

REVIEW

Schizophrenia genetics: uncovering positional candidate genes

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The efforts to decipher the genetic causes of schizophrenia, one of the most devastating mental illnesses, have reached a turning point. Several linkage findings in schizophrenia have been replicated and, in the last few years, have been followed by systematic fine-mapping efforts to identify positional susceptibility genes. Here, we outline the evidence supporting each of the proposed positional candidate genes and identify some general areas of caution in their interpretation. Several of these findings hold considerable promise both for understanding the neuropathology of this brain disorder, the causes of which remain a mystery, but also for development of novel, mechanism-based treatments for the patients.

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Introduction

Schizophrenia is a devastating psychiatric disorder characterized mainly by 'positive symptoms' that include delusions and hallucinations, 'negative symptoms' that include blunted emotions and social isolation, and cognitive deficits that include impairments in executive function, attention and working memory.¹ The disease onsets usually in late adolescence or early adulthood and follows an episodic and deteriorative course where the prognosis becomes worse with each episode.^{2,3} It is estimated that 1% of the population may suffer from schizophrenia worldwide, but the disorder is more prevalent in families where schizophrenia has previously been diagnosed.⁴ Similar to many common, complex disorders, schizophrenia is a multifactorial disorder characterized, to a large extent, by the contribution of multiple susceptibility genes, which may interact, in a stochastic manner, with epigenetic processes and environmental

factors.⁵ Furthermore, it is likely that the disease presents etiologic heterogeneity, in the sense that different combinations of these factors could lead to very similar phenotypic outcomes.

Gene identification is an important milestone for understanding the disease pathophysiology. However, it has proven to be an extraordinarily difficult task because no single gene is necessary or sufficient to cause the disease but instead, many susceptibility genes with small effects act in combinations to increase the risk of illness. In the past 3 years, significant advances in gene discovery have taken place fueled by the completion of the sequencing of the human genome, the readily available technology for high-throughput genomic analysis, and the generation of new analytical and bioinformatics tools. Several susceptibility genes have been proposed, each supported by varying degrees of evidence. Gene discovery ensued after approximately 20 genomewide scans took place. In this recently emerged context, a critical reviewer of the literature should be concerned with issues regarding the extent of coverage of the implicated loci, consistency of the risk allele or risk haplotype across studies, the structure of the samples used in the original and replication studies, publication bias against negative reports, phenotypic heterogeneity and supporting biological data. As it is

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becoming increasingly clear that unreliable results may be obtained when allele frequencies differ notably among subpopulations not represented equally between cases and controls,⁶ the possibility that original or replication studies using case-control samples are false positives (or negatives) is a major source of concern. This issue is relevant to all common, complex disorders, but it is likely to be more pronounced in genetic studies of psychiatric disorders, which are confounded by a larger degree of phenotypic heterogeneity. In addition, several of the original or 'replication' samples have been used repeatedly in genetic association studies making the issue of multiple testing corrections highly relevant. These are not merely theoretical considerations as they can lead to striking inconsistencies among variant alleles and haplotypes implicated in various replication studies. Publication bias almost certainly affects the level of confidence ascribed to any given susceptibility gene. For example, negative studies are less likely to be submitted for publication and when they are submitted they are less likely to be published in the same journals where the original discovery was reported. As an end result, negative studies are more likely to accumulate with considerable delay or not at all. As alluded to above, phenotypic heterogeneity can also contribute to the uncertainties and inconsistencies associated with genetic research in schizophrenia. Phenotypic heterogeneity is to be expected due to the complexity of the affected organ (the brain), but the majority of genetic studies by relying on a categorical binary diagnosis ('affected' vs 'unaffected') do not take into account the possible differences in representation among different samples of the various components of the illness. Therefore, claims that 'gene X has been replicated in eight out of 10 studies' should be taken with a grain of salt and a more careful analysis of the properties of the employed samples and the methods used is necessary to determine the validity of such claims.

