

Genetic Insights into Schizophrenia

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Objective: To outline new insights into the genetic etiology of schizophrenia.

Methods: We discuss several commonly held beliefs about the genetic issues in schizophrenia.

Results: The complex genetic nature of the illness poses a challenge for investigators seeking causative genetic mutations. Multiple independent research findings are, however converging to identify a relatively small number of chromosomal locations that appear to contain schizophrenia susceptibility genes. Also, a clinically relevant genetic subtype of schizophrenia (22qDS) has been identified. We are developing a better understanding of how schizophrenia relates to other psychiatric disorders. While investigations into the possible roles of dopaminergic and serotonergic systems continue, other approaches that do not require theories of the mechanism of illness are also being used to identify candidate susceptibility genes.

Conclusions: Research to date suggests that our understanding of the pathophysiology of schizophrenia will soon be fundamentally altered by genetic approaches to this complex disease.

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Key words: genetics, schizophrenia, linkage, 22q deletion syndrome, psychiatric genetics

Strong and consistent evidence for the importance of genetic factors in schizophrenia comes from family, twin, and adoption studies conducted over the past 70 years (1,2). Recent research findings add significantly to this longstanding body of work. Although no specific genes have yet been identified, there is now convincing evidence for schizophrenia susceptibility loci on both chromosome 1 (3) and chromosome 13 (4,5), together with identification of a syndromic form of schizophrenia, 22q deletion syndrome (6–9). Despite the historical and recent support for genetic origins for schizophrenia, however, the complexities of the disorder present challenges to a straightforward understanding. Some common misconceptions about schizophrenia genetics have been addressed previously (10). This paper provides insights into the genetics of schizophrenia, presenting several commonly held beliefs and outlining current knowledge in this area.

Belief

The concordance rate is lower than 100% in monozygotic twins, therefore much of schizophrenia must be caused by environmental factors.

There are several aspects to this belief. First, the concordance rate in monozygotic (identical) twins for schizophrenia ranges from 41% (11) to 86% (12). Higher concordance rates are observable if probands have more severe forms of schizophrenia (12) or if schizophrenia-related disorders, in addition to narrowly defined schizophrenia, are considered in co-twins (13). There remains a degree of true discordance of phenotypic expression. However, if one follows discordant monozygotic twins into the next generation, offspring of both affected and unaffected monozygotic co-twins show similar rates of schizophrenia (14,15). These studies indicate that monozygotic twin discordance is due to non-expression of genetic susceptibility (incomplete penetrance) (16), not purely environmentally caused phenocopies of schizophrenia as is commonly believed. Mechanisms other than external environmental factors therefore must be involved.

Mechanisms for Discordance. Discordance in monozygotic twins is a commonly observed phenomenon in genetics. Monozygotic twins with Down syndrome, for example, are often discordant at birth for individual features of Down syndrome, such as congenital heart defects (17). How does this occur when both twins have “identical” genotypes and have shared the same intrauterine environment? There are several plausible explanations (18). First, there are stochastic (random or chance) factors at work from the time of conception, determining, for example, which particular cell in the developing embryo lies next to another particular cell at a certain

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time, changing the microenvironment (17). Clinical variability among individuals with the same genotype may thus be determined by chance alone (17). Second, there may be minor but potentially significant differences in the intrauterine environment, such as inequalities in fetal blood supply, that may have an impact on growth and development. As most recently highlighted by research on HIV disease, identical twins may be discordant for developing infection despite exposure to the same viral agent in utero. Third, these stochastic or intrauterine environmental differences can influence epigenetic mechanisms such as imprinting or X-chromosome inactivation that may also differentially affect individuals with the same inherited genotype, even in monozygotic twins. These postzygotic differences have been observed in discordant monozygotic twins with fragile X mental retardation (19) and Rett syndrome (20). Fourth, after conception, *de novo* mutations may occur at any time, causing both genotypic and phenotypic differences between individuals who originally inherited the same initial genotype (18). Such a “second-hit” mutation could produce either a protective or a deleterious effect on the individual who carries a genetic susceptibility to schizophrenia. An illustration of a protective effect associated with the observation of incomplete penetrance is provided by a recent molecular genetic study of deafness. It reported that an autosomal dominant modifier locus appears to suppress the deleterious effects of an autosomal recessive locus for deafness on another chromosome (21). Thus, both nongenetic (for example, chance or epigenetic mechanisms) and genetic (*de novo* mutations) factors may explain the incomplete penetrance observed in discordant monozygotic twins in schizophrenia (16).

