

Identification of Genes for Schizophrenia Susceptibility

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Abstract

Introduction: Advances in genotyping, mapping and genome analysis methods over the last few years offer great promise towards the discovery of genes involved in the pathogenesis of schizophrenia, a mental disorder with a high degree of heritability. **Methods:** This article draws on published reports in major international journals in the field of schizophrenia and human genetics. **Results:** We summarise the major findings from family linkage studies, genome scan with microsatellite markers and association studies with polymorphisms in candidate genes. However, although recent developments in the technology for genotyping and gene identification have provided new leads to genetic abnormalities underlying schizophrenia, they have yet to result in the identification of any disease gene. There are both positive and negative data for reported linkages to specific chromosomal regions and candidate gene polymorphisms. **Conclusions:** Conflicting data and nonreplication of association and linkage studies are problems that need to be addressed. One solution might be clearer and narrower definition of subphenotypes and use of only a specific phenotypic marker in linkage and association studies. When successful, identification of susceptibility genes will lead to better understanding of cognitive functions and socio-emotional behaviour and also help in the formulation of preventive strategies for those found to be at high risk.

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Introduction

Schizophrenia, described as “the most human of all diseases,”¹ affects about 0.5 % to 1% of the population and typically develops in the early 20s in men and the late 20s to early 30s in women. It is one of the most severe, if not the most severe, of all mental disorders, causing enormous personal suffering, social and vocational impairment, family burden, and cost to society.² In a recent survey by Choo,³ schizophrenia was the most frequently diagnosed disorder among the 3000 new cases seen within one year in Woodbridge Hospital, the only state mental hospital in Singapore.

Schizophrenia is also associated with higher mortality from both suicide and natural causes. A 15-year follow-up study of a cohort of Chinese patients in Singapore found that the rate of patients who died from suicide and those from natural causes were 60 times and 10 times that of the general population.⁴

Schizophrenia is a complex disorder with diverse symptoms. The main disturbances comprise positive symptoms, negative symptoms and disorganisation.⁵ Positive symptoms are represented by active distortion of mind functions like hallucinations, delusions, disorganised thinking and bizarre

behaviour. Negative symptoms are represented by loss or decrease of normal functions which are manifested as affective flattening (impaired affect), avolition (lack of drive, ambition and spontaneity), anhedonia (diminished interests and pleasures), alogia (poverty of speech and reduced ability to relate to others) and poor attention.

The risk factors of this disorder include a family history of schizophrenia and a foetal history of obstetric complications.⁶ It is almost generally acknowledged as a brain disorder in general and a neurodevelopmental disorder in particular^{7,8} with cumulative adverse gene-environment interaction (e.g. exposure to environmental toxins, viral infections, birth injury or genetic disposition).¹ Although schizophrenia also fits some of the criteria for neurodegenerative disease such as being a chronic and progressive illness, the difficulty with the neurodegenerative theory is that there is no evidence of cell death and no characteristic histopathologic changes that can be verified by light microscopy or immunocytochemistry.⁹

It is an acknowledged fact that schizophrenia tends to be concentrated in families. Earlier classical genetic studies have established the important role of genetics in the aetiology of schizophrenia. Data from family, twin and

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adoption studies suggest that 65% to 85% of the susceptibility to schizophrenia can be attributed to genes.^{10,11} However, as the pattern of transmission of schizophrenia is complex and does not follow Mendelian inheritance, it is unlikely to be due to a single major gene. The general consensus from quantitative analysis of schizophrenia family data is that it is a polygenic disorder with the involvement of environmental factors.

Various strategies are used in schizophrenia genetic research. The following sections summarised the pertinent findings of the different approaches.

Phenotypic Susceptibility Marker

For a complex disorder with a whole range of symptoms, one or more of the more specific manifestations may have a stronger genetic component. Genetic studies could be carried out with a stricter and narrower definition of a subphenotype. This approach has been adopted for Type 2 diabetes in which serum glucose level was used¹² and in allergic asthma with serum IgE level as one of the phenotypic markers.¹³

For schizophrenia, one of the most robust findings among patients and their relatives is that of eye movement impairment. The quality of smooth eye movement in this group includes the disruptions of smooth eye pursuit by saccadic eye movements which is present in about two-thirds to three-quarters of schizophrenic patients.¹⁴ Eye movement impairment is present in about half of the relatives of schizophrenia¹⁵ suggesting that this impairment may be a genetically determined latent trait.

