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Paper Title: Genetics of Schizophrenia and other Psychotic Disorders

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**Abstract:**

Research into the genetic basis of schizophrenia is advancing rapidly. This review gives a broad overview of results from successive phases of studies in this field, linking these with recent findings and likely future research directions. Among recent findings, large-scale epidemiological studies based on Scandinavian population registers, have provided further evidence of substantial heritability and evidence that a wide range of psychotic and non-psychotic disorders partly share genetic risk factors with schizophrenia. In molecular genetics, large collaborative genomewide association studies (GWAS) are providing evidence of common risk variants, each of small effect, and many more variants are likely to be found as samples sizes increase further. A range of rarer chromosomal copy number variants (CNVs) have been associated with schizophrenia, and both GWAS and CNV studies have provided molecular evidence of genetic overlap between schizophrenia and other disorders. There is increasing interest in phenotypes beyond diagnosis, including further clinical variables and endophenotypes. Next-generation sequencing studies are beginning, with the potential for fast, inexpensive sequencing of the whole genome in large samples, and there is an increasing focus on the functional effects of the candidate risk variants that are being identified.

**Keywords:**

Endophenotype

Genetics

GWAS

Heritability

Linkage

Psychosis

Schizophrenia

Schizoaffective

## Introduction

Research into the genetic basis of schizophrenia is advancing rapidly. In quantitative genetics, the evidence for substantial heritability has been further substantiated by large-scale analysis of a range of types of relatives **using national population registers**, and there is a lengthening catalogue of other psychotic and non-psychotic disorders that are likely to share some genetic risk factors with schizophrenia. In molecular genetics, genomewide association studies (GWAS) are providing evidence of many common genetic variants which each make a small contribution to risk. At the chromosomal level, studies of copy number variants (CNVs) are showing rarer variants which have a larger effect on risk. Both types of study are reinforcing the theme that schizophrenia shares some genetic influences with a range of other disorders. In an effort to understand the genetics of schizophrenia by going beyond the diagnosis, there has been interest in both additional clinical phenotypes and the use of endophenotypes. Work is also beginning in the use of next generation genetic sequencing to find new genetic variants and in moving further downstream to find the functional consequences of risk variants. In this article, **we give a broad overview of these recent research developments against the background of successive phases of previous research**, and consider the probable next stages of research in this field.

## Family Studies

It is well established that the risk of schizophrenia is increased in the relatives of those with schizophrenia. While the lifetime risk for schizophrenia in the general population is approximately 0.8-1% [1], the average risk to the siblings of those with schizophrenia is approximately 9%, to parents 6% and to offspring 13% [2, 3]. Recently, large scale epidemiological studies from Scandinavia, which have linked national population registers with mental health service registers, have provided further information on the patterns of familial risks. One such study found the risk of schizophrenia in the offspring of couples who had both been admitted to a psychiatric facility with a diagnosis of schizophrenia was 27.3% (increasing to 39.2% when schizophrenia-related disorders were included) [4]. This was compared with a risk of schizophrenia of 7% in the offspring of couples with only one parent ever admitted for schizophrenia and 0.9% in the offspring of couples where neither had ever

been admitted [4]. Another study provided relative risks for a range of familial relationships, including strengthening the evidence of lower risks to half-siblings than to siblings. The relative risk to maternal half-siblings was 3.6, and to paternal half-siblings 2.7, compared with a sibling relative risk of 9.0 [5]. Overall these findings reinforce the evidence that the risk of schizophrenia increases with the number and degree of relatedness of affected family members.

### **Twin Studies**

The classical twin study approach is to compare concordance in monozygotic (MZ or identical) twins, who inherit virtually 100% of alleles in common, with dizygotic (DZ or non-identical) twins, who inherit on average 50% of alleles in common. Studies of this kind assume that MZ and DZ twin pairs have an equal sharing of environmental risk factors for schizophrenia. Pooling of older studies of clinical schizophrenia gave an MZ concordance of 46% and DZ 14% [6]. Subsequent studies employing operational research diagnoses have given similar results with probandwise concordances of 41–65% in monozygotic (MZ) pairs and 0–28% in dizygotic (DZ) pairs [7], consistent with a genetic contribution to the aetiology of schizophrenia.