Belief

The clinical variability of schizophrenia means that multiple genes and other factors must be involved.

Variable expressivity (variable extent and intensity of phenotypic signs among individuals with the same genotype), a common feature of most genetic conditions (18), is also likely in schizophrenia (2). Schizophrenia spectrum disorders such as schizoaffective disorder, nonaffective psychoses, and schizotypal and paranoid personality disorders likely represent variable expressions of the same disorder as schizophrenia. Family studies (22) and twin studies (13) have indicated that, although schizophrenia and mood disorders may be largely separate entities, in some families these 2 conditions may be genetically related. Interestingly, one of the significant linkage findings in schizophrenia is to a region on chromosome 13q (4,5) that has recently been reported to show significant linkage to bipolar disorder (23). This clinical variability is not necessarily due to multiple different genes. As exemplified by neurofibromatosis and most other genetic conditions, even single-gene disorders demonstrate variable expressivity, the mechanism of which is unknown but likely

includes genetic background, epigenetic and non-genetic factors (18).

Belief

There are so many genes for schizophrenia it will be impossible to find any single one of them.

As with most genetic conditions, there are likely to be several genetic forms (genetic heterogeneity) of schizophrenia (2). Even with substantial genetic heterogeneity, however, research into other complex disorders suggests that gene localization should be possible. For example, research involving families multiply affected with either syndromic or non-syndromic forms of deafness has led to the identification of over 35 loci (24) and 18 genes (25) related to familial (mendelian) forms of hearing impairment. These molecular genetic discoveries have led to new understandings of the etiology, nosology, and pathogenesis of human deafness (24). Alzheimer's disease presents another example where several genes have been identified (26). However, genetic heterogeneity reduces the power of linkage studies to localize susceptibility genes for disorders, including schizophrenia.

Genetic Linkage Studies. Announcements about possible genetic findings for schizophrenia have occurred many times in the past decade or so. At the same time, the field of schizophrenia genetics has appeared to be struggling with the localization and identification of susceptibility genes. Guidelines for linkage studies of complex disorders (27) are therefore essential to help interpret this plethora of genetic findings. Results from 14 complete genome scans (systematically testing linkage of schizophrenia to DNA markers across the human genome) have been published (3,5,28–39), representing a significant body of work. Two of these genome scans (3,5) have produced linkage results that satisfy strict criteria for statistical significance (27) on chromosomes 1 and 13. The finding on chromosome 1q21-q22 (3) is particularly likely to lead to a susceptibility gene for schizophrenia because it meets criteria for “highly significant” linkage (27). The fact that there are significant linkage findings to 2 different chromosomes in the same set of Canadian families with familial schizophrenia (3) supports the likelihood of multiple genetic etiologies in schizophrenia.

Effects of Genetic Heterogeneity on Power to Localize Genes for Schizophrenia. Only 2 of the 14 genome scans reported to date have presented the results of analyses under the model of genetic heterogeneity; that is, the possibility that fewer than 100% of study families were linked to the locus in question (3,28). The results of these simulation studies illustrate how genetic heterogeneity reduces the power to localize susceptibility genes. Coon and others (28) reported that the power to detect linkage using conventional significance thresholds was 70% if a single gene was involved in all of the families in the study and the marker used was located at the involved

gene. However, if the gene was not involved in disease in only 20% of families, then the chance of detecting linkage dropped precipitously to 18% to 39%, depending on the mode of inheritance. Similarly, Brzustowicz and others (3) predicted excellent power to detect linkage when a single gene was active in all or most families, even if the gene were located halfway between 2 markers. However, power in this study dropped to 50% to 75% when the gene was not active in 25% of families.

