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Searching for schizophrenia genes

Nicholas J. Bray and Michael J. Owen

Schizophrenia is characterized by profound disturbances of cognition, emotion and social functioning. It carries a lifetime risk within the general population of approximately 1%. Genetic epidemiological studies have shown that the syndrome has a high heritability, indicating a significant genetic component to its aetiology. However, the undoubted complexity and probable heterogeneity of the disorder continue to confound research, and the precise underlying neurobiological mechanisms remain largely unknown. Although molecular-genetic approaches face formidable difficulties, the identification of susceptibility genes is likely to provide valuable insights into the aetiology and pathogenesis that could lead to the development of more effective treatments.
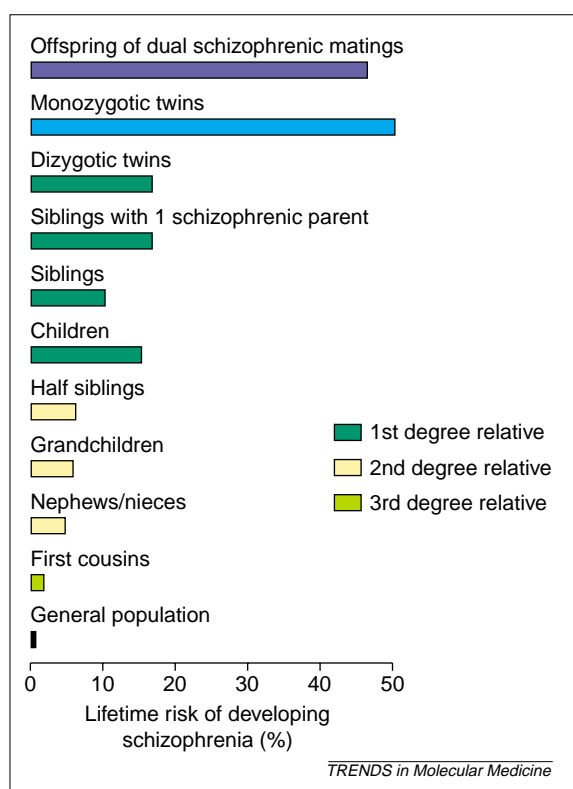
The symptoms that define schizophrenia are diverse and variably expressed, and include disorganized thought patterns, delusional beliefs, auditory hallucinations, blunted or incongruous mood, apathy and social withdrawal. In most cases, schizophrenia has an onset in early adulthood, and individuals have long periods of illness, are unable to work, and have difficulty in sustaining family relationships because of their condition. Although diagnosis is based entirely on clinical presentation, and embraces conditions with a variety of symptoms, courses and responses to various treatments, the use of structured interviews and explicit operational diagnostic criteria make it possible to achieve a high degree of diagnostic reliability. Since its original description a century ago, researchers have sought to discover the biological basis of the disorder. However, the precise pathological mechanisms remain obscure.

Neurobiological theories of schizophrenia

Attempts to elucidate the biological correlates of schizophrenia have traditionally focused on one of several levels of explanation, including the neuropsychological, the neuropathological and the neurochemical. The view that schizophrenia is caused by disturbances in particular neurotransmitter systems arose during the 1950s and 1960s, given credence by the lack of obvious structural pathology in the schizophrenic brain and the observed anti-psychotic or psychotomimetic effects of certain chemical compounds. The 'dopamine hypothesis'[1,2], which holds that schizophrenia is associated with disturbances in dopamine neurotransmission, has prevailed as the dominant neurochemical theory of the disorder. However, although the therapeutic effects of classical anti-psychotic drugs appear to be largely mediated by actions at dopamine receptors[3], firm evidence for a primary dopaminergic abnormality in schizophrenia is yet to be established. Post-mortem and *in vivo* neuroimaging studies of dopamine receptor densities in the schizophrenic brain have yielded inconsistent results, complicated by problems of ligand specificity and the influence of anti-psychotic medication[4,5]. Moreover, the clinical efficacy of newer anti-psychotic drugs appears to be partly associated with actions on other neurotransmitter systems, and there is evidence to support hypotheses of serotonin[6], glutamate[7] and GABA (Ref. 8) dysfunction in schizophrenia. As neurotransmitter systems do not function in isolation, it seems likely that more than one will be disturbed in schizophrenia, and more recent neurochemical theories have centred on the complex interactions between these various systems.