The recent gene discovery studies promise to provide researchers with important clues regarding the genetic causes of schizophrenia. In the absence of a 'smoking gun' for most candidate genes, that is a well-defined and fully penetrant mutation of the kind found in Mendelian disorders, it is important to balance human genetic and hard biological evidence against the need for timely identification of targets and improvements in therapy. Biological data can be obtained by genetic studies of endophenotypes, provided they are designed to avoid all the pitfalls described above (such as population stratification), which are associated with genetic studies of the clinical syndrome. Most importantly, in our opinion, biological insights can be provided by generation of reliable animal models. Identification of susceptibility genes will permit the design of much more incisive studies to illuminate the physiological and biochemical etiology of the disease by examining the gene products in the context

of a model organism and their impact on the development of the disorder.

Candidate genes through positional cloning

In this review, we discuss the genetic data for recently emerged strong positional candidate genes that were identified through systematic follow-up of linkage signals (in chronological order of appearance of the reports), their possible function(s), as well as biological data accumulating from relevant animal models, when applicable. With one exception for the gene for catechol-O-methyltransferase (COMT), space constraints do not allow us to discuss available genetic data for a set of candidate genes (such as *PPP3CC* or *RGS4*), located in the general vicinity of linkage signals and identified through convergent genetic and biological evidence, rather than systematic positional cloning approaches. Indeed, the location of these genes begs the question whether the recurrent observation of clustering of candidate susceptibility genes may indicate that more than one gene may contribute to at least some of the linkage signals observed in psychiatric disorders. Finally, due to space limitations, other genes that could be good candidates (such as *DRD3*, *CHRNA2*, *BDNF*, *GAD2*, *AKT1*), but do not strictly conform to the criteria outlined above, are also not discussed here.

In 2002, four strong candidate schizophrenia susceptibility genes were identified through systematic positional cloning efforts⁷ in regions of linkage. The genes were: *PRODH* (proline dehydrogenase, chromosome 22q11), *DTNBP1* (dystrobrevin-binding protein 1, or dysbindin, chromosome 6p), *NRG1* (neuregulin 1, chromosome 8p) and *G72* (chromosome 13q).⁸⁻¹¹ More recently, additional candidate genes have been identified by linkage disequilibrium (LD) mapping methods using single nucleotide polymorphisms (SNPs) in previously identified linkage peaks.

Proline dehydrogenase

PRODH encodes an enzyme that metabolizes L-proline, a putative neuromodulatory amino acid that may directly influence glutamatergic transmission,¹² which is believed to play a central role in the pathophysiology of schizophrenia. The gene maps to chromosome 22q11. An unequivocal association between hemizygous deletions of the 22q11 locus and schizophrenia has been established. In light of positive linkage findings at the same locus, individual genes from this locus have been examined in systematic fine-mapping efforts.¹³ LD analysis using 72 SNPs in family samples identified an overtransmission of a haplotypic variant located at the 3' end of the *PRODH* gene.^{8,14} This finding was recently replicated in two independent family samples, including a very large collection of 528 families from China¹⁵ and 274 families of Ashkenazi Jewish origin,¹⁶ although one negative family

study has also been reported.¹⁷ Moreover, 3' end variants of the gene were also identified as a risk factor for development of psychotic symptoms during adolescence in children with 22q11 microdeletions.¹⁸ The functional consequences of the implicated haplotypic variants, which are consistently located at the 3' end of the gene, are still unknown. However, the Liu *et al*⁸ study identified additional rare variants of the *PRODH* gene, which affect highly conserved amino acids. These variants are present either exclusively or in higher frequencies in schizophrenic patients and are generated through gene conversion from a nearby pseudogene.⁸ Several of these variants lead to drastic reductions in enzymatic activity.¹⁹ The same variants were described in schizophrenic patients in an independent study, which also identified a small deletion encompassing the *PRODH* gene in a schizophrenic patient.²⁰ In addition to being one of the most variable genes in the human genome, the *PRODH* gene is haploinsufficient: heterozygous deletions of *PRODH* and the presence of heterozygous mutations of the *PRODH* gene are associated with moderate hyperprolinemia (300–600 mmol/l).^{20,21} As a result of the hemizygous nature of the 22q11 microdeletions, haploinsufficiency (gene dosage-dependence) is likely to be an important property of any gene that modulates the emergence of the 22q11 psychiatric phenotypes, as it was the case for *Tbx1*, a gene that modulates in a dosage-dependent manner the cardiac features associated with these microdeletions.²² A mutation in the mouse ortholog of the human *PRODH* gene in the Pro/Re hyperprolinemic mouse strain has been described.²³ These mice demonstrate an increased neurotransmitter release and abnormal plasticity at glutamatergic synapses, as well as distinct abnormalities in dopamine turnover and signaling in the frontal cortex.²⁴ Cortical dopaminergic dysregulation is accompanied by local increase in transcript and protein levels of the *Comt* gene (also located within the 22q11 microdeletion locus, see below) that is likely to represent a homeostatic response. Thus, these animal model studies strongly suggest that, within the context of the 22q11-associated schizophrenia, *PRODH* deficiency likely acts as a primary deficit whose effects are buffered by COMT activity and provide a framework for understanding the genetic architecture of the schizophrenia risk.