### **Adoption Studies**

Like family studies, adoption studies investigate an elevated risk of schizophrenia in the relatives of affected individuals. However, because relatives have been separated by the adoption process and thus there is less environmental sharing, a finding of elevated risk in biological relatives is consistent with the presence of a genetic contribution to the aetiology of schizophrenia. Schizophrenia has been found to be more common in adoptees than in the general population, and it is therefore important in adoption studies to employ adoptee controls, rather than general population controls.

An example is the Danish Adoption Study of schizophrenia [8, 9, 10], which ascertained probands who had been adopted early in life and subsequently developed schizophrenia. 7.9% of first degree biological relatives of proband adoptees had DSM-III schizophrenia compared with 0.9% of first degree relatives of control adoptees [10]. The Finnish Adoptive Study of Schizophrenia [11-13] took a

different approach. The researchers ascertained a sample of mothers with schizophrenia or a related disorder, who had a child adopted soon after birth, and investigated how frequently these offspring developed DSM-III-R schizophrenia. They found a significantly greater lifetime prevalence of 4.4% among index adoptees compared with 0.5% among control adoptees.

More recently, further evidence has come from a large Swedish population register study [5] that investigated a range of familial relationships including adoptive relationships. The relative risk of schizophrenia in adopted offspring of a parent with schizophrenia was 13.7, and the relative risk to adopted away siblings was 7.6, both significantly elevated and providing further substantiation of the elevated risk of schizophrenia in adopted-away biological relatives of those with schizophrenia.

### **Heritability**

Estimating heritability is the commonest approach to quantifying the relative contribution of genetic and environmental influences. Heritability of schizophrenia refers to the proportion of variance in liability to the disorder in a population that is accounted for by genetic effects, and is most commonly calculated from twin concordances and the lifetime population risk for schizophrenia. In their meta-analysis of 12 published twin studies of schizophrenia, Sullivan et al. [14] found that the heritability of schizophrenia was high, at 81% (95% CI 73%-90%), and they also determined that there was a small but significant common familial environmental effect on liability to schizophrenia amounting to 11% (95% CI 3%-19%), with the remaining 8% due to individual-specific environmental effects.

Subsequently, Lichtenstein et al. [5] calculated heritability based on their large study of family and adoption data. They found a somewhat lower, but still substantial, heritability of 64% (95% CI 61.7%-67.5%) with shared environmental effects of 4.5% (95% CI 4.4%-7.4%). The reason for the difference from the twin study results is not clear, but taking all these results together we may still say that the heritability of schizophrenia is substantial and between 60 and 80%.

### **Mode of Inheritance**

The pattern of risks from family, twin and adoption studies is consistent with schizophrenia generally having a multi-factorial aetiology. There are probably many genetic and environmental risk factors, which do not have a large enough effect to cause schizophrenia on their own, but as an individual is burdened by an increasing number of these risk factors, their risk of developing schizophrenia increases. In some generally multi-factorial diseases, such as breast cancer and Alzheimer's disease, there are also relatively rare families where a single genetic mutation causes a Mendelian subform of the disease. There is no conclusive evidence for Mendelian subforms of schizophrenia at present, but neither has this possibility been excluded.

### **Overlap with Other Disorders**

Family, twin and adoption studies during the 20<sup>th</sup> Century provided evidence that, in addition to an elevated risk of schizophrenia itself, relatives of probands with schizophrenia have an elevated risk of a number of other disorders, such as schizoaffective disorder, schizotypal and paranoid personality disorders, and psychotic affective disorders [10, 15-19], consistent with a degree of overlap between genetic influences on schizophrenia and these other 'schizophrenia spectrum' disorders. However, whether there was an overlap with genetic influences on mania/bipolar disorder or non-psychotic depressive disorders remained controversial.