Belief

There are no consistently positive genetic findings for schizophrenia.

Familial Forms of Schizophrenia Many genome scans and related linkage studies have produced “suggestive” but non-significant linkage results involving a number of different chromosomal regions, contributing to the sense that there are no consistently positive genetic findings. Repeated suggestive findings, while not significant on their own, might nevertheless contribute some support for linkage to a given area. One problem in determining when a series of such suggestive results might be supporting linkage to the same gene is that the ability to precisely localize a linked gene is poor, particularly when power is low. Roberts and others have recently demonstrated that the localization of a linked locus can easily vary from 10 to 30 centimorgans (cM, genetic distance) in sequential samples, with larger variations in position as the power of the samples decreases (40). This variation can easily span several cytogenetic bands on a chromosome and contain many hundreds of genes. Table 1 lists the 2 regions with significant linkage results as well as regions from full genome scans where 3 or more suggestive findings (at pointwise $P < 0.01$) have clustered within a 20 cM interval. In addition to the results from the 14 full genome scans, the results reported to date from the Irish Study of High-Density Schizophrenia Families (41–44) are also included. Only the marker with the highest score is listed when multiple adjacent markers from one study met significance criteria for listing.

While it might initially seem that it is unlikely for 3 independent studies to map a susceptibility locus at the $P < 0.01$ level to the same 20 cM interval, this will in fact happen not infrequently in a series of 15 consecutive genome scans that each test between 300 and 450 markers. It is unlikely, however, for 4 such studies to map a locus to the same interval, and it is also unlikely that all of the loci mapped by only 3 studies are false positives. A reasonable interpretation of these results would therefore seem to be that there are true schizophrenia susceptibility loci located on chromosomes 1q21–q22, 6p24–p23, 10p14–p11, and 13q32, with additional loci possible at chromosomes 2q11–q14, 8p21–p22, and 10q23–q24. Evidence from this collection of studies supports the concepts of multiple susceptibility genes and genetic heterogeneity in schizophrenia.

A Syndromic Form of Schizophrenia. Further evidence for genetic heterogeneity in schizophrenia involves the recent description of a syndromic form of schizophrenia. The schizophrenia susceptibility locus associated with 22q deletion syndrome (22qDS) involves a physical genetic abnormality: a small deletion on chromosome 22q. This deletion is detectable with a clinically available blood test involving a specialized type of chromosomal analysis, fluorescence in situ hybridization, using a molecular probe from the commonly deleted region (45). Approximately 25% of individuals with this syndrome develop schizophrenia (46), and up to 2% of individuals with schizophrenia may have 22qDS (47), indicating that 22qDS is a syndromic genetic subtype of schizophrenia (7–9). Rates of 22qDS in subpopulations of schizophrenia, such as childhood-onset schizophrenia (48) or dual-diagnosis schizophrenia and mental retardation (49), are likely to be significantly higher (50).

The clinical, structural brain, and cognitive profiles of 22qDS schizophrenia are all similar to other forms of schizophrenia (6,51,52). However, 22qDS, which encompasses velocardiofacial syndrome and DiGeorge syndrome (53), has multiple other associated features, including learning difficulties, mental retardation, characteristic facial features, palatal anomalies, cardiac defects, hypocalcemia, and thrombocytopenia (54). The phenotype is highly variable and often subtle, and 22qDS is therefore underrecognized, especially in adults (7,54), but may be detected using clinical screening criteria (7). The phenotype of 22qDS is variable even within families (53)—including monozygotic twins (55,56)—with the same extent of deletion. The expression of the behavioural phenotype as a psychiatric illness most commonly takes the form of schizophrenia, although other psychiatric disorders, including mood disorders, may be expressed (46,54,57,58), and many adults with 22qDS have no diagnosable psychiatric phenotype. Interestingly, 22qDS-schizophrenia usually presents as a “sporadic” form of schizophrenia because most cases of 22qDS that are identified involve spontaneous mutations (7,50).

