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The molecular genetics of schizophrenia: an emerging consensus

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Schizophrenia is perhaps the most debilitating mental disease and determining the underlying cause has become a challenging area of psychiatric research. It is relatively well established that genes play a role in the aetiology of schizophrenia. In this article, a review of important findings related to schizophrenia as a genetic trait will be provided, including a discussion of family, twin and adoption studies. Molecular genetic studies of specific candidate genes are then reviewed. Some controversies within the literature are examined and possible directions for future research are discussed.

Schizophrenia is a disorder characterised by delusions and/or hallucinations, looseness of associations, blunted or inappropriate affect, disturbances in the victim's sense of self, and bizarre or inappropriate behaviour. It ravages the life of the patient, is disastrous for the patient's family and friends, and places an onerous cost upon societal resources. To exacerbate the problem, the inability to appreciate objective health threats, as well as the lack of personal concern that is often characteristic of the disorder, places schizophrenics at higher risk of contracting other serious conditions such as AIDS (Ref. 1). For these reasons, gaining a better understanding of schizophrenia is one of the highest palliative priorities in the mental health field; it is also one of the most obdurate clinical and research challenges in psychiatry.

Various estimates of the prevalence rates of schizophrenia in the United States range from 6 to 11 per 1000 (Ref. 2). A serious impediment in identifying better treatments and potential

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preventative techniques is the fact that the root causes of schizophrenia have proven elusive. The most encouraging line of research concerns work on the genetic substrata of the disease.

Although attempts to ascribe a genetic basis for many types of mental illness have sometimes been controversial, it has been suspected for many decades that genes play a role in the aetiology of schizophrenia. Recent technological progress in genetic research, culminating with the Human Genome Project, has facilitated the search for genes that increase the risk for psychiatric disorders (Ref. 3). Like most areas of genetic research, the examination of schizophrenia has begun with work that establishes a familial transmission of the disorder. In turn, these studies have provided a basis for a consideration of specific routes of genetic transmission. This article begins by discussing the genetic data yielded by family, twin and adoption studies, and subsequently reviews research involving specific genetic systems that have been imputed in the transmission of schizophrenia.

Genetic epidemiological research on schizophrenia

Family studies

Investigation into the possible genetic basis of schizophrenia began as early as 1916, when the first systematic family studies of the disease were undertaken. As many as 40 European studies, undertaken between 1920 and 1987, that were similar in their diagnostic and ascertainment procedures have been reviewed by Gottesman (Refs 4, 5). This body of work has shown that relatives of schizophrenics are at considerably greater risk of contracting the disease themselves than are individuals with no history of the disease within the family. Specifically, the approximate lifetime risks to first-degree relatives were estimated to be 6% for parents, 9% for siblings, 13% for offspring with one schizophrenic parent and 46% for offspring with two schizophrenic parents. (The fact that parents had the lowest rate is due to the fact that schizophrenics are considerably less likely to reproduce than are non-affected individuals.) The approximate risk to other relatives were 6% for half-siblings, 2% for uncles and aunts, and 2% for first cousins.

A problem with many of the early studies was the lack of a control group that would permit a comparison of rates within a single study. By contrast, individual family studies compared rates of schizophrenia in the general population (Ref. 6). Differences in diagnostic criteria between the family studies and research among the general population therefore made interpretation difficult. Moreover, those who performed the diagnosis often knew the probands' diagnostic categories and could therefore have been biased in their diagnostic decisions.

Recent research on the familial transmission of schizophrenia has utilized more-rigorous techniques and narrower criteria for a diagnosis of the disease, employing neurological as well as clinical observations. This approach has yielded lower risk estimates than those reported by Gottesman. For example, Tsuang et al. (Ref. 7) reported an overall risk to first-degree relatives of schizophrenics of 3.2% when using the Washington University criteria. This rate increased to 3.7% with DSM-III-R criteria (for definition, see http://www.psy.med.rug.nl/0023), and then rose to 7.8% when the schizophrenia category was broadened to include atypical cases (e.g. schizoaffective disorder, psychosis not otherwise specified). These outcomes underscore the point that, when the definition of schizophrenia is broader, higher rates of risk are generated (Ref. 8). Conversely, as the inclusion criteria are defined more rigidly, lower estimates are produced. Nevertheless, it must be emphasised that modern family studies have continued to provide support for the notion that there is a genetic component in schizophrenia.

