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Genetics of Schizophrenia

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Abstract

The genetic basis of schizophrenia has been a hotly debated research topic for decades, yet recent studies, especially in the past year, have confirmed genetics as the major cause of this complex condition. Psychiatry has come of age: it is perhaps more difficult for the current generation of psychiatrists, to comprehend how the biological root of the condition could have been denied for so long. Here we review how highly collaborative global efforts to pool samples, utilise the very latest advances in genotyping and high throughput sequencing technologies, and application of robust statistical analysis have reaped phenomenal rewards. The major findings are that schizophrenia is a highly polygenic disorder with a complex array of risk loci, many include genes implicated also in intellectual disability, autism spectrum disorders, bipolar disorder and major depressive disorder. These candidate genes converge on key neuronal signalling pathways identifying novel targets for potential future therapeutic intervention.

Keywords

Schizophrenia; Genetics; Copy number variants; Single nucleotide polymorphisms; Common variants; Rare variants; Neurodevelopmental disorders

Introduction

Schizophrenia is a severe psychiatric disorder affecting approximately 1 % of the population worldwide. Like many other common diseases, schizophrenia is complex and multifactorial, with contributions from multiple susceptibility genes, epigenetic, stochastic, and environmental factors [1]. The search for candidate genes has proven difficult and has been hampered by clinical and genetic heterogeneity. Family, twin and adoption studies have shown that genetic factors play a major role in the development of schizophrenia, which has

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an estimated heritability between 60-85 % [2], and a number of candidate risk genes have been shown to associate [3]. A neurodevelopmental model for schizophrenia has been postulated from epidemiological, developmental and neuroimaging studies where symptoms of psychosis are the end result of processes that started to go awry years before the illness onset [4, 5].

Schizophrenia has long been assumed to be a disorder of neuronal signalling: either dopamine- or glutamate-related [6]. The dopamine hypothesis of schizophrenia is based on the assumption that schizophrenia results from excess dopamine activity and drugs which increase dopamine activity (dopamine agonists such as amphetamines), can induce psychotic symptoms [7]. A second piece of evidence in support of dopamine, is that selective dopamine receptor antagonists are effective antipsychotics, and their efficacy is closely correlated with their ability to block dopamine D_2-like receptors. This is the pharmacological basis of our current treatments for schizophrenia, which are partially effective but unfortunately none are disease-modifying. Glutamate dysfunction has also been implicated in schizophrenia. The glutamate hypothesis is based on the fact that antagonists of the N-methyl-D-aspartate receptors (NMDA-R) subtype of glutamate, such as phencyclidine (PCP) and ketamine cause behavioural and cognitive symptoms similar to the positive, negative and cognitive symptoms of schizophrenia when given to healthy individuals [8]. Increasingly, many genetic risk variants which associate with neurodevelopmental disorders such as schizophrenia, intellectual disability (ID), and autism spectrum disorders (ASDs) are being linked to glutamatergic neurotransmission pathways raising the potential for new glutamatergic compounds for the treatment of these disorders in future.

Two main hypotheses have been proposed to underlie the genetics of schizophrenia and include the '*common disease-common variant*' (CD-CV) model and the '*common disease-rare variant*' (CD-RV) model. The CD-CV model, based on large genome-wide association studies (GWAS) of hundreds of thousands of single nucleotide polymorphisms (SNPs), proposes that schizophrenia is caused by a large number of common variants that each in itself causes only a modest effect [9]. The CD-RV hypothesis however proposes that some rare, highly penetrant copy number variants (CNVs; segments of DNA with duplications and deletions) play an important role in schizophrenia susceptibility as shown by their increased frequency in disease from a number of genome-wide CNV studies and also alludes to a broader neuropsychiatric spectrum for schizophrenia than previously conceived [10]. Furthermore, it also opens the door in future to the possibility of clinical diagnostic subtyping of schizophrenia based on genotype as well as phenotype data. In this review, we have presented the latest genomic findings in schizophrenia research and consider their implications to our current understanding of the condition.

Common Variants

GWAS are based on the identification of multiple SNPs, both in cases and controls for a specific trait, in order to assess whether an allelic variant is more prevalent in cases compared to controls. Once this association has been found, the genes that co-segregate with this specific SNP will be putatively associated with the trait. These studies require a large

number of participants in order to achieve enough statistical power to find variants with low relative risks with whole-genome significance, and this is thought to be the reason why earlier GWAS in psychiatry failed to find robust and replicable gene candidates. Multiple genes have since been found in schizophrenia GWAS, supporting the *CD-CV model*. In this model common genetic variants, present in the general population, would account for only a small contribution towards the risk of developing the disease. Although each allele has a low odds ratio (usually around 1.2), the totality of the genes could amount as much as 32-36 % of the genetic variance of the condition [11]. However, one criticism of GWAS has been population stratification. This concept refers to the possibility of obtaining spurious results due to allelic ancestral differences between the subpopulations in the study, rather than those associated to the studied trait [12]. Another problem may arise from underpowered studies that give rise to false negatives and the elimination of mitochondrial DNA and sex chromosomes from the studies could also prevent finding some associations [12].