Belief

If schizophrenia is associated with a genetic syndrome, it is not schizophrenia.

This is a frequently expressed belief with respect to 22qDS and schizophrenia. Schizophrenia as a diagnostic classification comprises a collection of signs and symptoms describing an entity that has clinical utility with respect to treatment and prognosis, but not necessarily individual causation. This is equally true for many other medical conditions, such as deafness, where there are multiple syndromic (associated with multiple non-hearing-related features) and nonsyndromic (hearing alone affected) etiologies, none of which detract from the usefulness of the diagnostic designation. Interestingly, syndromic deafness is also genetically heterogeneous,

Table 1. Chromosomal regions with significant linkage results and/or 3 or more suggestive linkage findings for schizophrenia

Chromosomal region	Study	Marker	Map position ^a	Range
1q21–q22 ^b	<i>Brzustowicz and others (3)</i>	<i>D1S1679^c</i>	170.84	10.65 cM
	Shaw and others (29)	D1S196	181.49	
2q11–q14	Moises and others (30)	D2S135	116.02	9.16 cM
	Faraone and others (31)	D2S293	118.16	
	Levinson and others (32)	D2S410	125.18	
6p24–p23 ^b	Bailer and others (39)	D6S309	14.07	18.55 cM
	Straub and others (41)	D6S296	14.07	
	Moises and others (30)	D6S274	32.62	
	Schwab and others (35)	D6S274	32.62	
8p21–p22	Kendler and others (42)	D8S1715	39.25	10.80 cM
	Brzustowicz and others (3)	D8S136	43.96	
	Blouin and others (5)	D8S1771	50.05	
10p14–p11 ^b	Ekelund and others (38)	D10S2325	32.80	12.90 cM
	Straub and others (44)	D10S674	41.79	
	Faraone and others (31)	D10S1423 ^d	44.72	
	Schwab and others (35)	D10S1714	45.70	
10q23–q24	Levinson and others (32)	D10S1239 ^d	125.44	13.03 cM
	Rees and others (36)	D10S190	138.47	
	Williams and others (37)	D10S542	138.47	
13q32 ^b	<i>Brzustowicz and others (3)</i>	<i>D13S779^c</i>	82.93	1.94 cM
	Blouin and others (5)	D13S779 ^e	82.93	
	<i>Blouin and others (5)</i>	<i>D13S174^c</i>	84.87	

^aMap position in cM from pter (end of the short arm of the chromosome) on Marshfield sex-averaged maps.

^bRegion where true schizophrenia susceptibility loci are most likely to be located according to significant or multiple (>3) suggestive findings.

^cSignificant finding (27) (shown in italics).

^dPosition inferred from comparison with other maps.

^eResult from independent replication sample reported in same study.

and even clinical subforms of individual syndromes, such as Usher's syndrome, have been found to have several causal genes (24). An example that may be more familiar in psychiatry is the dementia associated with Down syndrome (trisomy 21). This dementia is called Alzheimer's disease because this is the best descriptor for the clinical and neuropathological entity commonly found in older Down syndrome patients. This association between Down syndrome and Alzheimer's disease also aided in finding a disease gene (beta amyloid precursor protein) on chromosome 21 for a familial form of Alzheimer's disease (59).

We can therefore consider 22qDS as a syndromic form of schizophrenia of immediate clinical utility, separating patients with this subtype from other forms (7,50). In contrast to individuals with other forms of schizophrenia, diagnosis of 22qDS can alter medical management and affect prognosis with respect to known associated conditions, such as hypocalcemia, and has important genetic counselling

implications (60). In addition, receiving a specific genetic diagnosis may relieve parents of guilt or inappropriate blame for causing behavioral manifestations of the condition (61).

Belief

Researchers need to know more about the mechanism of illness before finding genes.

