrenia GWAS**

A cost-efficient alternative to simply increasing the sample size of genome-wide association studies (GWAS) is to apply statistical methods that increase the yield of existing GWAS by incorporating information about which SNPs are most likely to influence the phenotype. In standard GWAS analyses, all SNPs are considered to have an equal probability of being associated with the phenotype. Hence, individual SNPs must surpass a genome-wide significance threshold of $P < 5 \times 10^{-8}$ to be considered associated with the phenotype, and identified associations also require validation in independent cohorts.

Given that common variants associated with schizophrenia have very small effect sizes, a large fraction of such variants will remain undetected even at GWAS sample sizes of >100,000 participants (FIG. 4). However, accumulating evidence shows that some SNPs are particularly likely to be associated with a given phenotype and that associated SNPs are not randomly distributed across the genome[91,92]. In complex phenotypes such as schizophrenia, stronger associations are found for SNPs in regulatory and coding regions compared with those in intronic regions, whereas intergenic regions are relatively depleted of associated SNPs[91,92]. Moreover, the probability of discovering SNPs with genome-wide significance increases with the amount of genetic variation they tag (that is, the number of SNPs that a given SNP is in linkage disequilibrium with), whether the SNP is associated with more than one phenotype[84,181] and with increased population frequency of the minor SNP allele[84,91]. Statistical models that incorporate the effects of these factors (which are known as enrichment priors) can both increase the power of GWAS for SNP discovery[181,182] and increase the probability that the detected SNPs can be replicated in independent cohorts[84,91].

For example, the conditional false discovery rate method[100,181] incorporates shared associations between related phenotypes to increase the statistical power of GWAS. Conditional false discovery rate studies have discovered schizophrenia risk loci shared with neurological disorders[183–185], cardiovascular traits[100], cognitive functioning[104,106,107], personality traits[113] and brain structure volumes[108] that were below the genome-wide significance threshold in the primary schizophrenia GWAS. Similarly, a reanalysis of the dataset from the Psychiatric Genomics Consortium GWAS of schizophrenia[34] using the covariate-modulated mixture modelling approach, which leverages multiple enrichment priors[84], increased the number of loci associated with schizophrenia from 108 to 414 and also improved replication rates[84].

in schizophrenia[82]. These data therefore provide support for the dopamine, glutamate and GABA hypotheses of schizophrenia[13–15]. However, to date, in what way synaptic activity, neurotransmission and excitability are affected in schizophrenia remains unclear.

Corroborating the findings of earlier GWAS[71,72], the strongest genetic association with schizophrenia identified in the PGC GWAS localized to the major histocompatibility complex (MHC)[34], a genomic region with intricate linkage disequilibrium spanning ~8,000 kb on chromosome 6. The MHC region contains many genes linked to the immune system, which strengthens the hypothesis that the immune system has a role in schizophrenia aetiology[34]. Structural variants in the *C4* gene, which encodes complement component 4 (C4), underlie part of the association between the MHC region and schizophrenia[35]. C4 is a member of the classical complement cascade, which is part of the innate immune system and contributes to synaptic reorganization during development[37,38]. Moreover, increased schizophrenia risk is associated with increased expression of *C4A*, which encodes the isoform of C4 that is present at human synapses and neuronal components[35], and *C4*-deficient mice have dysfunctional synaptic connectivity[35]. Together, these observations indicate that C4 variants might increase susceptibility to schizophrenia by perturbing synaptic maturation. However, the MHC region only explains a small proportion of the variation in the risk of schizophrenia.

A meta-analysis of GWAS data published in 2018 combined the PGC dataset[34] and an independent dataset from the CLOZUK cohort[66], totalling 40,675 individuals with schizophrenia and 64,643 controls. This meta-analysis identified 145 loci with genome-wide significance[66] and validated the majority of the associations identified in the PGC2 study[34]. Six CNS-related gene sets were independently associated with schizophrenia, including the 5-hydroxytryptamine receptor 2C (5HTR2C) complex, voltage-gated calcium channel complexes and three gene sets related to behavioural and neurophysiological correlates of learning[66]. The most strongly associated gene set comprised targets of fragile X mental retardation protein (FMRP). FMRP binds to mRNAs from several hundred genes and regulates diverse developmental processes, including synaptic formation[85]. Deficiency of FMRP causes fragile X syndrome, which is the most common inherited cause of both intellectual disability and autism spectrum disorder (ASD)[86].