The need for extensive samples in order to detect these variants led to the establishment of different consortia, including the International Schizophrenia Consortium (ISC), Molecular Genetics of Schizophrenia (MGS), SGENE and the Schizophrenia Working Group of the Psychiatric Genomics Consortium (SWG of PGC). The first meaningful result came from a combined sample between the ISC, SGENE and MGS and identified the major histocompatibility complex (MHC) as a risk factor (with a genome-wide P value of $9.5x10^{-9}$ for rs13194053, an SNP in the MHC region) [11]. Further studies showed association of schizophrenia with new loci: 1p21.3 (*MIR137*), 2q32.3 (*PCGEM1*), 8p23.2 (*CSMD1*), 8q21.3 (*MMP16*) and 10q24.32-33 [13]. Another 13 regions were described in a combined sample of PGC and Swedish participants, amongst them *CACNB2*, *MAD1L1* and lincRNAs [14].

It is worth highlighting that MHC is the most extensively associated gene for schizophrenia in GWAS: a locus on chromosome 6, that includes MHC, is by far the most significant association found to date. An immune factor in the disease can be implicated from the fact that maternal infection has been proposed as one of the factors increasing schizophrenia risk, which could account for as much as one-third of cases [15]. Moreover, studies have shown that offspring of mice injected with poly(I:C), a dsRNA that mimics viral infection, present alterations that resemble some schizophrenia features (e.g. enlarged ventricular volume, behavioural abnormalities) [16]. Further support for the role of MHC in schizophrenia comes from the fact that the molecule has also been found on synaptosomes in the adult mammalian CNS, in visual cortex synapses [17] and in neurons and neuronal precursor cells in the prenatal mouse brain [18]. In cultured neurons before and during the peak of synaptogenesis, MHC-I negatively correlates with glutamatergic synapses, being MHC more present in proximal dendrites and glutamatergic synapses in distal dendrites [17]. This inverse correlation was further observed *in vivo*, with an increase of more than 50 % in synaptic density in ‘knock-out’ MHC-I mice [17]. The implication for MHC-I, seen in glutamatergic synapses, is a strong argument for a possible role in the aetiology of schizophrenia, given the alterations in glutamate neurotransmission observed in patients [8].

The immune system link has been further supported from recent biological insight reported in the findings of the SWG of PGC where by far the most significant locus includes a region

containing the MHC [19••]. This latest paper comprised a multi-stage schizophrenia genome-wide association study of up to 36,989 cases and 113,075 controls and is the largest molecular genetic study of schizophrenia conducted to date [19••]. It identified associations spanning 108 conservatively defined loci of genome-wide significance (75 % protein coding genes; 40 % were a single gene and a further 8 % within 20 kb of a gene), 83 which had never been reported previously. A number of interesting associations were noted as relevant to existing hypotheses of schizophrenia aetiology including Dopamine Receptor D2 (*DRD2*) the gene target of current antipsychotic medications used in clinical practice. Other candidates genes, involved in glutamatergic neurotransmission and synaptic plasticity (such as *GRM3*, *GRIN2A*, *SRR*, *GRIA1*), were also revealed as well as genes which encode voltage-gated calcium channel subunits (i.e. *CACN A1C*, *CACNB2 and CACNA11*), again extending earlier findings of an overlap between genes affected by rare variants and those within GWAS loci, which were speculated to have a putative role in schizophrenia by resulting in abnormal glutamatergic synaptic and calcium channel functioning. Genes strongly expressed in cortical and striatal neuronal lineages were enriched for association also providing further evidence of a neuronal pathology in schizophrenia. Furthermore, closer scrutiny of the findings of this recent paper also reveals that the genetic effects in schizophrenia are enriched in regions outside the MHC that are also involved in acquired immunity [19••] providing further speculation to the longstanding theory that schizophrenia is a disorder of acquired immunity.