The more recent large register-based studies have further substantiated the previous findings. For example, the relative risk of schizoaffective disorder in siblings of probands with schizophrenia has been found to be 7.1 [20]. In addition, there is now substantial evidence from family, twin and adoption studies of a partial overlap in aetiological influences on schizophrenia and mania/bipolar disorder [4, 5, 21-25], with the two disorders having a genetic correlation of approximately 0.6 in both family/adoption [5] and twin studies [21]. The large-scale family studies have also provided evidence that relatives of probands with schizophrenia have an elevated risk for a very wide range of additional disorders including recurrent depression, autism and ADHD, and substance abuse [23].



These quantitative genetic studies provide a foundation for molecular genetic studies, in particular linkage and association studies, which aim to locate DNA susceptibility variants for schizophrenia and related disorders.

### **Linkage Studies**

A substantial number of genome-wide linkage studies of schizophrenia have been conducted in affected sibling pairs or families with multiply-affected members spanning more than one generation. They have generally investigated the inheritance of several hundred genetic markers in total, spread along each chromosome, seeking chromosomal regions that could contain one or more genetic risk variants for schizophrenia. This is an example of a positional cloning approach, where the initial investigation focuses on the potential location (position) of risk variants, without reference to gene function. Genetic association studies are then conducted on candidate genes within the chromosomal region of interest.

Many candidate regions have been identified, including on chromosomes 1q, 6p, 8p, 13q, 10p, 10q and 22q [26], but results have been difficult to replicate consistently across studies. In a meta-analysis of 20 studies in 2003, Lewis et al. identified genome wide significant linkage at 2q, and a number of additional locations that the researchers agreed were strong candidate gene regions [27]. A more recent meta-analysis of 32 studies [28] confirmed a region on chromosome 2q and also on chromosome 5q, and in samples of European descent possible linkage on 8q.

### **Association Studies**

While linkage studies investigate the inheritance of genetic markers in multiply-affected families, association studies are population-based, and most commonly involve a case-control design. An initial methodological concern with association studies was potential confounding if the cases and controls had different allele frequencies due to differences in their population genetic histories. However, such population stratification can now largely be taken into account by advances in analytical approaches [29].

The first wave of association studies focused on genetic markers in functional candidate genes with a known function that had a plausible relationship with schizophrenia. A weakness of this approach was that, due to our limited knowledge about the pathophysiology of schizophrenia, it was difficult to find strong candidate genes. Meta-analyses supported associations with markers in, for example, **5HT2a (HTR2a, serotonin receptor 2A, 13q) [30]** and **DRD3 (dopamine receptor D3, 3q) [31]**, but genetic variants with clearly relevant functional effects were not found.

The second wave of association studies involved investigation of positional candidate genes in regions of interest identified by linkage studies. This approach led to the identification of a number of positional candidate genes, including **DTNBP1 (dysbindin, 6p) [32]**, **NRG1 (neuregulin 1, 8p) [33]** and **DAOA (D-amino acid oxidase activator, 13q) [34]**. While many associations have been replicated in different samples, there have also been studies in which they failed to replicate. The pattern of associated alleles and haplotypes across samples has also been somewhat inconsistent [35]. However, these candidate genes remain under investigation and this has also led to the identification of further candidate genes. An example is the investigation into the **DTNBP1 gene, which is part of the BLOC-1 complex (biogenesis of lysosomal organelles complex-1), and** had been implicated in susceptibility to schizophrenia [36]. It was therefore postulated that genes encoding other members of the complex might also be involved in susceptibility to schizophrenia. Morris et al. [37] investigated this hypothesis by performing an association analysis of seven BLOC-1 genes and reported association between BLOC1S3 and schizophrenia.

#### Genomewide Association Studies (GWAS)

In recent years it has become technically feasible to undertake genome-wide association studies. These studies aim to systematically survey the genome in detail for alleles associated with a disease [35]. These are very large-scale investigations. **A recent mega-analysis of independently conducted** GWAS studies of schizophrenia assayed more than one million genetic markers (single nucleotide polymorphisms (SNPs)), by a combination of direct measurement and imputation, in a combined sample of over 50,000 individuals [29]. GWAS became possible because of a number of different

technological advances. These include the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005. Both of these have provided a great deal of information about the human genome and its variation. Alongside these, advances in information technology and statistical approaches mean that whole-genome samples can be analyzed for genetic variants that contribute to a disease. In this context, GWAS are particularly geared to the detection of common genetic variants that each makes a small contribution to disease risk.