Twin studies

Another strategy for examining whether schizophrenia is genetically transmitted is to compare concordance rates among monozygotic twins (MZ; twins who share 100% of their genetic material) versus dizygotic twins (DZ; twins who share approximately 50% of their genetic material) (Ref. 9). Kendler has reviewed the results of twin studies and found a rate of concordance of approximately 53% for MZ pairs and 15% for DZ pairs (Ref. 10). In a similar review, Gottesman (Ref. 4) found a concordance rate of 46% for MZ pairs and 14% for DZ pairs. These reports indicating that MZ twins are about three times more likely to exhibit concordance than are DZ twins provide persuasive evidence of a genetic component in schizophrenia. This is further strengthened by research concerning the concordance rate of 12 pairs of MZ twins who were reared apart and who

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were systematically evaluated for schizophrenia (Refs 4, 11). The finding of a 58% rate of concordance provides further verification that genetics at least partially underlie schizophrenia. However, it must be stressed that, because MZ twins were not completely concordant, genes cannot be the sole cause of the disorder. In fact, when the relative contribution of genetic and environmental factors are obtained by translating genetic concordance rates into 'heritabilities' (i.e. the proportion of the liability to schizophrenia that is due to genes), 60–70% of the variance is attributable to genes.

As an alternative to examining concordance rates, Gottesman and Bertelsen (Ref. 12) examined the risk of developing schizophrenia in the offspring of MZ and DZ twins who were discordant rather than concordant for schizophrenia. They reasoned that, if there is a genetically transmitted susceptibility to schizophrenia that was not expressed (presumably owing to environmental factors), then the offspring of a non-afflicted MZ twin should manifest schizophrenia at the same rate as the offspring of the afflicted MZ co-twin. This notion received some substantiation: the children of non-afflicted co-twins displayed a morbid risk (17.4%) that was similar to that of the schizophrenic twin's offspring (16.8%). By contrast, whereas the risk of developing schizophrenia for the offspring of a schizophrenic DZ twin (17.4%) was similar to that of either group of MZ twins, the risk for an offspring of a non-afflicted DZ co-twin was much lower (2.1%). This finding again underscores the fact that, whereas environmental influences are certainly involved in an individual's development of schizophrenia, genetic factors also underlie the manifestation of schizophrenia.

Adoption studies

A third approach to examining a genetic contribution to schizophrenia is to study the prevalence of the disease in adopted children as compared with their biological and adoptive relatives (Ref. 9). For example, Heston (Ref. 13) examined 47 children of schizophrenic mothers who were adopted at infancy by parents with whom they had no biological relationship. This group was compared at maturity with a control group of 50 adoptees who were separated from non-schizophrenic mothers. The results supported a genetic aetiology of schizophrenia: whereas five children of schizophrenic mothers developed schizophrenia, none of the children of non-afflicted mothers developed the disorder. In a much larger project, Kety (Ref. 14) studied 5483 Danish children who were adopted between 1923 and 1947. Again, more adoptees who were separated from a schizophrenic biological parent developed schizophrenia or a related disorder than did control adoptees (32% versus 18%, respectively). In a variation of this strategy, Kety and colleagues also identified schizophrenic adoptees, and then determined prevalence rates for schizophrenia and related disorders in their biological relatives. It was found that 21% of the biological relatives of 33 schizophrenic adoptees were diagnosed with schizophrenia or a related disorder, in contrast to 11% of the biological relatives of 33 non-schizophrenic adoptees. Moreover, no differences in the rates of schizophrenia were observed between the adoptive relatives of the schizophrenic and non-schizophrenic adoptees. Furthermore, children born to non-schizophrenic parents but raised by a schizophrenic parent did not show rates of schizophrenia above those predicted for the general population. These findings have been replicated more recently (Refs 15, 16, 17).

A potential problem with designs that focus on either the adoptees themselves or on the adoptees' relatives (e.g. Ref. 18) is that, during gestation, a schizophrenic mother could possess or transmit some non-genetically-based biological/physiological defect (e.g. eclampsia) that could later result in schizophrenia. Kety and colleagues addressed this issue by comparing rates of schizophrenia of paternal half-siblings of schizophrenic adoptees with paternal half-siblings of non-schizophrenic adoptees. They found that 13% of the half-siblings of schizophrenics developed the disorder, whereas 2% of the half-siblings of non-schizophrenics suffered from the disorder. Inasmuch as paternal half-siblings have different mothers, the higher rate of prevalence among the schizophrenic siblings could not have been due to some effect of the uterine environment.