As linkage disequilibrium patterns are strongly population dependent and most large schizophrenia GWAS have been conducted in individuals of European ancestry, the generalizability of these GWAS findings to other populations has been questioned. In 2017, a schizophrenia GWAS including 7,699 individuals with schizophrenia and 18,327 controls of Chinese ancestry[65] reported bidirectional concordance for the increased risk of schizophrenia associated with particular SNPs between this Chinese GWAS and the independent PGC dataset (which included mainly participants of European ancestry)[34]. Although, as expected, these two GWAS showed some discrepancies in which individual loci reached genome-wide significance[34,65], the overall consistency between their findings indicates that a large part of the genetic risk of schizophrenia is shared by both European and Chinese populations and also implies the potential value of multi-ethnic GWAS. A subsequent meta-analysis of the PGC and Chinese datasets (which included 43,175 individuals with schizophrenia and 65,166 controls) identified 109 loci with genome-wide significance, of which 26 were novel[65]. The high degree to which the genetic risk of schizophrenia is shared across populations was further corroborated by a 2019 report demonstrating a strong genetic correlation ($r_g = 0.98$) between the findings of a schizophrenia GWAS of East Asian individuals and those of the PGC dataset, which indicates that the biological pathways underlying schizophrenia are consistent across these populations[68]. Interestingly, in the East Asian cohort, the MHC region showed no significant association with schizophrenia. However, this omission is likely to reflect either population differences in linkage disequilibrium patterns or decreased frequencies of schizophrenia risk alleles within the MHC region in East Asian populations rather than true population heterogeneity in the pathophysiology of schizophrenia. A meta-analysis of the European and East Asian datasets identified 176 schizophrenia-associated loci with genome-wide significance, 53 of which were novel[68]. Of importance,

the predictive ability of PRSs is far lower when applied to populations with a different ancestry to that of the training dataset, which presents an additional concern regarding their clinical utility. Accordingly, an increased diversity in GWAS populations is warranted to improve the accuracy of schizophrenia PRSs[87].

The molecular and cellular consequences of risk loci associated with schizophrenia remain challenging to infer. The fact that several genes and many potential causal variants can be present within a given trait-associated locus is one of the main difficulties limiting the mechanistic implications of GWAS data. Despite the biological plausibility of the genes and gene sets identified by GWAS as associated with schizophrenia, how these loci — individually, collectively and in concert with environmental factors — affect gene expression and thereby increase the susceptibility to schizophrenia is still poorly understood[88] (FIG. 1). Notably, the presence of multiple schizophrenia risk variants can affect gene expression in a synergistic manner[89], an observation that underscores the importance of studying the combinatorial effects of risk variants to understand their biological consequences.

The mapping of SNPs and risk loci to specific genes within a schizophrenia-associated locus warrants caution. Current practices mostly focus on genes lying within a certain physical distance (typically within 10 kb) of a given SNP, expression quantitative trait loci (that is, genomic loci associated with changes in mRNA expression or protein levels in a given tissue), and genes implicated owing to long-range interactions between specific SNPs and other DNA regions that are attributable to the three-dimensional organization of chromatin[90]. The large fraction of schizophrenia-associated variants that reside in non-coding DNA[91,92], including enhancer and promoter regions, suggest that most variants exert their effects indirectly through regulatory mechanisms rather than by directly altering protein structure. The translation of GWAS findings into plausible biological mechanisms is further restricted by the incomplete characterization of the function of many genes and proteins as well as of their interactions in signalling networks and pathways. These factors greatly limit the mechanistic interpretation of GWAS data at present[93]. Thus, tremendous numbers of animal studies and cell-biology experiments are needed to fully characterize the genetic risk architecture of schizophrenia. An emerging approach, termed biophysical psychiatry[94], combines GWAS findings with computational neuroscience tools to help in characterizing the neurophysiological effects of the many genetic loci associated with schizophrenia.

Evidence of genetic overlap

A considerable proportion of the vast number of trait-associated loci identified by GWAS during the past decade are linked to more than one phenotype, indicating abundant genetic pleiotropy across complex human traits and disorders[95,96]. Indeed, schizophrenia shows a genetic overlap with a range of other complex phenotypes, including psychiatric disorders[97–99], comorbid somatic traits and diseases[100], substance use[101,102], measures of cognitive function[103–107], brain structure volumes[108–110], creativity[111] and personality traits[112,113]. This overlap has implications for understanding the epidemiological relationships between these phenotypes and potentially also the shared underlying molecular genetic mechanisms. For example, some of the concordance between schizophrenia and comorbid cardiovascular disease or substance use could reflect shared genetic predispositions rather than schizophrenia being a cause or consequence of substance use or cardiovascular disease[100–102]. However, the extent to which these overlapping associations reflect shared or independent causal variants remains unclear[114].