Before this recent landmark study from the SWG of PGC, other studies that had gone before it had adopted a different approach to analyse more samples. It has been estimated that around 15 % of cases initially diagnosed with bipolar disorder were later reclassified as schizophrenia and 4 % of schizophrenia cases were later reclassified as bipolar disorder, with only 47.1 % of schizophrenia cases retaining this diagnosis over a 10-year period [20], which is thought to be due to a considerable overlap between the symptoms of these conditions. Moreover, coheritability of SNPs between disorders has shown a common genetic background between schizophrenia and bipolar disorder (genetic correlation coefficient, r_g =0.68) and schizophrenia and major depressive disorder (r_g=0.43) [21]. Therefore, some studies have pooled cases from different disorders in order to increase the statistical power of the study and identify a shared genetic risk. In a joint analysis between schizophrenia and bipolar disorder, three genes reached genome-wide significance: *CACNA1C*, *ANK3* and *ITIH3-ITIH4* [13]. Furthermore, a combined analysis of five psychiatric disorders (schizophrenia, bipolar disorder, major depression, autism spectrum disorder and attention-deficit hyperactivity disorder) found three loci associated with the totality of the disorders (*ITIH3*, *AS3MT*, *CACNB2*) and validated the previous finding of *CACNA1C* in schizophrenia and bipolar disorder [22]. Another relevant finding is *MIR137*, which is a microRNA implicated in neurogenesis and neuronal maturation and has *CACNA1C* and other schizophrenia risk genes as targets [13]. Mir-137 risk variant rs1625579 is associated with prefrontal cortex hyperactivity together with baseline levels of memory and cognition, which has been noted as neuronal inefficiency caused by mir-137 intervention in abnormal connectivity [23]. Furthermore, overexpression of mir-137 downregulates a subset of genes under the category of ‘regulation of neuronal

differentiation' [24] and high levels of mir-137 increase neuronal proliferation and inhibit neuronal differentiation in an *in vivo* assay [25].

Rare Variants

A problem that is apparent from the aforementioned studies in the CD-CV model is the missing heritability. Since all the variants, in the large-scale studies conducted thus far, cannot entirely explain the heritability values set for schizophrenia, there has been a need for a complementary approach to potentially explain this discrepancy. In the CD-RV model the disorder is proposed to be caused by mutations in a single gene, which would localize to a diverse subset of genes. The main criticism to the CD-RV model however, is that rare, highly penetrant mutations would be negatively selected [26].

One of the first single gene studies supporting this model found an association of a translocation between chromosome 1 and chromosome 11 with several mental disorders in a large Scottish pedigree [27, 28]. This translocation disrupted a gene in chromosome 1, which was accordingly named *disrupted-in-schizophrenia-1* (*DISC1*), and a non-coding RNA, *DISC2*, which is transcribed antisense from *DISC1*. A study in a large cohort of 1542 cases (schizophrenia, bipolar disorder and recurrent major depressive disorder) and controls detected 905 SNPs in *DISC1* with more than 1 % MAF (*minor-allele frequency*) and 3777 SNPs with less than 1 % MAF ('rare'), of which 40 % were previously unknown. Amongst the rare variants, a R37W mutation that falls into a nuclear localization sequence was highlighted since it is algorithmically predicted to have a functional impact [29]. Further studies of *DISC1* have shown its role as a scaffolding protein with a prominent function in brain development, neurogenesis and neuronal migration and in synaptic function (*DISC1* interactome has been found to be enriched in synaptic proteins and proteins associated with NMDAR signalling). A role in oligodendrocyte development has also been suggested [30]. A role for *DISC1* in mitochondrial trafficking has been proposed, through its interaction with Trak1, an interaction that is altered in R37W mutated *DISC1*. This is relevant due to the role mitochondria have in brain development and function as a response to changing energy needs [31]. Mouse models with mutated forms of *DISC1* are also available and these have shown subtle brain alterations (reviewed in [32]).

Recent exome-sequencing studies have also found evidence of an enrichment of rare variants in schizophrenia. These advances in gene sequencing allow us to identify rare pathogenic single base pair changes as well as insertion deletion polymorphisms. A polygenic burden of rare mutations, with minor allele frequencies of less than 0.5 % or singletons (alleles present in only one heterozygous individual), were significant in a Swedish sample of schizophrenia cases and controls [33•]. Moreover, these mutations were more prominent in the activity-regulated cytoskeleton-associated scaffold protein (ARC) of the post-synaptic density and post-synaptic density-95 (PSD-95) complexes and in genes related to calcium channels (such as *CACNA1C*) [33•]. In another important study which established an enrichment of *de novo* mutations in schizophrenia and linked them to specific biological pathways, an increased occurrence of mutations in genes previously implicated in the disease was found, especially in the NMDAR and ARC complexes and in Fragile X mental retardation protein (FMRP) targets [34••]. These results not only support the importance of rare mutations in

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schizophrenia, but also implicate specific pathways, such as calcium signalling and glutamate neurotransmission, that had been proposed already in GWAS.