Summary of genetic epidemiological research

Members of families with a schizophrenic relative are more likely than others to develop the disorder. Similarly, MZ twins are more likely than DZ twins to be concordant for schizophrenia.

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Finally, adoptees born of schizophrenics are more likely than adoptees born of non-schizophrenics to become schizophrenic themselves, regardless of the status of their adoptive families. Taken together, studies concerning the familial transmission of schizophrenia have consistently provided evidence of a genetic component of the disease.

Models of genetic transmission

Although it is generally agreed that genetic factors are involved in schizophrenia, the genetic mechanisms of transmission have yet to be identified. The simplest possibility would be that a single mutation causes the disorder. However, in the absence of any contrary evidence, there is a *prima facie* reason that many genes act in consort to give rise to the disease, since this has been found to be the case with most psychiatric disorders with genetic components (Ref. 9). A resolution to the issue is at least possible, since processes of genetic transmission obey laws that can be subjected to statistical model-fitting techniques. These techniques can be applied to the findings yielded by family, twin and adoption studies to determine which genetic model can best explain the prevalence of schizophrenia.

The results of statistical model-fitting procedures indicate that no single aetiological model will account for all cases of schizophrenia. To at least some extent, the clinical heterogeneity evident in schizophrenia is caused by an underlying aetiological heterogeneity. For example, some cases are probably attributable to environmental antecedent, such as neurotropic viruses (Ref. 19), whereas others probably reflect the influence of limited numbers of rare genes (Ref. 20). However, despite the likelihood of their occurrence in some cases, neither of these aetiologies best accounts for either the familial rates of transmission or the majority of cases of schizophrenia.

A classic Mendelian explanation for the mode of inheritance of schizophrenia also does not suffice in most cases (Ref. 21). According to a Mendelian hypothesis, if a fully penetrant dominant gene caused schizophrenia, 50% of the offspring of one schizophrenic parent would develop the disease. In fact, the rate of inheritance is much lower (approximately 13%) (Refs 4, 5). Furthermore, if a fully penetrant recessive gene underlies schizophrenia, every child who has two parents with schizophrenia would also develop schizophrenia. Again, the observed rates are much lower (approximately 36–50%) (Ref. 4). Another flaw in a Mendelian explanation is the fact that most schizophrenics do not have any first-degree relatives with the disorder. Thus, it appears that a more complex model must be developed to account for the genetic transmission of schizophrenia.

Single-locus models

One model to describe genetic transmission is the single major locus (SML) model, wherein the pair of genes at a single locus causes the transmission of a disease. A SML model can yield predictions of the prevalence of schizophrenia in the general population, the prevalence among children of schizophrenics and the concurrence of the disorder among siblings. However, segregation analyses do not generally provide support for models based on single gene transmission. Even studies that did not exclude a SML model acknowledge that it underestimates the risk to both MZ twins and also to the offspring of two schizophrenic parents.

Latent structure analysis models

Another approach to investigate the genetic basis of disease is the use of latent structure analysis (Refs 22, 23), a statistical model that presumes the existence of a latent trait that can cause schizophrenia and/or other related phenotypic phenomena (e.g. deficits in some aspects of attention or working memory, associated with prefrontal cortical loci). This model presumes a latent trait that displays Mendelian transmission with a high degree of penetrance, even though the observable trait (e.g. schizophrenia, schizotypal personality disorder, etc.) does not always conform to the same pattern. According to the hypothesis, the overt manifestation of schizophrenic symptoms is a relatively uncommon outcome of a more common condition. For example, schizophrenics and controls have been tested for abnormalities on smooth pursuit eye movements (SPEM), a task in which the eyes only (not the head) are moved in space to track a moving visual target by keeping the target on the fovea via a 'calculation' of how fast the target is moving. It has been shown that 65–80% of schizophrenics display saccadic intrusions on SPEM tasks, as do 40–45% of their first-degree relatives; whereas only 8% of the general population display the phenomenon (Ref.