Another feature of schizophrenia is attentional dysfunction which is associated with a loss of inhibitory function. This can be assessed in the laboratory by measuring the P50 response. This is a positive wave occurring 50 msec after an auditory stimulus. This first stimulus also triggers inhibitory pathways which would suppress a subsequent stimulus. The length of time for which this inhibition has been found to be abnormal in patients with schizophrenia as well in many of their first degree relatives.^{16,17} There is evidence that this abnormality may be transmitted in a co-dominant manner.¹⁸

Cytogenetics

An excess of sex chromosome abnormalities has been found in schizophrenic patients,¹⁹ indicating that disturbance of the balance of gene products from sex chromosomes may trigger psychotic illness in susceptible individuals. There is also some evidence of a psychosis susceptibility gene on chromosome X.²⁰ Although the transmission of the schizophrenia is autosomal and not sex-linked, different relative risks and treatment outcome indicate there might be a minor modifier locus on chromosome X or the pseudoautosomal region of chromosome Y. Although no

linkage to specific chromosome X markers was found,^{21,22} analysis with affected sibling pairs turned up one positive linkage with DXYS14²³ for the pseudo-autosomal region but the result was not replicated by other groups.^{24–26}

Several cases of partial trisomy 5 have been associated with schizophrenia.²⁷ The regions involved include 5p14²⁸ and 5q11.2–q13.3.²⁹ Proximal 5q markers are found to cosegregate with schizophrenia and related disorders in several British and Icelandic families.³⁰

The 22q11 deletion syndrome (22qDS) has been proposed as a genetic subtype of schizophrenia.³¹ It is characterised by variable clinical presentations which might include congenital dysmorphic features and learning disabilities and is also associated with psychiatric illnesses such as schizophrenia.³² Interstitial deletions of about 3 megabases in 22q11 have been identified in some schizophrenia patients.³³

Linkage Analyses

The basis of linkage analysis is that all affected members of a pedigree will have inherited exactly the same chromosomal region around the disease-causing allele. Sequences close to the region of interest would be physically “linked” to the allele which “marked” the chromosome. Once an allele that segregates with the disease is found, analysis can be carried out in families with multiple affected members.

Sherrington et al³⁴ reported the existence of a dominant schizophrenia susceptibility locus on the long arm of chromosome 5. However, subsequent studies, including a combined reanalysis of several data sets, failed to replicate the original findings.³⁵ Positive results were also obtained with several markers on the short arm of chromosome 6.^{36,37} There was also support for a susceptibility locus on 18p³⁸ and chromosome 22q12³⁹ and for chromosome 13 in Caucasian but not Oriental populations.⁴⁰

Genome Wide Scans

Families with multiple affected individuals required for traditional linkage analysis are not easy to come by. In the absence of strong linkage to any chromosomal region or candidate gene, several groups have initiated genome-wide search for schizophrenia susceptibility loci using such families.

Several chromosomes (1, 2, 4, 11 and 13) were identified as having at least one marker with a LOD (logarithm of odds) score of >2.⁴¹ Using nonparametric linkage analysis for genome wide scan data, suggestive linkage was obtained for chromosomes 2, 6, 8, 9 10 and 15.^{30,42,43}

In general, results of genome scans have thus far been inconsistent and disappointing. One probable explanation

could be that many genes of small effects are involved, and some of the genes involved might even be different in different populations with different ethnic background, social history and environment. A recent genome wide screen with 20 affected families in a homogeneous subpopulation in Finland also suggests the presence of multiple susceptibility loci.⁴⁴

Association Studies

Association studies complement genome scans in the detection of susceptibility genes. It is usually performed if a defective biochemical pathway or biomolecule has been identified or after positive linkage of a specific chromosomal region is obtained. To ensure meaningful results from such studies, it is essential to ensure the use of controls matched for ethnicity and age. As linkage disequilibrium depends on a population's history, differences in allele frequency between different population groups are common. Any positive finding would need replication in other data sets, in both the same population group and in other ethnic groups. Only after multiple reports of positive associations can it be inferred that the allele causes disease or the allele is in linkage disequilibrium with the actual disease-causing gene.