In addition to point mutations which have been discovered from recent sequencing studies, CNVs as mentioned earlier, have been found enriched in schizophrenia cases (1.15 case/control ratio)[35]. Duplications and/or deletions of numerous genomic regions have been implicated in the disease, and many of these include more than one gene (see Table 1 for a list of some CNVs reported to associate with increased risk of schizophrenia). A relevant characteristic of CNVs in schizophrenia is the preponderance of *de novo* cases. It has been estimated that *de novo* CNVs are 8-fold more frequent in schizophrenia cases compared to controls, whereas sporadic schizophrenia cases are only 1.5-fold more likely to harbour inherited CNVs than controls [36]. Further analysis has shown an enrichment of *de novo* CNVs in synaptic genes, explained mostly by enrichment in the ARC complex and NMDAR genes [37••]. This is especially relevant, not only due to the pathophysiological links to the GWAS findings, but because this elevated *de novo* mutation rate has been proposed as a possible mechanism maintaining schizophrenia in the population, despite strong negative selection and the fact that the overall fertility of patients with schizophrenia, autism and anorexia nervosa is reduced [38].

Conclusions

Schizophrenia genetics is an example where persistence, collaboration, and utilisation of the latest technologies has been duly rewarded. Over the past few years there has been a flurry of important high impact papers from GWAS [14, 19], CNV [37••], and sequencing studies [33•, 34], which all suggest the importance of a number of genes involved in synaptic plasticity including ARC, NMDAR complexes, FMRP targets and voltage-gated calcium channels. The most recent of these studies was produced from a collaboration of over 80 research institutions world-wide, which comprise the SWG of PGC, and identified 108 genetic loci to schizophrenia, 83 of which are new [19••], and have brought renewed optimism to the field [40].

The extensive list of genes implicated in the pathophysiology of schizophrenia also brings it’s own challenges clinically. Pleiotropy refers to the genetic overlap between disorders, and it certainly appears that many of the conditions we diagnose in clinic including schizophrenia, affective disorders, ID, ASD, and attention-deficit hyperactivity disorder (ADHD) have shared genetic risk factors alluding to the possibility that they all share similar underlying disease pathways and cellular mechanisms so perhaps schizophrenia is best viewed as part of a spectrum of neurodevelopmental disorders. The concept of endophenotype may increasingly be adopted in psychiatric research where an endophenotype is defined as a measurable trait that is more related to the genetic underlying of a disease than clinical phenotype [41]. Different endophenotypes have been proposed, although one of the most cited is the P300 inhibition, which has been found associated with specific SNPs in *mir-137*, *DISC1*, *ABCB1* and *BDNF* [42]. The development of a solid knowledge of endophenotypes and their genetic underpinnings may in future be helpful in redefining classification systems in psychiatric research given the large number of gene targets.

The fundamental goal of psychiatric genetics research is to achieve a greater understanding of the pathophysiological mechanisms underlying disease with a view to developing more tailored effective therapies in future. The studies discussed thus far have identified risk genes associated with schizophrenia but it is now essential to functionally validate these variants to shed light on the biological mechanisms underpinning the disease. An elegant study has recently been published using stem cells from patients with 15q11.2 CNVs [43••]. The authors took a multifaceted approach to investigate why 15q11.2 CNVs are prominent risk factors for schizophrenia and autism. Even in normal control subjects, carriers of the 15q11.2 deletion have cognitive deficits and structural changes on MRI scanning [44], which has raised interesting questions about how this genetic variant brings about the structural and functional changes seen in the carriers. They showed that human iPSC-derived neural progenitor cells carrying 15q11.2 microdeletions exhibited deficits in adherens junctions and apical polarity resulting from haploinsufficiency of *CYFIP1* (a gene within 15q11.2 that encodes a subunit of the WAVE complex which regulates cytoskeletal dynamics) [43••]. Furthermore, they showed that deficiency in CYFIP1 and WAVE in the developing mouse cortex affects radial glial cell migration causing ectopic localisation outside of the ventricular zone. Therefore, by integrating human neural stem cells, *in vivo* animal modelling and targeted human genetic association studies they have provided a mechanistic understanding of how 15q11.2 microdeletions affect neural development. In future it will be possible to use such a multi-faceted biological approach to unravel the cellular architecture of complex neuropsychiatric disorders building on what we have learned from the genetic studies.

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Table 1

List of CNVs associated with increased risk of schizophrenia [39]

Region	Type of CNV	Region	Type of CNV
1q21.1	deletion/duplication	15q11.2	deletion/duplication
2p16.3	deletion/duplication	15q13.3	deletion/duplication
3p26.1	deletion/duplication	16p11.2	duplication
3q29	deletion	16p13.1	deletion/duplication
5p13.2	deletion/duplication	17p12	deletion
7q11.2	duplication	17q12	deletion/duplication
7q22.1	duplication	22q11.2	deletion
7q36.3	deletion/duplication	15q13.1	duplication