At Issue: Genes, Experience, and Chance in Schizophrenia—Positioning for the 21st Century

by Steven O. Moldin and Irving I. Gottesman

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Abstract

Genetic factors make important contributions to the etiologies of schizophrenia. The mode of familial inheritance remains unknown, but it is highly likely that multiple genes and idiosyncratic environmental factors are involved. Rapidly evolving genetic technologies have been applied in the genetic analysis of schizophrenia, and several genomic regions have been posited as harboring susceptibility genes. Currently, the strongest evidence implicates chromosomes 6 and 8, but these linkages are not yet confirmed. In this article we discuss genetic risk factors, gene–environment interaction, the feasibility of genetic testing, psychiatric genetic counseling, and the dangers of genetic discrimination as they apply to schizophrenia. We also address and correct specific misconceptions about the genetics of schizophrenia held by many in the scientific community and in the media, and discuss a blueprint for future genetic research and informed dissemination of findings to the public and to lawmakers.

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Schizophrenia, which afflicts about 2 million adults in the United States and has an estimated total yearly cost of over $70 billion (Wyatt et al. 1995), is clearly a major public health concern. Family, twin, and adoption studies conducted over the past 30 years have provided very strong evidence that both genes and environment play a role in its complex etiology (see Gottesman 1991; Kendler and Diehl 1995). In this article we discuss genetic risk factors, gene–environment interaction, the feasibility of genetic testing, psychiatric genetic counseling, and the dangers of genetic discrimination as they apply to schizophrenia. Our discussion serves as a bridge between past work and the next decade or more of intensive genetic research on schizophrenia.

Studies of Familial Transmission

Although the majority (>80%) of individuals who are first-degree relatives of someone with schizophrenia do not themselves develop schizophrenia, data from more than 40 family studies spanning seven decades of research consistently show that risks to different relatives of affected individuals are in fact significantly greater than the population risk (Gottesman 1991). Risk varies as a function of the degree of genetic relatedness to an affected individual, with the highest risk (48%) being to the monozygotic (MZ) cotwin of an affected individual—these two individuals share 100 percent of their genes in common.

The median MZ concordance rate (46%) for schizophrenia is approximately three times the corresponding dizygotic (DZ) concordance rate (14%) in six twin studies published in the past 25 years (Prescott and Gottesman 1993). This MZ:DZ ratio of more than 3:1 strongly implicates genetic factors, and the MZ concordance rate of significantly less than 100 percent implicates the role of nongenetic factors.

Model fitting using schizophrenia twin data from recent studies yielded a heritability of 89 percent, with no contribution from the common environment (McGuffin et

Reprint requests should be sent to Dr. S.O. Moldin, NIMH, NIH, Parklawn Bldg., Rm. 10C–26, 5600 Fishers Lane, Rockville, MD 20857. (email: steve@kohut.nimh.nih.gov)

al. 1994). A model of somewhat lower heritability (74%), also without contribution from the common environment, provided the best statistical fit to the transmission of definite schizophrenia in an earlier analysis of twin and family data (McGue et al. 1983). Nongenetic factors that influence risk to schizophrenia are thus likely to be nonshared environmental effects: that is, systematic or nonsystematic idiosyncratic environmental events.

A polygenic (multilocus) model has been supported consistently—and a single major gene model excluded consistently—in the quantitative analysis of actual and simulated schizophrenia family data (Gottesman and Shields 1967; Rao et al. 1981; O'Rourke et al. 1982; McGue and Gottesman 1989; Moldin 1994). Risk ratios for classes of relatives of schizophrenia probands in pooled Western European twin and family studies were consistent with the influence of two or three major loci in interaction (Risch 1990). These empirical observations are congruent with a multilocus model for schizophrenia proposed 30 years ago (Gottesman and Shields 1967).

In summary, it is clear that a single major locus does not account for a large proportion of the familial aggregation of schizophrenia. The number of susceptibility loci, the disease risk conferred by each locus, and the degree of interlocus interaction all remain unknown.

Gene–Environment Interaction

Environmental effects that likely contribute to liability to schizophrenia include nonspecific stressors, obstetrical complications, and illicit drug abuse (Gottesman 1991). However, the predictive power of these factors for a schizophrenia phenotype (i.e., the probability of developing schizophrenia given the exposure to one of these factors) is low.

The Finnish Adoptive Study of Schizophrenia found evidence for gene–environment interaction, with genes controlling sensitivity to the environment (Tienari et al. 1994). Communication deviance in adoptive parents based on projective test results—a nonspecific environmental factor commonly found in many families—in conjuction with high genetic risk was associated with increased risk to schizophrenia.