The first promising GWAS result was for the SNP rs1344706, in the zinc finger binding protein 804A gene (ZNF804A, 2q) [38]. Evidence for the association strengthened when the affected phenotype included bipolar disorder, suggesting that alleles in the vicinity of ZNF804A influence risk to a broader psychosis phenotype. These findings were further substantiated in a larger meta-analysis [39].

Subsequent increases in sample size, which resulted from increasing collaboration between research groups, have led to the discovery of genome-wide significant associations at markers in the major histocompatibility complex (MHC) region on chromosome 6 [40], and additional significant SNPs in or near neurogranin (NRGN) (11q24.2) and transcription factor 4 (TCF4) (18q21.2) [41].

The recently-published results of the largest GWAS mega-analysis on schizophrenia and bipolar disorder to date, from the Psychiatric Genome-Wide Association Study Consortium (PGC), have shown genome-wide significant associations with schizophrenia for seven loci, five of which are new (1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33) and two of which have been previously implicated (6p21.32-p22.1 and 18q21.2) [29]. The strongest of the new findings was for a marker in microRNA 137 (MIR137, 1p), which has a role in the regulation of neuronal development. The study also provided further evidence for loci that increase risk of both schizophrenia and bipolar disorder (CACNA1C, ANK3 and ITIH3-ITIH4). In keeping with the focus of GWAS, the identified risk variants are likely to each have a small effect on risk (odds ratios around 1.1). This study did not include ZNF804A among its top findings, but this locus remains a strong candidate due to the evidence from other studies and emerging evidence of associations with endophenotypes (see below).

A more recent study by Hamshere et al. used a sample of 2640 individuals with a clinical diagnosis of schizophrenia attending a clozapine clinic, 2504 cases with a research diagnosis of bipolar disorder, and 2878 controls. Of the genomewide significant associations from the PGC analysis, this study found independent confirmation of associations for SNPs marking *CCDC68*, *CNNM2* and *NT5C2*. *MIR137* almost reached significance with a p value of 0.074. This sample was also combined with the PGC data leading to three new variants reaching genomewide significance for schizophrenia: *ITIH3/4*, *CACNA1C* and *SDCCAG8* [42].

In addition to investigations of individual genetic markers, GWAS have jointly analysed many markers to provide molecular evidence that the genetic contribution to schizophrenia includes a polygenic component (i.e., due to the cumulative influence of many genetic variants of small effect), and that again there is partial overlap in the polygenic contribution to schizophrenia and bipolar disorder [43].

### **Chromosomal Abnormality Studies**

While GWAS employ genetic markers involving only variation in a single DNA base, chromosomal studies focus on much larger genetic variants. Chromosomal abnormalities which may be associated with schizophrenia have been identified in the hope that they may help in the localisation of causative genes and in understanding the complexity of the genetics of schizophrenia [44]. Chromosome 22q11 microdeletions provide the most comprehensive evidence of an association between a chromosomal abnormality and schizophrenia [44]. Chromosome 22q11 deletion syndrome (22qDS) causes Velocardiofacial, or DiGeorge, syndrome. 22qDS leads to a variable clinical picture which may include learning difficulties, mental retardation and later psychiatric illnesses such as schizophrenia. One study [45] found that 13 out of 50 adults with 22qDS had schizophrenia or schizoaffective disorder. Research has also been conducted into a chromosomal abnormality in the disrupted in schizophrenia (DISC) gene locus. It was found that a balanced translocation between chromosomes 1 and 11 (Disrupting the *DISC1* and *DISC2* genes) led to cosegregation with schizophrenia, bipolar disorder, and recurrent major depression [46, 47]. If an individual inherits the translocation, their risk of developing one of these disorders is up to 50 times that of the general population [48], but to date it has only been found in this one family. Sex chromosome aneuploidies have also been associated with higher rates of

schizophrenia. Rates of 47 XXY and 47 XXX in schizophrenia are about 4-6 times the general population rates [49].