Dystrobrevin-binding protein 1, or dysbindin

Fine-mapping efforts undertaken as a follow-up to evidence for linkage on chromosome 6p24–22 in a sample of Irish families, led to identification of an association with schizophrenia of genetic variants in the *DTNBP1* gene (dysbindin).⁹ Most replication samples used ($N=9$) were case–control samples.^{25–29} Replication of this association has also been attempted in seven family samples, with replications observed in five of them.^{16,30–33} In the positive studies there are inconsistencies among the

implicated alleles or haplotypes. If these inconsistencies are not a product of population stratification or multiple testing, they could be explained by the presence of distinct variations affecting different functional elements within the gene that have emerged independently on a more recent ancestral background. Alternatively, the signal may be due to variants in a neighboring gene or genes in LD with *DTNBP1* variants. Recently, functional significance has been ascribed to some of the implicated alleles or haplotypes.³⁴ *DTNBP1* is a member of the biogenesis of lysosome-related organelles complex (BLOC), as well as the dystrophin protein complex (DPC).^{35,36} The protein is ubiquitously expressed in the brain. Two recent studies showed a decrease of *DTNBP1* mRNA in dorsolateral prefrontal cortex (DLPFC) and hippocampus of schizophrenic patients when compared to controls.^{37,38} Preliminary *in vitro* evidence suggests that knockdown of endogenous dysbindin protein results in the reduction of presynaptic protein expression and glutamate release, suggesting that dysbindin might influence exocytotic glutamate release.²⁷

Neuregulin 1

A broad region on chromosome 8p12–21 has been consistently implicated in schizophrenia by multiple linkage studies, including a study of 33 extended Icelandic families. Fine-mapping across the genomic region of maximal linkage in this set of families detected an association between schizophrenia and several haplotypes at the *NRG1* locus. A core haplotype at the 5' end of the gene comprising several markers within a 290-kb block of LD showed highly significant association with schizophrenia.¹⁰ While several replication studies have taken place it is still unclear which variants or haplotypes are involved. Eight of the replication samples used were case–control samples.^{39–46} In addition, 8 family samples were also used for replication. In these, less than half show some evidence for association, but with haplotypes other than the one originally described.^{16,33,44–49} Of concern are some dramatic differences in the frequency of haplotypes reported between different samples,^{45,46} where the frequencies range from 1 to 10%. This could indicate either substantial heterogeneity in the LD structure across the *NRG1* locus or the presence of multiple risk alleles. In the absence of any functional significance for any of the implicated haplotypes it is difficult to interpret further the genetic data that is published at the time of this writing. The *NRG1* gene is an attractive candidate as it encodes a well-characterized protein involved in a wide variety of neuronal, complex functions, ranging from neuronal survival to myelination and synaptic plasticity.⁵⁰ Several general and conditional *Nrg1* knockout mice have been described,^{51,52} but it is not clear if they can be used reliably to model the gene's contribution to schizophrenia since the nature of the

pathogenic contribution of this gene to schizophrenia is currently unknown.