Most investigations of genetic overlap focus on estimating the genetic correlation (r_g) between two traits, which provides a single measure of genome-wide genetic overlap with values ranging from –1.0 to 1.0 (REFS[97,115,116]). Such methods have revealed a large degree of overlap between various psychiatric disorders[98] in accordance with their high degree of shared clinical characteristics. For schizophrenia, the strongest genetic correlation is with bipolar disorder ($r_g = 0.70$)[117], which indicates that these two conditions have a substantial shared genetic basis. Intriguingly, fewer genetic correlations are seen between different neurological disorders or between psychiatric disorders and neurological disorders, which suggests that neurological disorders are more likely than psychiatric disorders to have a distinct genetic aetiology[98]. In addition, schizophrenia seems to be genetically correlated with some somatic traits. For example, genetic risk of schizophrenia is inversely correlated with BMI[118], which is somewhat unexpected given the increased average BMI observed in clinical cohorts[119]. The increased BMIs observed in individuals with schizophrenia might therefore result from socioeconomic and treatment-related factors such as a poor diet, low activity levels and the adverse metabolic effects of medication. Uncertainties in the current GWAS data on BMI in individuals with schizophrenia preclude further discussion of this topic, but future studies (for example, using the MiXeR model[76]) are keenly anticipated.

Measures of genetic correlation can shed no light on the specific genomic loci involved nor on the directions of effect contributed by the various alleles at genetic loci that are shared between phenotypes[97,115,116]. Consequently, two phenotypes that seem not to be genetically correlated (that is, the r_g value is small or the association is non-significant) might still share many genomic loci (FIG. 2). To obtain a complete overview of the genetic relationship between two phenotypes, measures of genetic correlation must be complemented by tools that enable the discovery of shared loci regardless of the directions of their allelic effects (BOX 3). For example, schizophrenia often coexists with impaired cognitive function[120] and shows a moderate inverse genetic correlation with cognitive traits (r_g between –0.2 and –0.4)[103,121]. However, not all individuals with schizophrenia have cognitive deficits[120,122]. Genetic studies published in 2017 and 2019 identified multiple loci that jointly influence these phenotypes[104,106]. Although most schizophrenia risk alleles were associated with poor cognitive performance, others were associated

Genetic pleiotropy
A genetic variant that affects more than one phenotype.

with improved cognitive performance[104,106]. These findings might help explain the wide spectrum of cognitive function observed in patients with schizophrenia[120,122]. Of note, bipolar disorder shows no genetic correlation with cognitive performance[117] despite substantial genetic overlap[106]. These results imply that bipolar disorder is genetically dissimilar to schizophrenia, in line with the differences in cognitive performance between these two populations of patients[106].

The publication of large-scale GWAS on neuroimaging measures[123] has facilitated investigation of the genetic relationship between schizophrenia and brain structures, which could help shed light on the aetiology of the brain abnormalities associated with schizophrenia[41–43]. An initial comprehensive analysis of GWAS of schizophrenia[34] and subcortical brain volumes[123] reported no evidence of any genetic overlap[124]. However, the application of statistical enrichment methods (BOX 3) revealed an overlap in genomic loci associated with schizophrenia and those associated with hippocampal, putamen or intracranial volumes[108]. Another study found that schizophrenia risk variants explained a substantial proportion of the SNP-based heritability of several brain anatomy phenotypes, among which the most robustly associated were intracranial volume and thickness of the superior frontal cortex[109]. A study from 2020, which included more participants derived from two GWAS of subcortical volumes[123] and schizophrenia[34], reported a modest but statistically significant inverse genetic correlation ($r_g = -0.18$) between schizophrenia and hippocampal volume, but found no statistically significant correlations between schizophrenia and other brain structure volumes[110]. Given that brain structures seem to be influenced by considerably fewer causal genetic variants than schizophrenia[125], the extent of genetic overlap between brain structures and schizophrenia is likely to be smaller than that between schizophrenia and highly polygenic phenotypes such as educational attainment (FIG. 3). Nevertheless, since all available GWAS of cortical and subcortical structures to date are still insufficiently powered to detect a meaningful fraction of the genetic associations estimated to be present[125], we expect that additional genomic loci shared between schizophrenia and brain structures will be detected as neuroimaging GWAS sample sizes continue to increase.

MiXeR, a statistical tool developed in 2019, can be used to estimate the proportion of unique and shared causal variants in compared phenotypes[76]. This approach has demonstrated considerable genetic overlap between schizophrenia and brain-related traits, including psychiatric disorders, cognitive measures and psychosocial phenotypes (FIG. 3). Intriguingly, many pairwise comparisons revealed substantial genetic overlap despite low or absent genetic correlations (FIG. 2). For instance, MiXeR estimates that schizophrenia, ASD and educational attainment share almost all their causal variants, although schizophrenia and ASD have a genetic correlation of only 0.29 and no genetic correlation is evident between schizophrenia and educational attainment. This apparent contradiction can be resolved if the shared variants include a balanced mixture of agonistic and antagonistic effect directions, a suggestion that is in line with prior investigations of genetic overlap[104,106,107] and GWAS[34,66,126]. The substantial genetic overlap thought to exist between schizophrenia and related complex phenotypes emphasizes that the polygenic architectures of these phenotypes are largely distinguished by a phenotype-specific distribution of effect sizes among the causal variants and that many variants are likely to influence multiple phenotypes, albeit to different degrees. Additionally, some variants seem to specifically influence schizophrenia but not other complex traits. For example, not all causal variants are shared by schizophrenia and bipolar disorder (FIG. 3). The condition-specific variants as well as variants that show