### Copy Number Variants (CNVs)

In recent years, it has been demonstrated that many chromosomal segments vary in copy number among individuals. These variations, known as Copy Number Variants (CNVs), which may be duplications or deletions, may range from about one kilobase to several megabases in size [50]. The 22q11 microdeletion is long-known example of a CNV, but the completion of the human genome project and associated studies demonstrated that CNVs are a widespread and common occurrence in humans [51].

Two main types of study have investigated the role of CNVs in schizophrenia. The first of these look at the total genomic load of CNVs, and whether CNVs are more common across the genome in cases than in controls. Recent papers have shown that large rare deletions and duplications are significantly more common in schizophrenia cases than controls [52, 53].

Secondly, studies have looked for an excess of CNVs at specific chromosomal locations. In large samples of patients with schizophrenia, some genomic hotspots have been found that hold structural variants associated with the disorder. CNVs at a number of loci, including 1q21 [54], 3q29 [55], 15q11 [54], 15q13 [54], 16q11 [56] and 22q11 [54, 57], have been found to be over-represented in schizophrenia patients compared with controls.

Compared with the common DNA variants of small effect that are the focus of GWAS, the specific CNVs associated with schizophrenia are usually rarer and of larger effect. However, the CNVs identified to date are not generally thought to be sufficient to cause schizophrenia on their own, as they are occasionally found in unaffected individuals. For example, two studies identified the 1q21 deletion. They found that it was a rare variant, with an occurrence of 0.2% in control subjects, and had an odds ratio of 9.1 [54]. A deletion at 15q13 [54] was present in 0.2% of individuals with schizophrenia, but

more than 10 times rarer in control subjects, and had an odds ratio of 11.4. Recently, evidence for a duplication at 16p11.2 was reported in a meta-analysis to have an OR of 8.4 [56].

An important issue in the analysis of the findings of CNV studies is that, due to their size, they can include chromosomal areas that include multiple genes. This is not always the case however, as several studies have identified CNVs which disrupt the neurexin1 (NRXN1) gene and are associated with schizophrenia [58, 59]. In these studies the probability of individuals with schizophrenia having exonic CNVs in NRXN1 was much higher than in controls, with an odds ratio of 9.97 [60].

There is evidence that the associated CNVs at specific chromosomal locations are likely to be relatively recent de novo mutations, which are selected out of the population in just a few generations. They continue to be found because of relatively high mutation rates at these loci [61].

Studies of CNVs have also discovered evidence of partial genetic overlap between schizophrenia, autism, mental retardation and ADHD because these disorders are also associated with CNVs in similar chromosomal regions [62, 63]. The current situation regarding CNVs in bipolar disorder is unclear. Some studies have suggest that, in contrast to reports of an increased burden of rare CNVs in schizophrenia cases compared with controls, there is no such increase in bipolar disorder cases [64]. However, there is some evidence of an excess of CNVs in bipolar disorder [65, 66].

### **Further Clinical Phenotypes and Endophenotypes**

The phenotype of schizophrenia is heterogeneous and attempts have been made to sub-divide it in order to identify whether some aspects have a greater genetic component than others, or show differences in genetic influences. A popular approach is to create quantitative symptom dimensions derived from factor analysis. Frequently, three main psychotic symptom dimensions are found (positive, negative and disorganized) and two affective dimensions (manic and depressive) [67-72]. Among the psychotic symptom dimensions, the evidence is currently strongest for the disorganized dimension as having a substantial genetic contribution. It consistently shows significant familial aggregation in pairs of affected siblings or other relatives [72] and has an estimated heritability of 84% (95% CI 18-93%) [73].

It has been noted that the genetic influences appear to be partly due to modifying effects independent of **liability to psychosis**. Studies of familial or genetic influences on other symptom dimensions have been less consistent in their results, but there has been evidence of familiarity in some studies [74-86].