Such association studies have included the following:

HLA System

There was extensive investigation on the association of schizophrenia with specific alleles of the human leukocyte antigen complex (HLA) but the results showed no consistent pattern.⁴⁵ Recently, based on the observation that schizophrenia patients rarely develop rheumatoid arthritis, an autoimmune disorder associated with the HLA DRB1*04 gene, the frequency of this allele was investigated and was found to be significantly lower in schizophrenic patients.⁴⁶

Dopamine System

Association studies with the various dopamine receptor genes have been carried out but no conclusive result has been obtained. Linkage studies with both nuclear families and sibpair analysis also showed no association for the dopamine transporter gene.⁴⁷⁻⁴⁹

Serotonin System

The role of serotonin (5HT) in the pathogenesis of schizophrenia is still unclear. Postmortem studies of serotonin receptor subtypes in schizophrenia have been inconclusive and contradictory. Findings include a reduction in 5HT_{2a} receptors and 5HT reuptake sites in the dorsolateral prefrontal cortex, alteration of serotonin transporter in the hippocampus of subjects with schizophrenia, particularly in those who committed suicide.^{50,51}

There are several reports of the linkage of the C102 allele (which codes for the 5HT_{2a} receptor) with schizophrenia,

but there are also a large number of negative reports. A Singapore study with Chinese males, however, showed excess of the T allele instead.⁵²

NMDA Receptors

The excitatory amino acids, glutamate and aspartate, are of interest to schizophrenia research because of their roles in neurodevelopment, neurotoxicity and neurotransmission. Recent evidence suggests that densities of glutamatergic receptors and the ratios of subunits composing these receptors may be altered in schizophrenia, although it is unclear whether these changes are primary or compensatory. NMDA receptor agonists like phencyclidine and ketamine have been found to induce psychosis and other symptoms characteristic of schizophrenia.⁵³

So far, results from molecular genetic studies have been negative. No association was found between a dinucleotide repeat in the 3'-untranslated region of the glutamate/aspartate transporter gene (SLC1A5) and schizophrenia.⁵⁴ There is also no association between a microsatellite trinucleotide repeat polymorphism at the glutamate (GluR6) receptor locus.⁵⁵

Catechol-O-methyltransferase (COMT)

Catechol-O-methyltransferase metabolises catecholamines such as dopamine, noradrenaline and adrenaline. The COMT gene is situated in a region of chromosome 22 (22q11) and negative association of polymorphisms in this gene with schizophrenia suggests that the COMT gene does not play a major role in the pathogenesis of schizophrenia.⁵⁶

14-3-3 eta Chain Gene

The 14-3-3 protein is abundant in the brain and regulates the synthesis and excretion of catecholamines and serotonin. The eta chain gene has been mapped to chromosome 22q12.1-13.1. An association between a variable number of tandem repeat (VNTR) in the 5'-noncoding region and early onset schizophrenia has been reported.⁵⁷ It has yet to be confirmed independently by other groups.

Apolipoprotein E

Proponents of the theory that schizophrenia is a neurodegenerative disorder cite evidence of progressive neurodegenerative process such as decreases in brain volume.⁵⁸ The apolipoprotein E gene (ApoE) was tested as a candidate gene for schizophrenia as it has been shown to be associated with Alzheimer's disease, a neurodegenerative disorder.⁵⁹ However, no association with either of two polymorphisms (-491A/T and -219G/T) in the regulatory region was found.⁶⁰

Trinucleotide Repeat Expansions

Suggested evidence of anticipation led to the hypothesis

that expansion of trinucleotide repeats might be involved in schizophrenia.^{61,62} There is some preliminary evidence that the distribution of CAG/CTG repeat size is larger in patients with schizophrenia compared to controls.^{63,64} In addition, an association between trinucleotide repeat expansions and childhood-onset schizophrenia was reported.⁶⁵ This association is particularly significant in the male population. There was also another report of expansion in early-onset female schizophrenia.⁶⁶ Studies with anonymous sequences containing trinucleotide repeats turned up large numbers of negative results.⁶⁷⁻⁷² Studies with 5 random novel trinucleotide repeats in 17 families did not find any difference in allele frequency. Three CAG repeat clones from chromosome 6 are also not expanded in 30 schizophrenic families.⁷³ Another investigation on CAG or GAA repeats in schizophrenia families and monozygotic twins also failed to find evidence of expansion in affected individuals.⁷⁴ In view of the large number of negative association in either case-control or family studies, it is likely that repeat expansion might play a role only in certain types of childhood/early-onset cases and pedigrees.