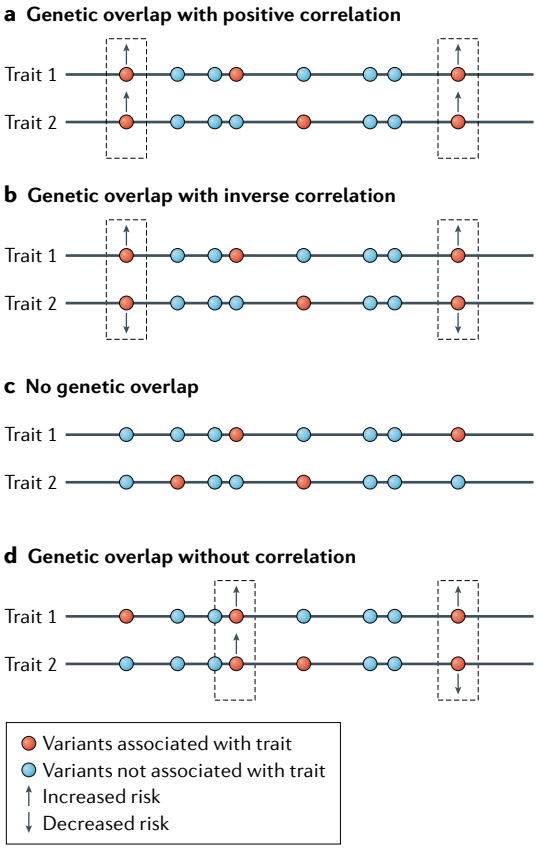

Fig. 2 | **A comparison of genetic overlap and genetic correlation.** The genetic relationship between two traits can be characterized as a positive correlation, a negative correlation or an overlap without correlation. **a** | A positive correlation requires an excess of shared genetic variance with agonistic allelic effects (arrows with the same directions). **b** | An inverse correlation requires an excess of shared variance with antagonistic allelic effects (arrows with opposite directions). **c,d** | A lack of genetic correlation might indicate either no genetic overlap (part **c**) or a balanced mixture of agonistic and antagonistic allelic effects (part **d**). The effect directions of a given allele are only shown for overlapping variants. Genetic overlap is present when the same variant is associated with both traits (dashed rectangles). In real scenarios of genetic overlap in complex phenotypes, such as schizophrenia, a mixture of genetic variants with agonistic and antagonistic effects is often present (that is, a combination of parts **a** and **b**)[104,106,119]. Black horizontal lines, DNA.