Illness history variables can also be analysed as phenotypes. In this context, age at onset of schizophrenia currently has most evidence for substantial genetic influences. There is consistent evidence for familial aggregation in pairs of affected relatives [87] and heritability estimates range from 33-70% [88, 89]. A caveat to the age at onset investigations is that it is not known to what extent the onset of illness in one relative acts as a precipitant to onset in another, thus increasing familial correlations for age at onset. This issue could be further clarified by studying relatives brought up apart. On the basis of these quantitative genetic investigations, a number of linkage and association studies of clinical variables within schizophrenia have been undertaken [90-94], and more definitive results are likely to be seen as investigation of these phenotypes makes use of techniques such as large-scale GWAS.

#### Endophenotypes

Endophenotypes are traditionally regarded as lying on the causal pathway between genotype and clinical phenotype. Their position closer to genetic effects, along with a possible reduction in phenotypic heterogeneity, potentially allows new insights to be gained into the processes underlying schizophrenia susceptibility. It was initially hoped that endophenotypes might be relatively simple from a genetic perspective, but they are now generally regarded as genetically complex phenotypes in their own right. A further development has been to look for evidence that endophenotypes are genetically correlated with schizophrenia, rather than simply on the causal pathway between genotype and clinical symptoms [95]. Gottesman and Gould [96] identified five criteria for an endophenotype. These are that an endophenotype is associated with illness in the population, that it is heritable, that it manifests in an individual whether or not illness is active, that endophenotype and illness cosegregate within families and that the endophenotype is frequently also present in unaffected relatives. The goal of studying endophenotypes is to allow researchers to define the **effects of associated** genetic variation on the brain and to eventually understand how that variation contributes to the development of schizophrenia. Some

of the main endophenotypes which have been studied in relation to schizophrenia are structural and functional brain imaging, event related potential measures, and neuropsychological or cognitive abnormalities.

Structural brain imaging has often been investigated as an endophenotype for schizophrenia. One early study [97] compared monozygotic and dizygotic twins for ventricular size and found high heritability. This was followed up by a family study which showed heritability of ventricular size that cosegregated with illness within families [98]. Although the relationship with brain structural abnormalities has been investigated in relation to many different polymorphisms, only two have been replicated relatively consistently. A number of studies have investigated the association between a functional polymorphism at codon 108/158 of the COMT gene and structural brain characteristics. The polymorphism results in a change from a valine (Val) to a methionine (Met) amino acid. The most consistent finding is a reduced volume of the anterior cingulate gyrus in those individuals with the COMT Val allele [99]. A number of studies have also focused on the association between a polymorphism in the Brain Derived Neurotrophic Factor (BDNF) gene and brain morphology in schizophrenia [100-102]. A polymorphism at codon 66 of the BDNF gene results in a Val to Met substitution. The studies found larger volumes in those with the Val allele in the hippocampus [101], temporal and occipital grey matter [100] and the cerebellar vermis [102].

Recently, a number of studies have investigated associations between ZNF804A risk genotypes and a range of endophenotypic measures, including structural and functional brain imaging and cognitive variables. In patients with schizophrenia, ZNF804A SNP rs1344706 has been associated with relatively intact brain volume [103] and memory function [104] in homozygous carriers of the risk associated-allele, while patients, their unaffected siblings and healthy controls homozygous for this allele have shown evidence of reduced functional connectivity within the prefrontal cortex and between the prefrontal cortex and other brain regions [105-107]. It should be noted that the rs1344706 SNP is in an intron, and the exact nature of the functional associations requires further clarification.

Another area in which research is being carried out into endophenotypes is that of Event Related Potentials (ERPs). An event-related potential (ERP) is any measured brain response that is directly the



result of a thought or perception. In a review of studies using ERPs as endophenotypes for schizophrenia heritability was found to be between 60% and 68% [108]. A study undertaken on a well-known family with a 1;11 chromosomal translocation, found that unaffected carriers of the translocation showed a significant reduction in the amplitude of the P300 ERP, which was similar to those with schizophrenia [109].