Data on gene–environment interactions in schizophrenia have been provided from studies of African-Caribbean subjects who emigrated to the United Kingdom. Sugarman and Craufurd (1994) found that the parents of African-Caribbean and white schizophrenia patients had approximately similar increased risks for developing the disorder (i.e., genetic predisposition is an important risk factor for schizophrenia in the African-Caribbean community). However, the sibs of second-generation African-Caribbean probands who were born in the United Kingdom were at significantly greater risk than any other relative group (i.e., environmental risk factors more common in the African-Caribbean immigrant community are operative). Hutchinson et al. (1996) replicated this result and found that, although morbid risks for schizophrenia were similar for parents and sibs of white and first-generation African-Caribbean patients, the morbid risk to sibs of second-generation African-Caribbean psychotic probands was seven times that of their white counterparts. The rate of schizophrenia among African-Caribbeans in their native environment is markedly lower than the high rates among second-generation African-Caribbeans in London (Bhugra et al. 1996). Therefore, genetic susceptibility, in combination with increased environmental risk factors specific to this population, is likely responsible for an excess of schizophrenia in this immigrant population. Possible candidate environmental risk factors include prenatal rubella infection, cannabis abuse, psychosocial factors such as failed assimilation, or other environmental factors common only to a particular birth cohort (Hutchinson et al. 1996).

A large-scale path analytical study for schizophrenia involving twins and a careful assessment of putative environmental risk factors (e.g., Kendler et al.'s [1995] study of major depression) has not been done. Such a study may permit discrimination between two models: an additive one versus one specifying genetic control of sensitivity to the environment (Kendler and Eaves 1986; Kendler et al. 1995). In the additive model, increases in risk associated with exposure to environmental risk factors are similar for individuals with low- and high-risk genotypes—environmental and genetic risk factors operate independently. In a model that specifies genetic control of sensitivity to the environment, increases in liability associated with exposure to environmental effects are greater for those with high-risk genotypes; thus, genes alter individual sensitivity to the schizophrenia-inducing effects of particular environmental factors. The interaction of genetic liability and environmental factors (stressful life events) in major depression was best explained by the latter model in a large population-based sample of female twins (Kendler et al. 1995). Such a model will likely permit a more accurate understanding of the etiology of schizophrenia, in which genetic and environmental risk factors interact in a complex way.

Linkage Studies

Despite the inability of the single locus model to explain the familial aggregation of schizophrenia, investigators have conducted traditional linkage studies under single

locus model assumptions. Evidence consistent with single locus inheritance was provided by a report of linkage of deoxyribonucleic acid (DNA) polymorphisms on chromosome 5 to schizophrenia in a sample of British and Icelandic pedigrees (Sherrington et al. 1988). However, numerous nonreplications of this finding have been published. A combined reanalysis of several data sets (McGuffin et al. 1990), among them the original report (Sherrington et al. 1988), excluded a susceptibility locus from chromosome 5. Analyses of chromosome 5 microsatellite markers in a new sample of British and Icelandic families led to exclusion of the entire region implicated on chromosome 5, and it is now clear that the original linkage report (Sherrington et al. 1988) was most likely a false-positive result (Gurling and Sharma 1994).

In the genetic investigation of complex diseases, it is of crucial importance to adopt a sufficiently stringent standard for the declaration of linkage in order to maintain a high likelihood that the assertion will stand the test of time. To infer linkage to a given chromosomal region, it is necessary to compare the odds in favor of the hypothesis of linkage versus the odds in favor of the hypothesis of no linkage. The odds ratio is expressed as the likelihood, or probability, of these events; the common logarithm of this likelihood ratio is the so-called lod score. In studies of classical Mendelian diseases, where the mode of familial transmission is known, the lod score criterion for declaring a linkage is 3. The nominal significance level (p value) of a lod score of 3, when testing a single marker in large samples, is 0.0001 (Ott 1991); that is, there is a probability of 0.0001 of encountering a lod score of 3 or larger under the null hypothesis of no linkage. A lod score of 3 can also be expressed in terms of an odds ratio: the observed data are 1,000 times more likely to arise under a specified hypothesis of linkage than under the null hypothesis of no linkage. The lod score and p value obtained in a sample will depend on whether there is linkage, on the informativeness of the marker, and on sample characteristics (e.g., the sample size, number of affecteds).

Ever-evolving genetic methods and technologies now permit systematic screening of the entire human genome as a strategy for the identification of susceptibility genes of small effect that influence risk to complex traits, such as coronary artery disease, obesity, schizophrenia, diabetes, inflammatory bowel disease, and multiple sclerosis. Increasing the numbers of markers being tested requires adjustment to the lod score cutoff of 3 used when testing a single marker, in order to prevent inflation of the Type I error rate. Lander and Kruglyak (1995) have proposed a set of guidelines to facilitate interpretation of linkage results of complex diseases. They distinguish the nominal significance level, which is the probability of encountering a linkage statistic (in this case, the lod score) of a given magnitude at one specific locus, from the *genome-wide* significance level, which is the probability that one would encounter such a deviation somewhere in a whole genome scan. A given lod score has a corresponding nominal p value and a genome-wide p value.