G72

Another strong linkage signal for both schizophrenia and bipolar disorder has been identified on chromosome 13q32–34. This linkage signal is one of the most consistent ones in the literature^{53,54} and has prompted fine-mapping efforts. Significant association with schizophrenia was described for several SNPs and haplotypes at the *G72* locus in a French-Canadian case–control sample, with the association for two SNPs being replicated in a Russian case–control cohort.¹¹ Interestingly, an association between variants at the *G72* locus and bipolar disorder has also been described.⁵⁵ *G72* association with schizophrenia has been observed in several additional samples (some case–control^{56–58} and some family-based samples^{59,60}) with evidence for allelic heterogeneity. Negative studies have also been reported.⁶¹ Enzymatic studies suggested a potential interaction with D-amino-acid oxidase (DAAO) that modulates its enzymatic activity and thus could indirectly affect glutamatergic signaling.^{11,62} The notion that *G72* acts via modulation of DAAO activity has acquired momentum in the field, but there is no direct *in vivo* demonstration of such effect.

Disrupted in schizophrenia 1

Disrupted in schizophrenia 1 (*DISC1*) is one of two genes isolated from a chromosome 1q42 translocation breakpoint previously described to segregate with psychopathology in a large Scottish family. The other gene is *DISC2* and is a noncoding, presumably regulatory RNA.⁶³ Alternative hypotheses about involvement of the reciprocal translocation breakpoint on chromosome 11 have been proposed.⁶⁴ Although *DISC1* was originally described 5 years ago, interest in it was renewed only recently when large-scale linkage^{65,66} and follow-up systematic association studies in families from Finland identified *DISC1* as a positional candidate from the 1q42 locus.⁶⁷ *DISC1* association with schizophrenia has been observed in some additional samples with evidence for allelic heterogeneity, although negative studies have also been reported.^{16,67,68} Interestingly, a family afflicted with schizophrenia and schizoaffective disorder was recently shown to segregate a rare frameshift variant of the gene.⁶⁹ In one recent preliminary imaging study variation in the *DISC1* gene was associated with altered hippocampal structure and function in healthy subjects,⁷⁰ whereas an independent study implicated *DISC1* variation in visual working memory performance.⁷¹ *DISC1* is a complex gene with poorly understood involvement in development and plasticity. It is associated with numerous cytoskeletal proteins, and it may be involved in a variety of cellular functions, including centrosomal and microtubule function, cell migration, neurite outgrowth, membrane

trafficking of receptors, mitochondrial function and phosphodiesterase signaling.⁷²

Carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase

Brzustowicz *et al*⁷³ have previously reported evidence for linkage at 1q22. Using 14 microsatellite markers and 15 SNPs from a subregion of the linkage locus⁷⁴ produced nominally significant evidence of LD between schizophrenia and a subset of markers located within the genomic region of carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase (*CAPON*), making it a prime positional candidate from the schizophrenia susceptibility locus on 1q22. An abnormal expression pattern of this gene was observed in brains from individuals with schizophrenia or bipolar disorder.⁷⁵ Two case–control replication studies (one positive and one negative) have been reported.^{76,77} *CAPON* is involved in NMDA receptor-coupled nitric oxide signaling.⁷⁸

ZDHHC8

This gene was identified in the same LD screen of the 22q11 locus that identified the association between the *PRODH* gene and schizophrenia.^{8,14} Five SNPs from an 80-kb LD block were significantly associated with schizophrenia. The most significantly associated SNP, rs175174, maps in intron 4 of the *ZDHHC8* gene and was shown to affect the ratio of an intron 4-containing unspliced form (that encodes a putative truncated form of the protein) over the fully spliced form by ~25–30%.⁷⁹ This small change in the levels of the active protein was associated with ~1.5-fold increase in the disease risk in two tested family samples of patients not carrying the 22q11 deletion.^{14,79} It is, of course, possible that other variants of the gene (affecting distinct aspects of its complex splicing or its expression level) might modulate the disease risk in other patient samples. One positive and one negative family-based study have been reported so far.^{80,81} Although the general involvement of this gene in schizophrenia awaits analysis of additional family samples, the effect of the gene is predicted to be much stronger in individuals with 22q11 deletions and schizophrenia, where a 50% (or ~65% when the nondeleted allele carries the risk SNP rs175174 variant) decrease in *ZDHHC8* activity levels is predicted. *ZDHHC8* is predicted to encode a transmembrane palmitoyltransferase that modifies PSD-95 among other targets (Mukai J, Dhillia A, MK, and JAG, unpublished) and could play an important role in excitatory synaptic transmission.⁸²