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Fig. 1. Average risk of developing schizophrenia. European studies 1920–1987. Adapted with permission from Ref. 57.

Offspring of dual schizophrenic matings
Monozygotic twins
Dizygotic twins
Siblings with 1 schizophrenic parent
Siblings
Children
Half siblings
Grandchildren
Nephews/nieces
First cousins
General population

■ 1st degree relative
☐ 2nd degree relative
■ 3rd degree relative

Lifetime risk of developing schizophrenia (%)

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However, at present, it remains unclear to what extent any neurochemical findings reflect primary rather than secondary, downstream pathology, compensatory mechanisms or environmental influences.

In recent years, schizophrenia has increasingly been regarded as a neurodevelopmental disorder[9,10]. Theorists differ in their assumptions as to the timing and nature of the supposed developmental disturbance(s), but the view that schizophrenia has its origins in early, perhaps even pre-natal, brain development is supported by epidemiological evidence of increased obstetric complications and childhood neuropsychological deficits in individuals who subsequently develop the disorder, together with a pattern of non-specific neuropathological anomalies[11]. At the anatomical level, neuroimaging studies have shown that increased lateral ventricle size – the most robust neuropathological finding in schizophrenia to date – is present at onset of symptoms[12] and in adolescents who carry a high

genetic risk of developing the disorder[13]. Volumetric studies have also shown a small but significant reduction in brain size, particularly within the temporal lobes[14], for which there may be a significant genetic component[15]. Histological studies, though prone to methodological problems, have provided evidence for subtle cytoarchitectural anomalies of putatively developmental origin within the frontal lobes and temporo-limbic structures such as the hippocampus[16]. Although frequently cited reports of neuronal displacement (e.g. Ref. 17) have proven difficult to replicate, a relatively consistent finding is that of a reduction in axonal and dendritic markers within these brain regions (e.g. Ref. 18). In the absence of classical degenerative changes, such findings could potentially reflect a defect in the development and/or maintenance of synaptic connectivity, which might provide a possible basis for currently popular disconnectivity theories of schizophrenia (e.g. Ref. 19). The development of mature synaptic networks is, however, extremely complex, involving a dynamic interplay between genetic, environmental and stochastic factors. Thus, despite some broad clues, the precise biological mechanisms underlying these putative neurodevelopmental disturbances remain largely speculative.

Genetic epidemiology of schizophrenia
Evidence for a strong genetic component to the aetiology of schizophrenia can be drawn from family, twin and adoption studies, which have shown that the risk of developing the illness increases exponentially with the level of genetic relatedness to an individual suffering from the disorder[20] (Fig. 1). Thus, in comparison with the 1% risk for schizophrenia in the general population, third-degree relatives (e.g. cousins) carry an approximate 2% chance of developing the illness, and the risk increases to 9% in first-degree relatives (e.g. siblings). Moreover, fraternal (DZ) twins of affected individuals show a similar risk to that of other siblings, whereas in identical (MZ) twins, the concordance rate is approximately 50%. Although epigenetic factors such as genomic imprinting might account for some of the observed discordance between MZ twins, that around 50% of such twins do not share a schizophrenic phenotype suggests that environmental factors play a significant role in the aetiology of the disorder. Conversely, adoption studies provide firm evidence that observed familial aggregation in schizophrenia is not the result of shared environmental factors, as individuals adopted into families containing an affected individual do not suffer an increased risk of developing schizophrenia, whereas the existence of a biological relative with schizophrenia does lead to an increased risk in adoptees. Overall, evidence from genetic epidemiological studies suggests that what is inherited is not the certainty of developing schizophrenia, but rather a predisposition to do so.