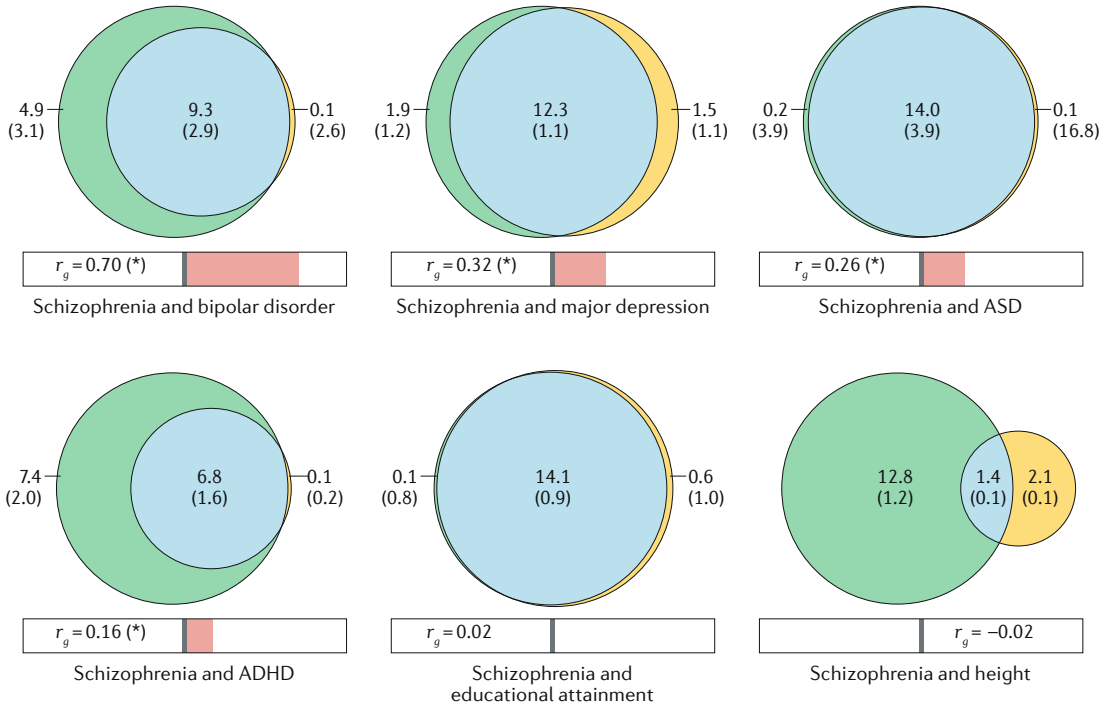

Fig. 3 | **The proportions of causal variants shared between schizophrenia and other phenotypes.** Both other than pale blueoverlapping (pale blue) and phenotype-specific (other colours) causal variants are components of the polygenic genetic architecture of schizophrenia modelled using the bivariate causal mixture (MiXeR) approach[76]. Substantial overlap is evident between schizophrenia[66] and bipolar disorder[117], major depression[173], autism spectrum disorder (ASD)[174], attention-deficit/hyperactivity disorder (ADHD)[175] and educational attainment[126]. Height, which is not associated with schizophrenia at the phenotypic level, is included as a somatic control[176]. The numbers indicate the estimated number of causal variants (in thousands) associated with each component, followed by the standard error in parentheses. The size of the circle reflects the extent of polygenicity: larger circles indicate that the phenotype is influenced by more causal variants. The estimates of genetic correlation (r_g values) were derived using linkage disequilibrium score regression[115]. Asterisks indicate genetic correlations that are significantly different from zero.

diverging effects in these two disorders[99] might represent molecular genetic mechanisms of high interest for distinguishing these disorders.

Evolutionary aspects

Common schizophrenia risk alleles persist in the population even though schizophrenia is associated with decreased reproductive fitness[127]. Large datasets of common risk variants associated with schizophrenia have enabled researchers to interrogate this paradox, although they have led to somewhat conflicting results so far. For example, common schizophrenia risk alleles are postulated to persist through balancing selection[128], meaning that the risk alleles might compensate for their debilitating effects by conferring reproductive advantages in healthy carriers. An increased risk of schizophrenia has been linked to behavioural traits, such as increased creativity[111] and openness to experience[112], which might be associated with increased reproductive success. Another possibility is that schizophrenia risk alleles might improve survival owing to an increased susceptibility to neuroticism[112] and cautious or risk-averse behaviour[129]. However, a 2017 study of the Icelandic population did not find any evidence of a reproductive advantage conferred by common schizophrenia risk alleles in individuals without a psychiatric disorder[130]. Another study of the UK Biobank cohort demonstrated a slight increase in fecundity among healthy individuals with an increased risk of schizophrenia[131]. Nevertheless, this effect did not compensate for the substantially reduced reproductive fitness observed in individuals with schizophrenia, suggesting that additional selection pressures maintain schizophrenia-associated common risk alleles in the population[131].

Some analyses of GWAS data support the hypothesis that schizophrenia is a by-product of human evolution[132]. For example, schizophrenia risk loci are more prevalent in genomic regions that have undergone positive selection pressure, resulting in an increase in frequency after the divergence of early *Homo sapiens* and Neanderthals[133]. Schizophrenia risk loci are also more prevalent in genomic regions that differ substantially between human and non-human species[134]. However, a 2018 report that compared different SNP-based signatures of evolutionary processes did not find any evidence of positive selection for common schizophrenia risk alleles[66]. Instead, the SNPs associated with schizophrenia were notably enriched in regions undergoing strong background selection (which decreases the genetic diversity of a genomic region)[135]. This effect enables common alleles with small deleterious effects to persist through genetic drift[135].

The persistence of schizophrenia despite the reduced fecundity of affected individuals could also be explained

by the emergence of novel risk variants with large effect sizes that are rapidly removed from the population as a result of negative selection pressure[136]. In line with this notion, rare schizophrenia risk variants with large effect sizes are also associated with decreased fecundity in individuals without a psychiatric disorder[130].

Contributions of rare variants

Schizophrenia risk is also influenced by rare de novo and inherited genetic variants, including rare SNPs and copy number variants (CNVs; deletions and duplications). 'Rare' in this context is defined as having minor allele frequencies of <1%. Given their scarcity, only rare variants with strong effects on schizophrenia (ORs 2–70, vastly surpassing those of common variants)[34,65,66] are discoverable[137–139]. Rare variants explain a much smaller fraction of the variance in the likelihood of developing schizophrenia than common variants[137,140,141], which contrasts with the large numbers of rare variants associated with other conditions, such as ASD[142]. Nonetheless, these rare variants can provide mechanistic hypotheses that are useful for further inquiry. However, the large effect sizes of rare schizophrenia-associated variants are not necessarily correlated with their clinical relevance, as many existing drugs converge on targets related to common-variant loci identified by GWAS[143]. Like common variants, rare schizophrenia-associated variants are highly pleiotropic, and the fact that affected patients often present with various intellectual, neurological and physical defects[137,139,144] suggests that key developmental programmes are perturbed[145].