While knowledge about a consistent neuropathology, as in Alzheimer's disease (26), may clearly be helpful when isolating disease genes, the molecular mechanism of illness is often uncovered after a gene is found. Positional cloning is an approach to gene identification that requires no prior knowledge of pathophysiology (62). The first step is localizing a susceptibility gene to a specific chromosomal location through linkage analysis. The region containing the gene is then narrowed through the testing of additional DNA markers and additional subjects. Next, genes within this minimum genetic region are identified, a process now aided by the Human Genome Project (63), and screened for possible mutations in affected individuals. The rate of any identified mutation is compared in subjects and in unaffected individuals to determine if the mutation is associated with the disease under study. If an association is suggested, functional experiments would subsequently be conducted to determine how the gene and mutation may be involved in the etiology of the disease.

Belief

Genes involved in the dopamine and serotonin systems are prime candidates for causing schizophrenia.

The dopamine and serotonin systems are implicated in the pathogenesis of schizophrenia largely because of their involvement in the presumed mode of action of antipsychotic medications. Candidate genes involved in monoamine neurotransmission have been widely used in association studies of schizophrenia (64). Although results are not conclusive and the null hypothesis cannot be confidently rejected, a recent review of candidate gene studies in schizophrenia, aided by metaanalyses involving large samples, indicated that both the serotonin 5HT_{2A} receptor gene on chromosome 13q14–q21 and the dopamine D₃ receptor gene on chromosome 3q13.3 have shown stronger evidence to date for association with schizophrenia than any other candidate gene variants (64). The large number of association studies and the variable methods used make this area especially difficult to evaluate.

Association studies assess genes of small to modest effect in a disease, in contrast to linkage studies that assess genes of moderate to large effect. The low prior probability of any candidate gene selected, given the almost limitless possibilities of candidate genes for illnesses of unknown pathogenesis, and multiple testing issues mean that a stringent burden of statistical proof needs to be placed on positive results (64). In addition, samples used are often underpowered, limiting the ability to draw conclusions from negative studies (64).

Most of association studies in schizophrenia are case-control studies, which have the advantages of being powerful for determining small genetic effects, using samples that are relatively easy to collect, and requiring simple statistical methods of analysis. However, the most notorious flaw in case-control studies is that of poorly matched controls, which can lead to population stratification, and therefore the possibility of false positive results. The presence of population stratification can be determined by typing the sample with random markers from various regions of the genome (65). If the groups are well matched, allele frequencies of these random markers should not differ appreciably between cases and controls (65). However, none of the approximately 35 schizophrenia association studies published in 2000 used this relatively simple procedure. Also, many of the case-control studies from 2000 that had negative findings did not appear to have reasonable power to detect association to the candidate genes tested.

Belief

A gene has already been found for schizophrenia.

No definitive causative mutations in a specific gene have yet been identified for schizophrenia. However, recent studies have identified specific chromosomal regions that are genetically linked to schizophrenia. Such linkage studies identify a specific region of DNA that likely contains a gene involved in schizophrenia. Other studies have indicated there is a syndromic form of schizophrenia that is identifiable using clinically available methods. While a discrete chromosomal region is involved in the 22q deletion syndrome, a specific causative gene in this region has not been identified. Finally, the results of association studies to date also do not meet criteria for definitive implication of any specific gene in schizophrenia (64).

Belief

If schizophrenia is genetic, you can't do anything about it; causal environmental factors would be much easier to control.

Consideration of certain traditional genetic models, such as fully penetrant single-gene autosomal recessive conditions that are diagnosable at birth (such as cystic fibrosis) but with limited therapeutic interventions available, or autosomal dominant conditions that may have later onset followed by

inexorable degeneration (such as Huntington's disease), has not been helpful for schizophrenia. These traditional genetic models may encourage the fallacy of genetic determinism—that all gene carriers will develop the (untreatable and unmodifiable) disease. They may also make it appear necessary to generate environmental explanations for the nonmendelian observations in schizophrenia genetics. While there is little evidence for environmental factors as the primary cause of schizophrenia (16), environmental factors are likely to be important modifying factors for age at onset and other manifestations over the course of illness.