Glossary

λs: The risk to siblings of an affected individual, compared with the general population. It can be used to assess the effect size of an individual genetic variant (i.e. the risk to siblings resulting from possession of the disease allele).
Epistasis: Interactions between two or more genetic loci.
Familiality: Increased risk of illness in relatives of an affected individual.
Polymorphisms: Variation in DNA sequence that produces two or more alleles at a particular locus, existing in significant (>1%) frequencies in the population. Polymorphisms can be pathogenic, or serve as genetic markers to track disease alleles in families.
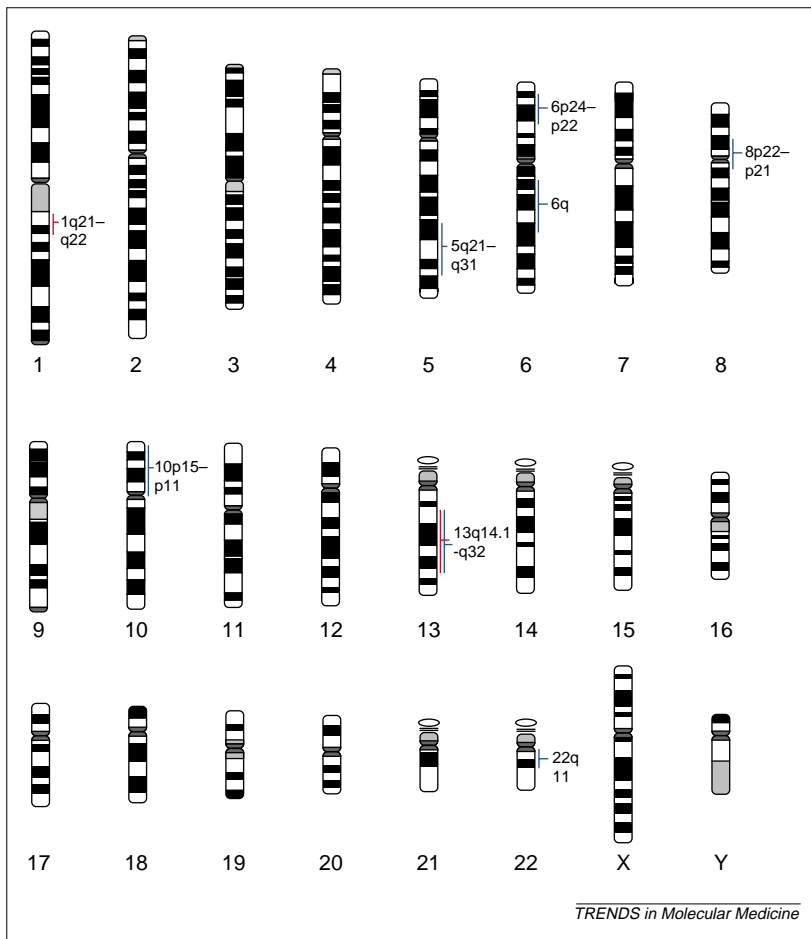
Fig. 2. Ideogram showing major chromosomal regions implicated by linkage studies of schizophrenia. Blue lines indicate areas for which evidence of linkage has been found in more than one data set. Red lines indicate regions where evidence of linkage has achieved genome-wide significance.

Using biometrical model fitting, the relative contribution of genetic versus environmental factors in the aetiology of schizophrenia has been estimated to be approximately 80% (Ref. 21). Thus, around 20% of the variance in liability to schizophrenia can be accounted for by individual-specific environmental effects, which have been postulated to include obstetric complications, maternal viral infection and social stressors[22], but which might also reflect the operation of stochastic factors. The nature of the genetic component to schizophrenia is assumed to lie in particular mutations within coding or regulatory regions of so-called susceptibility genes, which might influence the operation and/or expression of the neurobiological molecules they encode.