Trace amine receptor 4

A broad area on chromosome 6q (6q13–q26) has also been implicated in schizophrenia in linkage studies using European-ancestry and African American schizophrenia pedigrees.⁸³ Fine-mapping efforts focusing on band q23.2 using 31 SNPs and a follow-up higher density screen using

23 SNPs over a 21.6-kb region identified trace amine receptor 4 (*TAAR6*) as a prime positional candidate⁸⁴ for the schizophrenia susceptibility locus on 6q23.2. Two negative replication studies have been reported.^{85,86} However, an independent study implicated the trace amine receptor genes at 6q23.2 in susceptibility to bipolar disorder.⁸⁷ *TAAR6* is a GPCR widely expressed in the brain.⁸⁸

Epsin 4

Chromosome 5q33 is a region that has previously shown strong evidence of linkage to schizophrenia, with four LOD scores >3.0 in independent linkage studies. Four adjacent markers (and associated haplotypes) at the 5' end of the *Epsin 4* gene, which is located in this region, showed significant evidence of LD with schizophrenia in a fine-mapping study that employed 450 unrelated English, Irish, Welsh, and Scottish research subjects with schizophrenia and 450 ancestrally matched supernormal controls.⁸⁹ The *Epsin 4* gene encodes the clathrin-associated protein entropin, which has a role in transport and stability of neurotransmitter vesicles at the synapses and within neurons. No replication studies have been reported yet.

Gamma-aminobutyric acid receptor subunit gene cluster

Chromosome 5q31–q35 was implicated in Portuguese schizophrenia families⁹⁰ and was supported by subsequent meta-analysis. A group of gamma-aminobutyric acid (*GABA*)A receptor subunit genes (*GABRA1*, *GABRA6*, *GABRB2*, *GABRG2* and *GABRP*) that map within this linkage peak were investigated in Portuguese patients and associations with SNPs and haplotypes in *GABRA1*, *GABRP* and *GABRA6* were detected.⁹¹ The *GABRA1* and *GABRP* findings were replicated in an independent German family-based sample.⁹¹ These genes are plausible candidates based on prior evidence for GABA system involvement in schizophrenia.⁹²

Catechol-O-methyltransferase

The gene is located in the 22q11 region between the *PRODH* and *ZDHC8* genes (see previous section on positional candidate genes). *COMT* is also an attractive functional candidate gene since it is involved in the breakdown of dopamine. Several studies testing directly for association between variants from this gene and schizophrenia have taken place. One variant in particular, in codon 158 that affects enzymatic activity depending on the presence of Val (high activity) or Met (low activity), has been studied extensively. It has been proposed that the high activity Val allele increases the risk for schizophrenia, but the genetic association results are equivocal.^{93–99} The same allele was shown in some studies to impair executive function, which is affected in schizophrenic patients.^{100,101} More recent studies in animal models, however, suggested

that low activity of this enzyme could be a risk factor for schizophrenia by failing to buffer the effect of other primary mutations that affect dopamine turnover and signaling in the cortex.²⁴ This prediction was supported by the results of a longitudinal follow-up study of children with 22q11 microdeletions, which revealed that the low-activity form of the enzyme (Met158) is a risk factor for decline in prefrontal cortical volume and cognition, as well as for the consequent development of psychotic symptoms during adolescence, in these children.¹⁸ Overall, a potential contribution of *COMT* to schizophrenia in general, is likely to be complex.

Future directions

Two recent meta-analyses^{102,103} implicated (under moderate stringency) approximately 12 regions of the genome as likely to contain schizophrenia susceptibility genes (2p, 5q, 3p, 11q, 2q, 1q, 22q, 8p, 6p, 20p, 13q and 14q). This is most likely to be an underestimate. Nevertheless, even if we take the meta-analytic studies at face value, and assume that the already isolated positional candidates can solely account for the local linkage signals (a property that has not been demonstrated for any of them) there are still several 'orphan' linkage loci that await the identification of positional candidate genes. This task will be facilitated by the sequencing of the human genome and the identification of SNPs and their LD patterns over virtually all segments of the human genome.¹⁰⁴ It is the ultimate hope that the identification and *in vivo* characterization of schizophrenia susceptibility genes will lead to the discovery of novel, improved mechanism-based therapies that target susceptibility genes or affected molecular pathways.

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