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24). A saccade occurs when an object moves away from the fovea, and the eye quickly moves to bring the target back into the fovea. As just stated, schizophrenic patients do not display normal saccades during a SPEM task. This suggests that schizophrenia and SPEM dysfunctions are independent expressions of a single gene.

A test of the latent structure model on the non-psychotic parents of schizophrenic probands, and on children of discordant MZ and DZ twins, provided support for the view that SPEM dysfunctions and schizophrenia are expressions of a single underlying trait, transmitted by an autosomal dominant gene. However, this outcome must be interpreted with caution, because the latent trait model does not provide a sufficiently high estimate of the risk of schizophrenia among MZ twins or for children of two schizophrenic parents (Ref. 25). Nevertheless, the approach indicates the utility of neurobiological assessments in locating genes that underlie schizophrenia.

Polygenic models

The failure of SML models to account fully for SPEM dysfunctions and schizophrenia has prompted a consideration of polygenic models, which propose that aetiological genes are located at two or more loci. There are two types of polygenic model: an oligogenic model that implicates a specific, limited number of loci, and a multifactorial polygenic (MFP) model that proposes a large, unspecified number of loci. In connection with the latter, the term 'polygenic' has come to be associated with the notion of a very large number of genes, each of which has a very limited effect size. The term 'quantitative trait loci' (QTL) refers to multiple genes with variable individual effect sizes that, as a group, can determine the quantitative level of a trait (Ref. 26).

MFP models postulate that there are many interchangeable loci, and genes at those loci have variable, additive effects on the predisposition to schizophrenia. Those models assume that everyone has some degree of genetic 'vulnerability' to schizophrenia. If the effects of many genetic and environmental influences summate beyond some (unknown) threshold value, the result is the phenotypic expression of schizophrenia.

A variety of analytical techniques indicate that the MFP model is a promising approach; however, mixed models containing SML and MFP components are probably more useful (Ref. 27). Accordingly, neither SML nor MFP models alone can explain some features of schizophrenia, such as the high concordance rate among MZ twins but comparatively low risk to first-degree relatives (Ref. 21). However, the pattern of risk was predicted more accurately when epistasis (i.e. when a gene interferes with the phenotype of another) was included in the paradigm (Ref. 28). According to this model, it is assumed that there is a higher risk ratio for relatives than for the general population, that the disease conforms to a multilocus model and that epistasis can occur. The result of mixed model approaches is a sharper decline in risk as the extent of shared genes decreases, than the risk that would be predicted by a non-interactive, multilocus model.

Summary of models of genetic transmission

A straight-forward Mendelian model for the familial transmission of schizophrenia is not adequate to explain the occurrence of the disease because predictions of inheritance rates do not conform to the rates that have been empirically observed. Similarly, a SML model cannot account for the transmission of schizophrenia because it also does not provide accurate predictions regarding the transmission rate of schizophrenia (although, whereas Mendelian models over-estimate the transmission rate, SML models under-estimate it). MFP models are more accurate than SML models, but models featuring SML and MFP components are the most precise, particularly when epistasis is included in the paradigm.

Linkage analysis

Advances in DNA technology have provided important new tools in the effort to discover the genetic basis of schizophrenia. One of the most valuable techniques is linkage analysis, which is based on the fact that, when chromosomes cross over and exchange segments of DNA (i.e. recombine) during meiosis, genetic loci that are close to each other are more likely to be co-inherited than are loci that are more distant. This is important to the identification of genes that cause disease because, if an unknown disease gene is 'linked' (i.e. co-segregates) with a DNA marker having a known chromosomal location, the marker can

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be used to find the gene. This marker must be polymorphic (since variants must be specific to a disease). Linkage analysis became a powerful tool when molecular geneticists developed methods to identify many DNA markers throughout the genome.