Molecular genetic approaches
Unlike molecules studied in the brain, the primary genetic sequences that encode them remain fixed, being generally unaffected by environmental or compensatory influences. Attempts to identify the particular genetic variants that contribute to schizophrenia susceptibility thus have enormous potential to elucidate the primary pathological mechanisms. Unfortunately, molecular genetics shares many of the problems encountered by other forms of schizophrenia research, such as the probable heterogeneity of the disorder, and the unspecified environmental influences that partly determine its

expression. Moreover, studies of recurrence risk in various classes of relative suggest that the mode of inheritance is complex and non-Mendelian, involving the combined action of several genes, each of which might account for only a small increase or decrease in susceptibility to the disorder[23,24]. At present, the number of susceptibility loci, the disease risk conferred by each locus, and the degree of interaction between loci all remain unknown. The contribution of individual genes to the FAMILIALITY (see Glossary) of a disorder can be expressed in terms of λs. Risch[25] has calculated that the data for recurrence risks in the relatives of probands with schizophrenia are incompatible with the existence of a single locus of λs >3 (i.e. promoting more than a threefold increase in risk to siblings). Unless extreme EPISTASIS exists, models with two or three loci of $\lambda s \leq 2$ are more plausible[25]. These calculations are based upon a homogeneous population, and under a model of heterogeneity, it is possible that genes of larger effect are operating in some subpopulations of patients.

Thus, finding the genes that predispose individuals to schizophrenia presents a major challenge, particularly given that neurobiological research has provided only broad clues as to the pathological mechanisms that might be involved in the disorder, and which might in turn be influenced by many known (and as yet unknown) genes. In spite of these difficulties, molecular geneticists have employed a number of strategies aimed at identifying susceptibility genes for schizophrenia. These have traditionally fallen into three main groups: (1) linkage studies, which are often not driven by specific neurobiological hypotheses but rather seek to identify chromosomal regions containing susceptibility loci; (2) cytogenetic approaches, whereby chromosomal abnormalities in affected individuals are investigated as potential clues as to the location of susceptibility genes; and (3) association studies, which can be used to assess the contribution of individual candidate genes to susceptibility.

Linkage studies
Linkage studies examine the segregation of a given disorder with alleles of polymorphic genetic markers in multiply-affected families. Markers that are close to a gene tend to be inherited with it, therefore co-segregation of the disorder with a particular marker allele is suggestive of genetic linkage to a pathogenic locus. The availability of well-characterized markers spaced across all chromosomes has enabled genome-wide linkage studies to be performed. However, the parametric statistical tests commonly used to test for linkage require a precise genetic model describing the mode of inheritance, and are therefore suited for Mendelian disorders involving genes of major effect.

The initial application of traditional linkage approaches to schizophrenia rested on the hope that genetic heterogeneity might reveal families

segregating genes of major effect. However, early positive findings could not be replicated[26,27], suggesting that highly penetrant mutations causing schizophrenia are at best extremely rare and possibly non-existent[28]. In spite of the failure to identify genes of major effect, moderately significant evidence for linkage has been found in more than one data set in several, albeit rather broad, chromosomal regions (Fig. 2). Areas implicated, for which supportive data have also been obtained from large international collaborative studies, include chromosome 22q11–q12, 6p24–p22, 8p22–p21 and 6q (Refs 29–31). There are also several other promising areas of putative linkage, which have not received convincing support from international consortia. These include 13q14.1–q32 (Refs 32–34), 5q21–q31 (Refs 35,36) and 10p15–p11 (Refs 37–39). Other regions that are currently being investigated in collaborative studies include 1q21–q22 (Ref. 40) and 18p (Ref. 41). However, it should be noted that in every case, there are negative as well as positive findings, and in only two cases – those of chromosome 13q14.1–q32 and 1q21–q22 – did any single study achieve genome-wide significance at $P < 0.05$.

The findings from linkage studies of schizophrenia to date demonstrate several features that are to be expected in the search for genes for complex traits. First, no finding is replicated in all data sets. Second, levels of statistical significance are largely unconvincing, and estimated effect sizes are usually modest. Third, chromosomal regions of interest are typically broad (often >20–30 cM).

At present, the linkage literature supports the predictions made by Risch[25]: it is highly unlikely that a commonly occurring locus of effect size $\lambda s > 3$ exists, but there is suggestive evidence implicating a number of regions that is consistent with the existence of some susceptibility alleles of moderate effect (λs 1.5–3).