More hopeful models of gene-environment interaction are available even among single-gene disorders. Phenylketonuria is a classic example of an autosomal recessive, single-gene disorder that, in the presence of a normal diet, produces mental retardation. The understanding of the biochemistry of this disorder (altered phenylalanine metabolism) led to the simple dietary intervention of reducing phenylalanine intake to control blood levels and toxic effects, thereby greatly improving cognitive outcomes. There may be similarly ubiquitous environmental influences that interact with the genetic causes of schizophrenia to produce the illness. Understanding the genetics of schizophrenia should aid in the identification of any modifying environmental factors that may be more directly amenable to intervention than the underlying gene mutations. However, the fact that most psychiatric illnesses are already treatable makes it particularly likely that new knowledge about molecular mechanisms of illness will lead to further treatment advances. Genetic discoveries can also mean that targeting of specific treatments to specific molecular subtypes of the disorder may become possible, as it has in some forms of cancer (66).

Summary

Many misconceptions currently exist about the implications of the genetic etiology of schizophrenia. There is a clear genetic basis for the disease, and while the complex genetic nature of the illness certainly poses a great challenge for investigators currently seeking causative genetic mutations, multiple independent research programs are converging to identify a relatively small number of chromosome locations that appear to contain schizophrenia susceptibility genes (see Table 1). A clinically relevant genetic subtype of schizophrenia (22qDS) has also been identified. We are developing a better understanding of how schizophrenia relates to other genetic and psychiatric disorders. While investigations into the possible roles of dopaminergic and serotonergic systems continue, other approaches that do not require such detailed theories of the mechanism of illness are also being used to identify candidate susceptibility genes. The future undoubtedly will hold many additional challenges as we seek to develop useful clinical applications from our increased understanding of the genetics of schizophrenia. However, the progress to date

suggests that our understanding of the pathophysiology of this illness will likely soon be fundamentally altered by the synergy of genetic and other approaches to this complex disease (67).

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Implications:

- There is a clear genetic basis for schizophrenia with little evidence for environmental factors as the primary cause.
- There is a clinically relevant genetic subtype of schizophrenia, 22q deletion syndrome.
- Ongoing genetic studies indicate that our understanding of the pathophysiology of major psychiatric disorders will likely soon be fundamentally altered, with exciting prospects for new treatments and other interventions.

Limitations:

- No definitive causative mutations in a specific gene have yet been identified for schizophrenia.
- There are likely many genes that predispose to schizophrenia and environmental and other factors that modify gene expression.
- Misconceptions about the genetics of psychiatric illness may be barriers to understanding how genetic discoveries could change clinical practice.

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Résumé— Vues génétiques en schizophrénie

Objectif : *Présenter les nouvelles vues de l'étiologie génétique sur la schizophrénie.*

Méthodes : *Nous présentons plusieurs opinions répandues sur les questions génétiques concernant la schizophrénie.*

Résultats : *La nature génétique complexe de la maladie pose un défi aux chercheurs à la recherche des mutations génétiques causales. Toutefois, de multiples résultats de recherches indépendantes convergent vers l'identification d'un nombre relativement petit d'emplacements chromosomiques qui semblent contenir les gènes de susceptibilité à la schizophrénie. De même, on a identifié un sous-type génétique cliniquement pertinent de la schizophrénie (délétion 22q11.2). Nous comprenons de mieux en mieux la façon dont la schizophrénie est reliée à d'autres troubles psychiatriques. Bien que les recherches se poursuivent sur les rôles possibles des systèmes dopaminergique et sérotoninergique, d'autres approches qui ne nécessitent pas de théories sur le mécanisme de la maladie sont également utilisées pour identifier les éventuels gènes de susceptibilité.*

Conclusions : *Les progrès à ce jour indiquent que notre compréhension de la pathophysiologie de la schizophrénie sera probablement bientôt fondamentalement ébranlée par les approches génétiques de cette maladie complexe.*