Cognitive impairment is also used as an endophenotype for schizophrenia. An example is a recent twin study which showed the heritability of measures such as verbal and visual memory and that they shared a genetic variance with schizophrenia [110]. Family studies have also shown that as well as probands with schizophrenia having evidence of cognitive impairment, their unaffected relatives also showed impairment compared with healthy comparison subjects without a family history [111]. Further research into this area will be aided by the development of standardized batteries of neuropsychological tests such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) or the University of Pennsylvania Computerized Neurocognitive Battery, which was used in a recent study which showed association between cognitive endophenotypes and a number of schizophrenia candidate genes including NRG1 and ERBB4 [112].

### **Next Generation Sequencing**

Genome-wide association studies have demonstrated that common variants account for a proportion of the genetic component of schizophrenia. If small rarer DNA variants also play a role then the next stage in discovering this is likely to be through the use of next generation sequencing approaches, including whole exome and whole genome sequencing studies. These have become possible through improvements in technology which have greatly increased the speed with which sequencing can be accurately performed.

In the long term the aim will be to undertake studies similar to GWAS with very large sample sizes [113]. Until sequencing technology is inexpensive enough to perform these large sample studies various approaches have been suggested to further our understanding. These include selecting families that have multiple affected individuals (family-based sequencing), and selecting individuals that are at

the extreme ends of a trait distribution (extreme-trait designs) [114]. Results of initial sequencing studies have been reported, for example, employing exome sequencing [115, 116], with many more studies in the pipeline.

### **Functional Studies**

Having identified a range of candidate genetic variants for schizophrenia and related disorders, a major task in substantiating these candidates as true susceptibility variants, and in developing their potential for improving treatments, is to determine their functional effects at a physiological level. Studies include investigations of allelic expression via mRNA levels [39] and investigations of animal models. Although there are limitations, for example, in identifying valid equivalent phenotypes in animals, these approaches allow experimental designs which are important for demonstrating causality, and which are not feasible in studies of humans.

In an effort to discover more in this area, researchers have been able to construct mutant mice. These mice are constructed with disruption of a gene, which can be achieved either by deletion or insertion/over-expression. Researchers can then learn about the functional effects of disrupting particular genes and the proteins they encode for. In schizophrenia research these mouse model studies look at how a mutation in a schizophrenia-related gene is related to either aspects of the schizophrenia phenotype or to schizophrenia-related endophenotypes. These can include negative symptoms of schizophrenia, cognitive impairment or structural abnormalities.

One of the mouse models used in investigating schizophrenia uses mice with a DISC1 mutation resulting in loss of DISC1 function. Studies of these mutant mice have found a number of alterations which resemble aspects of schizophrenia [117, 118]. These include structural alterations such as enlarged lateral ventricles and reduced brain volume, negative symptoms such as reduced sociability, cognitive deficits such as impaired working memory, and deficits in prepulse inhibition that are reversed by antipsychotic treatment [117, 118]. Further mutant mouse models which have shown evidence of negative symptoms of schizophrenia and cognitive impairments include mice with deletions in the Neuregulin1 [119, 120] and Dysbindin [121] genes.

## Genetics of Other Psychotic Disorders

### Schizoaffective Disorder

Schizoaffective disorder is a controversial category. It is criticized for poor inter-rater reliability [122] and diagnostic instability [123], and debate continues over whether it is best regarded as a subtype of schizophrenia or affective psychosis, a mixture of these other disorders, due to the co-occurrence of these disorders, or a partly independent disorder on a spectrum between these other disorders [124-126].

Family studies of schizoaffective disorder have been reviewed by Bertelsen and Gottesman [125]. They found that the morbid risk to first-degree relatives ranged from 1.8% to 6.1%. Three blind controlled studies found morbid risks for relatives as opposed to controls of 2.7%/0.1% [127] and 1.8%/0.7% [128] and 6.1%/0.5% [129]. There is twin study evidence that schizoaffective disorder, and its manic and depressive subtypes, have substantial heritability of around 80% [130].

Family studies show a familial overlap with both schizophrenia and affective disorders [19-20, 127-129], and a twin analysis was consistent with the genetic contribution to schizoaffective disorder being entirely shared with genetic influences on schizophrenia and mania, while environmental influences were not shared [21].