Cytogenetic abnormalities
A second approach by which investigators have sought to locate susceptibility genes for schizophrenia rests on the identification of chromosomal abnormalities in affected individuals. Cytogenetic anomalies, such as translocations and deletions, can implicate a gene or region by disrupting the function of a gene directly, by having a positional effect on gene expression or by showing linkage with a susceptibility variant. Owing to the high prevalence of schizophrenia, a single incidence of a cytogenetic abnormality is, however, insufficient to demonstrate causality. To warrant further investigation, a cytogenetic abnormality should either be shown to exist in greater frequencies in affected individuals, to disrupt a region in which positive linkage or association has been found or show co-segregation with the condition in affected families. This approach has nevertheless yielded some intriguing findings. A noteworthy example is a t(1;11) balanced reciprocal translocation found to co-segregate with

schizophrenia in a large Scottish family[42], which has recently been reported to directly disrupt two genes, of unknown function, on chromosome 1 (Ref. 43). Valuable insights could also be provided by Velo-cardio-facial syndrome, a condition associated with small interstitial deletions of chromosome 22q11 (Ref. 44), in which high rates of schizophrenia have been reported[45]. That both these deletions roughly correspond to regions for which there is modest evidence of linkage suggests that they might contain susceptibility loci of more general relevance to schizophrenia.

Association studies
If, in the main, schizophrenia reflects the operation of multiple genes of weak effect (i.e. $\lambda s < 1.5$), the number of families required by linkage studies to localize these genes will be prohibitively large. Allelic association studies provide an alternative, and potentially powerful, means of identifying such genes in feasible sample sizes. Under this approach, it is usually gene variants themselves that are the unit of study, most commonly assessed on the basis of their relative distribution within unrelated groups of affected and non-affected individuals. Association studies can therefore be used to evaluate the contribution of specific genetic POLYMORPHISMS within neurobiological candidate genes that can influence the functioning or expression of the molecule. The choice of candidates allows particular neurobiological hypotheses of schizophrenia to be directly addressed, although, as mentioned previously, any system or process speculated to be involved in the disorder is likely to be controlled by numerous genes, both known and unknown.

Most candidate gene studies to date have been based on the dominant neurochemical models of schizophrenia, and have therefore focused on neurotransmitter receptors and metabolizing enzymes. In light of the dopamine hypothesis of schizophrenia, genes involved in dopamine transmission have been the subject of particular attention, although most, including the dopamine D2 receptor, have yielded negative results. Positive findings have been reported, however, for a genetic polymorphism causing an amino acid variation (Ser9Gly) in exon 1 of the dopamine D3 receptor gene (*DRD3*) (Ref. 46). This finding is of particular interest as the D3 receptor, which is functionally similar to the D2 subtype, is principally expressed within the nucleus accumbens – a region closely connected with temporal and pre-frontal areas – that appears to be a key target of modern anti-psychotic drugs. Although negative findings have also been reported for the D3 polymorphism, a meta-analysis of data from over 5000 individuals has confirmed a significant association between homozygosity at this locus and schizophrenia[47]. Nevertheless, if genuine, the size of the effect would appear to be rather small, with a putative odds ratio of 1.2. A second gene that has been

implicated by association studies encodes the serotonin 2A (5-HT$_{2A}$) receptor, which has been argued to mediate the efficacy of atypical anti-psychotics. Association has been reported for a T/C polymorphism at nucleotide 102 of the gene encoding 5-HT$_{2A}$ (Ref. 48), which, despite some conflicting results, has been supported by a meta-analysis of all available data[49]. Again, the putative odds ratio is small (~1.2). However, even if the association is real, it is unlikely that the T102C polymorphism is a true susceptibility variant as it neither alters the predicted amino acid sequence, nor is it in a region of obvious significance for regulating gene expression. Under the assumption that a susceptibility locus might be close enough to the T102C polymorphism to be in linkage disequilibrium with it, screening of the *5-HT$_{2A}$* has been undertaken by several groups in order to identify polymorphisms that might be of functional importance.