Statistical methods of linkage analysis involve computing the probability that the co-segregation of genetic markers and disease within pedigrees exceeds what would be expected by chance. Many linkage studies have been performed under SML conditions, in which the odds for linkage are analysed for a specified degree of linkage. If the odds against a random finding (expressed as the logarithm of odds ratio, or LOD score) exceed 1000 to 1, a LOD of 3 is assigned, and evidence of linkage between a gene and a trait is provided. On the other hand, a LOD score of –2 is considered to be a cutoff point used to exclude the possibility of linkage. These statistical decision rules have proven to be reliable for single gene diseases; however, for complex disorders such as schizophrenia, other factors such as the presumed mode of transmission, the definition of the phenotype, the degree of penetrance, the sample size and the number of affected family members, must also be considered in determining linkage (Ref. 29). Unfortunately, some of those factors, such as the mode of transmission and the degree of penetrance, are not yet known for schizophrenia. To compensate, linkage analyses can be performed repeatedly, with different values set for each parameter. However, a disadvantage of this approach is that positive results must be viewed conservatively, because the risk of false positive findings increases with the number of tests performed.

In general, linkage analysis is most useful in uncovering variance in important genes that follow Mendelian patterns of inheritance; it is less helpful in identifying genes that exert a small or moderate effect upon complex psychiatric disorders. This problem is exacerbated when definitions of phenotypes are not accurate. Despite these reservations, evidence has been aggregated that link schizophrenia to several chromosomal sites, as described below.

Chromosome 1

Several lines of research have indicated a linkage between schizophrenia and a locus on chromosome 1q. Early studies provided evidence of linkage between schizophrenia and a balanced translocation involving chromosomes 1 and 11, t(1;11)(q42.1;q14.3) (Ref. 30), and this has subsequently been replicated by Millar et al. (Ref. 31). An ensuing study also provided some evidence of linkage to chromosome 1: Hovatta et al. (Ref. 32) reported linkage between a 90% penetrant dominant locus with two loci on 1q, a region that is centromeric to the chromosome 1q42.1 region reported by Millar. Another schizophrenia-linkage study has shown that "multipoint analysis of chromosome 1 markers produced a maximum LOD score of 6.5 between markers D1S653 and D1S679, under a narrow recessive model and with an estimated 75% of families linked to that locus" (Ref. 33).

Chromosome 5

Early applications of linkage analysis to the aetiology of schizophrenia implicated partial trisomy of the long arm of chromosome 5, where an abnormality was found among two schizophrenics in a single family (Ref. 34), and among schizophrenics in seven other families across three pedigrees (Ref. 35). Subsequent research did not replicate this observation; in fact, some studies provided evidence against the role of chromosome 5 in schizophrenia. For example, McGuffin reported a LOD score of –40 for chromosome 5q11-q13 when data from several previous investigations were combined (Ref. 36). Subsequently, Diehl et al. reported a maximum heterogeneity LOD score of 3.35 ($p = 0.0002$) on chromosome 5q11 (Ref. 37). At the same time, a group at the University of Bonn (Germany) reported maximum LOD scores of 1.8 at marker IL9 on chromosome 5q31 in 14 pedigrees, and 1.27 at D5S399 in an additional 40 pedigrees (Ref. 38). Levinson et al. (Ref. 39) also examined the relationship between schizophrenia and chromosome 5, and concluded that a linkage could neither be proven nor disproved. Most recently, Gurling et al., one of the research groups that originally provided evidence for linkage, issued a report that provided new evidence for linkage to the chromosome 5q33.2 (Ref. 40).

Taken together, these results reflect the vicissitudes of linkage analysis: although the initial findings were followed by non-replications, more-advanced techniques and larger data sets have yielded new positive, as well as inconclusive, results.

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Chromosome 6

As with chromosome 5, research concerning chromosome 6p has received a substantial amount of attention, and has also yielded mixed results. An initial study (Ref. 41) reported evidence of linkage to chromosome 6p22 in a group of Irish families; however, a follow-up (Ref. 42) re-evaluated and expanded the sample, and stated that the likelihood of linkage was lower than originally claimed – in fact, only one LOD score was significant among the many analyses that were performed.

Several other recent studies have again indicated that there is a relationship between chromosome 6q and schizophrenia. Specifically, an area of about 40 cM on loci on chromosome 6p22-24 has been found to be linked (Refs 43, 44), although it should be added that non-replications have also been reported. For example, an illustration of the complexity of the issue is found in the work of Maziade et al. (Ref. 45) who did not find a linkage at 6p24-22 in 18 large, multigenerational pedigrees from Eastern Quebec, using a range of definitions for schizophrenia. Nevertheless, there was a trend towards linkage in one large pedigree, although this locus was linked both to schizophrenia and bipolar disorder (a disorder featuring both pathological depressive and manic states). This report highlighted the necessity of precision and uniformity in ascribing appropriate phenotypes for linkage analyses.