Owing to the insufficient sample sizes of currently available rare-variant studies, only two genes harbouring rare (protein-disruptive) variants have been robustly associated with schizophrenia thus far. *SETD1A* encodes a histone–lysine *N*-methyltransferase[138] and *RBM12* encodes RNA-binding protein 12, which is implicated in brain development[139]. However, exome-sequencing studies have identified additional rare protein-disruptive variants in individuals with schizophrenia[140,141,144]. These variants are clustered in biologically plausible and partly overlapping gene sets related to loss-of-function-intolerant proteins, including targets of FMRP, calcium channels and pathways related to NMDARs, and activity-regulated cytoskeleton-associated protein (ARC)[140,141,144,146]. Some of these gene sets further implicate disturbed glutamatergic synaptic plasticity and function in schizophrenia.

The first CNVs to be consistently associated with schizophrenia were discovered using an approach that selected for de novo variants[147]. The largest CNV study to date identified eight schizophrenia-associated loci with genome-wide significance, which were also considered likely to result in other developmental abnormalities and disorders[137]. The CNV most commonly linked to schizophrenia is the 22q11.2 microdeletion; almost 25% of carriers of this microdeletion have schizophrenia-like symptoms[148]. Overall, the CNVs linked to schizophrenia implicated the involvement of gene sets encoding synaptic components, including ARC and NMDAR complexes[137].

Transcriptomic studies

In the past 5 years, the rapid proliferation of large transcriptomic datasets derived from multiple tissues, cell lines and organisms[149–151] has brought new opportunities for investigating functional pathways disrupted in schizophrenia. Studies drawing together information from common-variant and transcriptomic datasets indicate that the dysregulation of hundreds of genes in different brain regions is implicated in schizophrenia[150,152–155]. These studies involved post-mortem tissue samples from both adult and developing brains[156,157].

One such study integrated the CLOZUK GWAS dataset[66] with mouse and human brain single-cell RNA sequencing data[158]. The researchers demonstrated specific enrichment of gene expression profiles related to striatal medium spiny neurons, cortical interneurons and pyramidal cells in the hippocampal CA1 and somatosensory cortex, suggesting that schizophrenia-associated common risk variants converge on a limited set of cell types within the brain[158]. In support of these results, several of the gene sets previously associated with schizophrenia also mapped to the same cell types, including genes encoding targets of FMRP, antipsychotic drug targets, the components of NMDAR complexes and the PSD95 (postsynaptic density protein 95, also known as disks large homolog 4) complex.

The iPSYCH and PsychENCODE consortia compared transcriptional dysregulation in the cerebral cortex across individuals with major psychiatric disorders and reported that patterns in gene expression that were shared by different disorders reflected the extent to which common variants are shared by the disorders[159]. This observation indicates that the genetic overlap between psychiatric disorders also manifests at the transcriptome level and suggests that transcriptional changes in the cortex might (at least in part) reflect primary pathophysiological mechanisms that are driven by genetic variance[159]. The PsychENCODE consortium further demonstrated complex patterns of dysregulation at several levels of the transcriptome in a large-scale RNA sequencing analysis of the cerebral cortex of 1,695 individuals, including 559 individuals with schizophrenia, 222 patients with bipolar disorder and 51 persons with ASD[36]. Dysregulated gene and protein isoform expression in the individuals with schizophrenia was linked to a similar range of CNS cell types, including excitatory neurons, interneurons, astrocytes, endothelial cells, oligodendrocytes and microglia, and these cells were differentially associated with distinct inflammatory, synaptic and signalling co-expression modules[36]. Intriguingly, variants that resulted in alterations at the protein isoform level showed both larger effect sizes and lower overlap with other disorders compared with the gene-level changes, which suggests that regulatory mechanisms determining the expression of specific protein isoforms might have disorder-specific effects[36]. Note that several confounding factors could influence gene expression profiles in the post-mortem brain, including drug and medication use and factors that affect RNA stability and integrity, such as agonal state and the interval between death and tissue processing[36,159]. These factors warrant careful interpretation of transcriptomic studies and further investigation[36,159].

Protein isoform
Many human genes encode multiple protein variants generated by alternative promoters, alternative mRNA splicing or post-translational modification.