Conclusions

From the summary of genome scan/linkage studies in Table I and those of association studies of candidate genes in Table II, it is obvious that neither genome scan nor association studies have convincingly identified a single susceptibility gene. The best data to date can only be considered as suggestive or tentative in the absence of unequivocal proof of linkage to any locus or gene variant.

TABLE I: CHROMOSOMAL REGIONS WITH REPORTED LINKAGE TO SCHIZOPHRENIA

Chromosomal region	Positive linkage	Negative linkage
1q	(44)	
2q	*	(75)
3p	(76)	(77, 78)
4q	(44)	
5p	(79)	(80)
5q	(34, 81, 82)	(78, 80, 83, 84)
6p	(85, 86, 87)	(78)
6q	(30, 88)	
8p	(76, 86, 89, 90)	(78, 91)
9	(44, 86)	(92)
10p	(42, 93, 94)	
11q	*	(24, 95, 96)
12	*	(97)
13q	(89, 98)	(99)
15q	(100)	(101)
18p	(38, 102)	
22q	(39, 103, 104, 105, 106)	(81, 107, 108, 109)
Xp	(23, 44, 110, 111)	(21, 22, 25, 26)

* balanced translocation

() numbers in brackets are references

The conflicting results from genome scan, linkage analysis and association studies could be due to the poor control of phenotypes included as cases or patients, thus introducing potential covariants. Instead of a clean or clear phenotype, patients might not share all the symptoms or have similar degree of severity of disease, or patients with other additional psychotic conditions might have been included in different studies. Different criteria of diagnosis and definition of phenotype (narrow versus broad) could explain some of the contradictory results obtained so far. If this disappointing progress is due to the heterogeneity of disease phenotypes, the development of clear objective measurements for some of the phenotypic markers would facilitate their individual use in genetic studies. One such vulnerability marker currently available is the reduction in P300 amplitude which has already been shown to be genetically transmitted.¹⁶⁶

There are many cases of positive linkage which cannot be replicated. One of the problems with the inconsistent results obtained for linkage analyses could be due to population stratification and heterogeneity, insufficient sample size, different criteria for diagnosis, differences in the frequency of susceptibility/modifier genes, or even ethnic differences in susceptibility genes. The burden of proof should thus be the replication in another data set and also the use of family-based association studies in addition to case-control studies. Meta-analysis could be used to resolve some of the problems.¹⁶⁷

TABLE II: SOME OF THE CANDIDATE GENES ASSOCIATED WITH SCHIZOPHRENIA

Candidate gene	Positive linkage	Negative linkage
CHRNA7	(genome scan)	(112)
COMT	(113, 114, 115, 116, 117)	(118, 119)
DRD2 -141C Del	(120)	(121)
DRD2 Ser311Cys	(122)	(123)
DRD3 Ser9Gly	(124)	(125, 126, 127)
DRD4 repeat (Exon III)	(128)	(129, 130)
DRD5 microsatellite	(131)	
HLA-DR4	(46, 132)	
IL-1	(133)	
LDL-PLA2	(134, 135)	
MTHFR	(136)	(137, 138)
Neurotrophin-3	(139, 140)	(141, 142)
Porphobilinogen deaminase	(143, 144)	(145)
14-3-3 protein eta chain gene	(57)	
Serotonin transporter s/l	(146, 147)	(148, 149, 150)
Serotonin R2a	(52, 151, 152)	(153, 154, 155, 156, 157)
SCA1	(158)	
SKCa3	(159, 160, 161)	(162, 163, 164, 165)

() numbers in brackets are references

One other problem is the difficulty of obtaining large numbers of patients or families with multiple affected members for each research group. Steps are already being taken to overcome this problem. The National Institute of Mental Health (NIMH) Genetics Initiative on Schizophrenia is a multisite collaborative study with a centralised clinical database and cell repository. The European Multicentre Association Study of Schizophrenia (EMASS) Group is another collaborative effort under the auspices of the European Science Foundation.¹⁶⁸ With the pooling of samples and greater collaboration between different groups, problems with sample size and inclusion criteria for patients would at least be overcome.

Much work lies ahead in the challenge to elucidate the genetic vulnerability of schizophrenia—not only in identifying the genes involved and but also in understanding their interaction with environmental factors. Such endeavours would yield valuable insights into this devastating disorder and based on this knowledge, new effective treatment and prevention could be devised.

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