Finally, candidate regions on chromosomes 6q were investigated for genetic linkage to schizophrenia among 734 informative multiplex pedigrees (Ref. 39). This research indicated that the most supportive for linkage to schizophrenia were regions from chromosome 6q. Once more, however, contra-indicative evidence has also been reported by Gurling et al. (Ref. 40), whose pedigrees did not indicate a linkage to chromosome 6q.

Chromosome 8

Linkage studies at chromosome 8p21-22 have produced some results similar to those obtained at chromosome 6. Initial reports have been at odds: whereas one group found linkage under both dominant and recessive models, another group, using a larger multinational study, failed to find significant results with a recessive model, although some evidence for linkage was still indicated (Refs 46, 47).

Chromosome 10

Initial examinations of chromosome 10 did not yield evidence of linkage to any of four markers on 10p (Ref. 48). In this study, all of the markers excluded linkage (LOD <–2.0) under an autosomal dominant model, and three excluded linkage under a recessive model. Moreover, Moises et al. (Ref. 49) also failed to find linkage with10p, and Barr et al. (Ref. 50) found no evidence of linkage to markers on chromosome10q, but did not evaluate linkage to 10p.

By contrast, later work yielded suggestive evidence for linkage to 10p14-p12 in a European-American sample (Ref. 51), but not in an African-American sample (Ref. 52). Other studies (Refs 53, 54) also reported a linkage with schizophrenia among Caucasians with 10p14-p12. Finally, the latest multicentre linkage study of schizophrenia candidate regions has indicated linkage for chromosome 10p14-p12, as well as evidence for intersample heterogeneity (Ref. 39).

Chromosome 11

As early as 1995, Maziade (Ref. 55) studied the chromosome 11q21-22 region among 242 individuals from four multigenerational pedigrees with high rates of schizophrenia, and found no linkage with the disease. Several subsequent studies also failed to uncover linkage; however, Craddock and Lendon (Ref. 56) asserted regions 11q22-q23 might bear some relationship to psychotic symptoms *per se*, such as those observed in Alzheimer's disease. Moreover, Gurling et al. (Ref. 40) recently uncovered at least prelimary evidence of a relationship between schizophrenia and 11q21.

Chromosome 13

Interest in chromosome 13q32 was first generated by Lin et al. (Ref. 57), who studied 13 moderate-to-large families from the UK and Japan. They reported a maximum LOD score of 1.62 for marker D13S119. In an attempt to replicate these findings, they studied four families from Taiwan and ten from the UK (Ref. 58). For the UK sample, the maximum LOD score was 1.72 at marker D13S128. The Taiwanese sample showed no evidence of linkage.

Further evidence of linkage to 13q32 came from a genome scan of 54 families (Ref. 59). The maximum LOD score in this region was 4.18 at marker D13S174. A smaller, yet suggestive, LOD

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score was reported for chromosome 13 from the genome scan of Shaw et al. (Ref. 60): in a sample of 70 pedigrees, they found a LOD score of 2.85 at marker D13S1293. Subsequently, Brzustowicz et al. reported a LOD score of 4.42 at marker D13S793 for a study of 21 Canadian families (Ref. 61). Because these findings from non-overlapping families cluster within the same region of chromosome 13q, they suggest the region might harbour one or more schizophrenia-predisposing genes. However, this notion must be regarded cautiously, as shown by Levinson et al. (Ref. 39), who studied linkage to 13q in 734 multiplex pedigrees containing 824 independent affected sibling pairs. In this very large sample, the maximum LOD score in the region was 0.09, which provides evidence contrary to the hypothesis that the region contains a schizophrenia-susceptibility gene. Data from the Veterans Affairs (VA) Cooperative Linkage Study of Schizophrenia are also consistent with the presence of a susceptibility gene in this region (S.V. Faraone et al., unpublished).