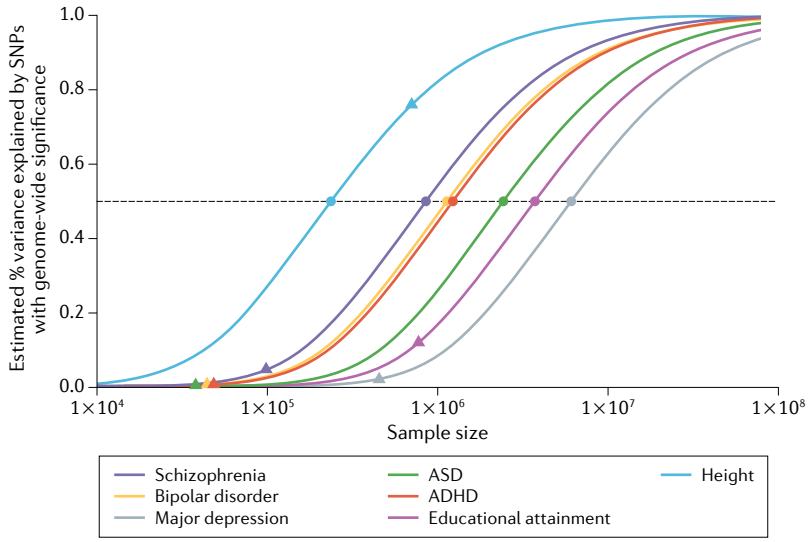

Fig. 4 | **Statistical power calculations for current and future GWAS.** The proportion of SNP-based heritability captured by the detected variants with genome-wide significance (vertical axis) can be calculated for increasing genome-wide association study (GWAS) sample sizes (*n*, horizontal axis) using the univariate causal mixture model[125]. The estimated GWAS sample sizes needed to capture 50% of the genetic variance (horizontal dashed line) associated with different conditions and traits are as follows: schizophrenia 860,000 (SE 27,000) participants[66]; bipolar disorder 1,100,000 (SE 81,000) participants[117]; major depression 6,100,000 (SE 280,000) participants[173]; autism spectrum disorder (ASD) 2,400,000 (SE 660,000) participants[174]; attention-deficit/hyperactivity disorder (ADHD) 1,200,000 (SE 150,000) participants[175]; educational attainment 3,700,000 (SE 64,000) participants[126]; and height 240,000 (SE 4,000) participants[176]. Triangles indicate the sample sizes of currently available GWAS, and circles indicate the estimated sample sizes needed to capture 50% of the genetic variance for that phenotype. Height is included as a somatic control (no genetic correlation exists between height and schizophrenia). SE, standard error. Bipolar disorder and height plots were reprinted from REF.[76] and adapted from REF.[125], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). ADHD, ASD and educational attainment plots were reprinted from REF.[76], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Future directions

The research community is still adapting to the new understanding that a large number of genetic and environmental risk factors with small individual effect sizes are involved in the aetiology of schizophrenia. This fundamental concept is important for the success of future research. As outlined in FIG. 4, we can expect to see a further substantial increase in the proportion of SNP-based heritability explained by variants with genome-wide significance as GWAS sample sizes continue to increase. Hence, international collaboration in large-scale GWAS remains imperative to continue the systematic exploration of the polygenic architecture underlying schizophrenia. For example, the PGC Schizophrenia Working Group is planning to further increase their GWAS sample size, which is an encouraging step[160]. In parallel, we can expect that developments in sequencing technology will dramatically reduce genotyping costs and facilitate these expanded sample sizes. As well as identifying additional common variants associated with schizophrenia, these initiatives are expected to clarify the role of rare variants in its aetiology. In particular, discoveries of rare protein-disruptive gene variants might accelerate drug discovery by providing novel druggable targets (as has been accomplished in other brain disorders)[161].

Arriving at a holistic understanding of the pathobiology of schizophrenia will ultimately require the integration of information from various biological levels: genomic, epigenomic, transcriptomic, metabolomic and proteomic as well as brain imaging findings and details of exposures to environmental and lifestyle factors (collected, for example, using mobile technologies). Collectively, these approaches would promote the development of improved risk-prediction tools. Large-scale coordination is warranted to harmonize the application of phenotypic and biomarker data and assemble cohorts of patients for adequately powered clinical trials. Although such research is unlikely to uncover a unifying cause of schizophrenia[27], the multitude of associations detected, despite each being of individually small effect, could still lead to the development of new and effective treatments that target these newly implicated biological pathways.

Deep insight into the genetic architecture of schizophrenia will facilitate research into its environmental triggers and causes and help disentangle their interplay with genetic risk. For example, a 2018 study noted a statistically significant interaction between schizophrenia PRSs and intrauterine and/or perinatal complications[162]. Specifically, PRSs explained more of the variance in risk of schizophrenia in individuals exposed to intrauterine or perinatal complications than it did in unexposed individuals, which indicates that the polygenic risk of schizophrenia (that is, the overall genetic susceptibility accounted for by multiple variants) might be more likely to perturb neurodevelopmental processes associated with schizophrenia after exposure to such adverse events[162]. Large-scale prospective studies, such as the ABCD study[163] or the Norwegian MoBa[164] study of 100,000 children, are expected to have a major effect on research into the interactions between genetic and environmental influences, which might reveal time windows during development when the interactions between genetic risk and environmental triggers are susceptible to being targeted. Promising new methods for studying resilience in individuals with schizophrenia[165] might also inform public health intervention strategies.