The *DRD3* and 5-HT$_{2A}$ findings illustrate two important points regarding association studies of schizophrenia. First, given that individual gene mutations appear neither necessary nor sufficient to cause the disorder, they might be expected to exist in unaffected individuals in frequencies not greatly dissimilar to those found in affected cases, and large sample sizes would therefore be required for their detection. Second, although genes might be implicated by tests of functionally neutral polymorphisms if they are in tight linkage disequilibrium with a pathogenic locus, a priority should be given to the screening of coding and regulatory regions for variations that might impact on protein structure and/or expression with which to test for association. However, any positive findings should also be viewed with a fair degree of caution, at least until a consistent pattern of replication has emerged. In light of the wealth of potential candidate genes and low prior probability of association, multiple testing poses a real danger of generating false positives. Researchers should also be careful that positive associations are not the result of population stratification. The more recent use of intra-familial designs such as the transmission/disequilibrium test, whereby untransmitted parental alleles constitute the 'control' comparison, are of value in this regard, although these could suffer from other weaknesses.

Despite these potential caveats, association studies might provide the most powerful means of elucidating the molecular basis of schizophrenia. In recent years, there has been increasing interest in the possibility of genome-wide association studies[50,51], which have the potential of allowing systematic searches for genes of small effect in polygenic disorders. Optimism has been fuelled by the fact that the most abundant form of genetic variation, the single nucleotide polymorphism (SNP), is usually bi-allelic and potentially amenable to binary, high-throughput genotyping assays, such as micro-arrays. Moreover, as the amount of sequence data

accumulates, it has become possible to contemplate the construction and application of very dense maps of hundreds of thousands of SNPs (Ref. 51). For the present, candidate gene studies, based on convincing neurobiological hypotheses and prioritized according to regions implicated by linkage studies, could yield valuable answers. Such studies are likely to benefit from clues provided by emerging transcriptomic and proteomic approaches to schizophrenia (e.g. Ref. 52).

New directions

A relatively recent development in the hunt for schizophrenia susceptibility genes has rested on the identification of traits that might more directly reflect the operation of fundamental processes of potential relevance to schizophrenia. These 'intermediate' phenotypes[53] should be measurable in individuals without schizophrenic symptoms, and might have a less complex genetic basis that is more amenable to linkage and association studies. Of particular note are studies showing abnormalities in the P50 brain-evoked potential in schizophrenic patients and their families, which appears to be linked to a locus on chromosome 15q (Ref. 54).

It seems probable that the phenotypic heterogeneity of schizophrenia results, in part, from genes that do not promote susceptibility *per se*, but which modify the expression of the illness. Although these gene variants are also likely to be common in the general population, their identification could serve to promote a better understanding of clinical variation that could potentially lead to more suitable treatments. To this end, researchers have begun to investigate the relationship between polymorphisms in candidate genes and symptom profiles (e.g. Ref. 55).

Predictions of response to current drug treatments might be provided by work in the rapidly expanding field of pharmacogenetics. Here, associations are sought between variations in genes thought to be involved in the action and metabolism of anti-psychotic drugs and treatment response[56].

Conclusions

Genetic epidemiological studies have provided evidence for a strong genetic component to the aetiology of schizophrenia. However, attempts to identify susceptibility genes face formidable challenges arising from both genetic and phenotypic complexity. Research to date has largely excluded the possibility that genes of major effect exist, even in a subset of families. Linkage studies have yielded some evidence for the location of genes of moderate effect, although, at present, none of these findings can be regarded as conclusive. Association studies have provided relatively robust data suggesting that allelic variation in genes encoding the 5-HT$_{2A}$ and D3 receptors confer a small degree of susceptibility. Future candidate gene studies might benefit from focusing on those genes located in a region of chromosome 22, where specific deletions have been

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found to increase markedly the risk of schizophrenia. As in other common diseases, advances are likely to come through the use of a new generation of genetic markers, and new methods of genotyping and statistical analysis. It is hoped that the eventual identification of susceptibility loci will promote further productive neurobiological research and, ultimately, more effective treatments for schizophrenia.

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