Chromosome 15

One approach to dissecting the complex genetics of schizophrenia is to examine quantitative heritable phenotypes that are believed to be influenced by one or more of the genes that increase susceptibility to schizophrenia. A compelling demonstration of this was presented by Freedman et al. (Ref. 62). The group found linkage between markers on 15q14 and a measure of sensory gating known to be abnormal among schizophrenics and some of their otherwise unaffected relatives. The strongest evidence for linkage was for marker D15S1360 (LOD = 5.3; $p < 0.001$), which is physically close to the gene encoding α7 nicotinic cholinergic receptor subunit (CHRNA). The implication of a defect in a nicotinic gene was particularly compelling given that: (1) schizophrenic patients have a very high prevalence of nicotine dependence (Ref. 63); (2) nicotine normalises sensory gating deficits in schizophrenics and their non-afflicted relatives (Ref. 64); and (3) schizophrenic patients have a decreased number of hippocampal nicotinic receptors (Ref. 65).

Additional studies using 15q14 markers have implicated CHRNA7 in schizophrenia though linkage methods (Refs 48, 52, 66, 67) and linkage disequilibrium methods (Refs 68, 69, 70). By contrast, several studies have not confirmed these results (Refs 40, 49, 51, 71, 72, 73, 74, 75, 76) and Lai et al. (Ref. 77) found that a CHRNA7 variant with a 2 bp deletion was not associated with schizophrenia.

Chromosome 18

One study (Ref. 78) has indicated evidence of linkage to chromosome 18p. This result is especially noteworthy because the highest LOD scores were yielded with a broad phenotypic definition that included relatives of schizophrenic patients with bipolar disorder and major depression, in addition to schizophrenia and schizoaffective disorder.

Chromosome 22

Initial work on chromosome 22q and schizophrenia has provided preliminary evidence of linkage; however, either small sample sizes or a wide range of modelling assumptions concerning the mode of transmission were usually involved (Refs 79, 80, 81). By contrast, a second, larger sample (Ref. 82) excluded linkage to chromosome 22 loci, as did non-replications of the original finding (Refs 83, 84). However, in another follow-up of the original sample, linkage could not be excluded (Ref. 85), and others demonstrated positive results (Refs 86, 87). Most recently, a combined analysis of data from 11 independent research groups (Ref. 88), using an affected sib-pair method, again provided evidence of a site on chromosome 22 (D22S278) that might account for a small proportion (approximately 3–5%) of the susceptibility to schizophrenia.

Summary of linkage analysis

Linkage analysis has provided persuasive evidence for linkage at multiple sites; however, the precise linkage in schizophrenia has yet to be definitively established (Refs 20, 89, 90, 91, 92, 93, 94, 95, 96). Nevertheless, with an increase in the number of studies and an application of more rigorous methodologies, a consensus is building. For example, the likelihood of similar findings in a great number of replications involving the same region on chromosome 6p by chance is small, which strengthens the degree of confidence in them. Overall, the linkage analyses for the chromosomal sites reviewed above present a profile of multiple susceptibility loci of small or moderate effect sizes.

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Conclusion

The study of the genetic basis of schizophrenia has provided what is perhaps the most important contribution to the understanding of schizophrenia. As stated earlier, however, the current status of research on genes and schizophrenia has not yet uncovered the specific genes that underlie the disease; as a result, of course, the relative contributions of these genes is also unknown (Ref. 97). Furthermore, the neurobiological substrata of schizophrenia, which are presumably the products of the genes, are also not well understood. A precise definition of the phenotypic expression remains to be developed (Refs 98, 99, 100).

In order for schizophrenia research in psychiatric genetics to continue to advance, the following developments should be made high priorities: (1) an improvement of psychiatric genetic disease classifications (nosologies) to specify useful phenotypes for linkage studies; (2) a focus on neurobiological dysfunctions that reflect more-proximal effects of aberrant genes, which can serve as phenotypes in linkage studies; (3) an improvement in statistical models that account for the multifactorial aetiology and heterogeneous nature of schizophrenia, including possible epistasis and intergenerational changes; and (4) continued large-scale studies with well-defined pedigrees to detect involved loci. The timing for those improvements would appear to be serendipitous because there is now an atmosphere of international cooperation and collaboration [e.g. the multicenter Schizophrenia Linkage Collaborative groups such as that of Levinson et al. (Ref. 39)] and this should effectively facilitate the improvements described here.

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Further reading, resources and contacts

The American Psychiatric Association contains information on psychiatric diseases for the general public.

http://www.psych.org/public_info/index.cfm

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