A key challenge in schizophrenia is to find ways to translate the findings of 'big data' studies to the individual patient in the clinic. With increasingly larger GWAS explaining progressively more of the genetic variance underpinning schizophrenia, we expect that more efficient PRS models will soon be developed. It is not unlikely that these tools will find clinical applications in diagnostic procedures and treatment decision-making in the near future. Hence, it is important to ensure that the validity of such tools is not limited to populations of European ancestry. The research community as a whole should strive to promote genetic studies of schizophrenia conducted outside the USA and Europe.

The high degree of genetic pleiotropy between psychiatric disorders could conceivably aid in the refinement of psychiatric nosology[166]. Although psychiatric disorders are categorized as distinct by current diagnostic systems[5,6], their overlapping clinical features and the fact that genetic risk transcends these diagnostic

boundaries suggests that their underlying aetiologies are not truly separate[97,98]. Intriguingly, several studies have reported strong associations between PRSs for schizophrenia and psychosis[99] as well as mood-incongruent psychotic features across the diagnostic groups of schizophrenia, schizoaffective disorder and bipolar disorder[167]. These observations indicate that genetic risk maps to clinical sub-phenotypes regardless of diagnosis. As cohorts of very thoroughly phenotyped patients are expected to be assembled in the coming years, including detailed data on their comorbidities, genetic studies of these individuals might assist in updating the classification of psychiatric disorders by delineating the diagnostic categories that have improved alignment with underlying aetiologies[168]. Such cohorts will also enable improvements in the design of clinical studies (beyond the current case–control design)[169] and improve our understanding of the heterogeneity in clinical characteristics, treatment response and outcome observed in individuals with schizophrenia. Legacy samples and genotype data from participants in treatment trials might also aid in the development of gene-based stratification tools for differentiating treatment responders from non-responders[170].

Increasing evidence indicates that the risk of developing schizophrenia is collectively accounted for by thousands of genetic variants that commonly occur in the population. This evidence is in line with a dimensional model of schizophrenia susceptibility that shows a continuum with variation in normal behavioural and neurobiological phenotypes. Further support for this model is provided by the extensive genetic overlap between schizophrenia and a broad range of cognitive[76,103,106] and psychosocial[111,112] traits. Hence, studies that address how the polygenic risk of schizophrenia is associated with complex traits in the general population (using resources such as the UK Biobank[171]) might be very useful for elucidating the genetic architecture of schizophrenia as has already been done for cognitive function[106]. The abundant genetic pleiotropy of schizophrenia-associated variants has also implications for improving GWAS discovery using statistical enrichment tools because combining related traits and measures in multivariate GWAS can dramatically increase both the effective GWAS sample size and its statistical power[172]. Promising statistical approaches include multivariate analytical methods to evaluate genetic overlap and the modelling of genetic architecture that accounts for mixtures of null and non-null causal effects, linkage disequilibrium and allele frequency. Open sharing of non-sensitive data from each GWAS study, such as within-sample linkage disequilibrium structures and allele frequencies in patients and controls, might promote the development of more efficient statistical methods.

Conclusions

The past two decades have witnessed a tremendous advance in our understanding of the genetics of schizophrenia. The polygenic architecture of schizophrenia comprises both common and rare genetic variants that imply a pathobiological role for disturbances of neuronal transmission and excitability, neurodevelopment and the immune system. However, we are still far from understanding the functional consequences of most genetic risk variants identified to date and a considerable proportion of the polygenic architecture of schizophrenia remains to be uncovered. Yet, the rapid pace of genetic research in this field suggests that, in the next few decades, these emerging genetic discoveries could become translatable to the clinic, facilitate drug development by revealing new mechanistic targets, improve diagnostic accuracy and help to refine psychiatric nosology. We expect that continued collaboration in large-scale data collection, in combination with novel analytical tools, will become the new cornerstones of approaches for disentangling the enigma of schizophrenia.

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Author contributions
O.A.A., O.B.S., O.F. and A.M.D. researched data for the article, contributed substantially to discussions of its content and participated in review or editing of the manuscript before submission. In addition, O.A.A. and O.B.S. wrote the initial draft.

Competing interests
O.A.A. declares that he has received a speaker's honorarium from Lundbeck and is a consultant for HealthLytix. A.M.D. declares that he is a founder of and holds equity interest in CorTechs Labs, that he is a member of the scientific advisory boards of CorTechs Labs and HealthLytix, and receives research funding from General Electric Healthcare. The terms of these arrangements have been reviewed and approved by the University of California San Diego in accordance with its conflict of interest policies. The other authors declare no competing interests.

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