A linkage study has been conducted which aimed at localizing genes that influence susceptibility to schizoaffective disorder [131]. The study identified regions of interest on chromosomes 1q42 (LOD = 3.54; significant genomewide), 22q11 (LOD = 1.96; suggestive genomewide), and 19p13 (LOD = 1.85; suggestive genomewide). The findings on chromosome 1q42 were of particular interest due to the existence, within this region, of the DISC1 gene.

Association studies into schizoaffective disorder have also shown association with DISC1 [132].

Further recent association studies provide evidence for relatively specific associations between GABA<sub>A</sub>

receptor gene variants and schizoaffective disorder, bipolar type [133, 134], as well as for the general utility of this schizoaffective subtype for picking up GWAS association signals [135]. Thus, while the twin study evidence points to schizoaffective disorder as being due to the co-occurrence of elevated genetic liability to schizophrenia and mania, if the results for GABA<sub>A</sub> are further substantiated, it would bolster the case for regarding schizoaffective disorder, bipolar subtype, as a partly independent disorder.

### Other Psychotic Disorders

There is much less information about genetic influences on other psychotic disorders. Reviews of genetic studies into delusional disorder [136, 137] have found that due to a lack of studies and various methodological difficulties, there has been no clear evidence for or against a genetic contribution to the aetiology of delusional disorder. They found no linkage studies of delusional disorder that had been carried out. A small number of association studies have been performed, based on a functional rather than a positional approach. A polymorphism in the dopamine D3 receptor gene (DRD3) has shown association with delusional disorder in one study [138], but not in another [139]. A polymorphism in the dopamine D4 receptor gene (DRD4) has also been associated with delusional disorder in one study [140].

In a twin study of depressive psychosis, MZ concordance was 10% and DZ concordance 5%. Genetic model-fitting established that there were familial effects, but it was not clear to what extent these were due to genetic or common environmental influences [130].

There is a substantial body of research into genetic influences on bipolar disorder, including bipolar disorder with psychotic symptoms, which is reviewed in another article in this series.

### Concluding Remarks

This review has highlighted some of the major themes in the rapidly progressing field of research into genetic influences on schizophrenia and related disorders. In the near future there are likely to be many

more significant association findings, as GWAS increase further in sample size [141]. There are also likely to be further CNV discoveries and efforts to specify whether key regions within those currently identified are particularly important for increasing risk. Once next generation sequencing studies are fully established, it is likely that associations with rarer small DNA variants will also be found. In all cases, there will be major efforts to connect genotype, relevant endophenotypes and clinical symptoms.

It is hoped that, in due course, these endeavours will lead to better targeting of existing drug treatments, although at present the extent this will be the case remains somewhat controversial, and pharmacogenomic studies are ongoing [142, 143]. It is also likely that the ongoing genetic discoveries will point to new pathophysiological pathways, with the potential to develop novel treatments targeting these. There is also the potential to better understand the interplay between genetic and environmental risk factors, including via epigenetic changes [144], again with the hope of developing better interventions in the future. A further issue is how the ongoing discoveries will influence our conceptualisation and classification of schizophrenia and related disorders. Although it is not inevitable that such discoveries will radically change our classification systems, it is likely that in due course they will have an impact, especially if the definitions of these disorders come to include biological variables in addition to clinical symptoms.

Finally, there is the issue of risk prediction in those who are currently unaffected. For monogenic disorders, such as Huntington's disease, predictive genetic testing can be conducted with great accuracy, but this is generally not the case for multifactorial disorders such as schizophrenia. If any single gene subforms of schizophrenia are discovered in due course, this could lead to the development of genetic testing and improved genetic counselling for the particular families where the, probably rare, genetic variant occurs. In the general population, there is interest in the extent to which using a range of genetic information, for example, in the form of polygenic scores based on GWAS data [43], perhaps combined with information on environmental risk factors, could be used to inform early detection and intervention strategies. However, much work remains to be done to clarify whether, or in which circumstances, such approaches could be clinically useful.

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