Lander and Kruglyak (1995) propose that linkage evidence be evaluated on the basis of genome-wide p values and be classified as either "suggestive," "significant," or "highly significant." Significant linkage evidence that is obtained in a second independent sample (with a less stringent nominal p value of 0.01) is considered confirmed. Suggestive linkage reports often reflect chance findings and are often wrong but worth reporting as tentative findings. Table 1 shows lod score values and associated nominal and genome-wide p values. Although genome-wide significance values are important, interpretation of linkage reports can also be facilitated through the

Table 1. Criteria for evaluating reports of linkage to schizophrenia

Linkage method	Nominal p value	Genome-wide p value	Number of random occurrences per genome scan	Equivalent lod score	Decision classification
Lod score analysis	1.70×10^{-3}	0.632	1.000	1.86	Suggestive
	4.88×10^{-5}	0.049	0.050	3.30	Significant
	6.37×10^{-7}	0.001	0.001	5.10	Highly significant
Allele-sharing methods	7.36×10^{-4}	0.632	1.000	2.20	Suggestive
	2.25×10^{-5}	0.049	0.050	3.61	Significant
	3.02×10^{-7}	0.001	0.001	5.41	Highly significant

Note.—Lod score analysis refers to methods in which lod scores are determined in whole pedigrees; allele-sharing methods refer to the analysis of pairs of affected relatives (thresholds shown are for affected sibling pairs). An "equivalent" lod score associated with the comparable nominal and genome-wide p value is also shown. Genome-wide p values are calculated assuming a human genome 33 morgans in length is scanned using an infinitely dense genetic map. Lod scores are calculated assuming the absence of genetic heterogeneity (i.e., all families are assumed to be linked). Adapted from Lander and Kruglyak (1995).

use of simulated genotype information on the sample to determine the probability of obtaining a false-positive result (e.g., Weeks et al. 1990).

Table 2 lists recent linkage studies in schizophrenia; only published peer-reviewed reports of positive evidence for linkage to defined chromosomal regions are included. A more comprehensive review and critique are provided elsewhere (Moldin 1997, and submitted for publication). Results are discussed below in reference to Lander and Kruglyak's (1995) criteria; only those meeting criteria for suggestive or significant linkage evidence are considered in detail.

The chromosome 6 finding reported by Wang and colleagues (1995) is the strongest evidence thus far for linkage in schizophrenia (genome-wide p value$\approx$0.03). However, correction for testing across multiple diagnostic and transmission models increased this p value to between 0.05 and 0.07. Augmentation of the sample by 79 new pedigrees from the same population, which would be expected to increase linkage evidence, resulted in somewhat *diminished* evidence (Straub et al. 1995); a genome-wide p value of about 0.13 was obtained, without adjustment for testing across multiple diagnostic and transmission models. Suggestive evidence for linkage to chromosome 6 was found in another study (Schwab et al. 1995). Analyses of 713 families contributed by 14 research groups worldwide failed to find more than suggestive linkage evidence to this region (Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 1996). Nonreplications of chromosome 6 linkage have been reported (Gurling et al. 1995; Mowry et al. 1995; Garner et al. 1996; Riley et al. 1996*b*). An additional concern is that the markers inplicated by the studies reporting suggestive evidence (Schwab et al. 1995; Straub et al. 1995; Wang et al. 1995) lie within a very large chromosomal region that contains many genes. S. Wang et al. (1996) found evidence for linkage disequilibrium between schizophrenia and a gene on chromosome 6 that causes spinocerebellar ataxia Type 1. The authors did not state how many other genes were examined, and thus it is difficult to fully interpret the statistical meaning of their finding; if valid, these results would narrow substantially the candidate disease gene region on chromosome 6.

Table 2. Recently reported chromosomal regions for schizophrenia by linkage analysis

Region	Reference
3p	Pulver et al. 1995
5q	Schwab et al. 1997; Straub et al. 1997
6p	Antonarakis et al. 1995; Moises et al. 1995; Schwab et al. 1995; Straub et al. 1995; Wang et al. 1995; Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 1996
6q	Cao et al. 1997
8p	Pulver et al. 1995; Kendler et al. 1996; Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 1996
9p	Moises et al. 1995
20p	Moises et al. 1995
22q	Coon et al. 1994; Polymeropoulos et al. 1994; Pulver et al. 1994; Lasseter et al. 1995; Vallada et al. 1995; Gill et al. 1996

Note.—p refers to the short arm of the chromosome and q to the long arm. See text for full interpretation.

Suggestive evidence for linkage to chromosome 8 was found in two studies (Pulver et al. 1995; Kendler et al. 1996); however, less than suggestive evidence would be obtained if the parametric analyses conducted by Kendler et al. (1996) were corrected for testing of multiple transmission and disease models. Analyses conducted in the collaborative sample of 713 families yielded suggestive evidence for linkage (Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 1996). Exclusion of the families in which the linkage was initially reported (Pulver et al. 1995), but not of Kendler et al.'s families (1996), resulted in suggestive linkage evidence in the remaining subset. At least one study has failed to find linkage to this region (Moises et al. 1995).

The evidence for susceptibility loci on other chromosomes is less compelling. Linkage to chromosome 5 markers was suggestive in one study (Straub et al. 1997) and nearly suggestive in another (Schwab et al. 1997), but at least one nonreplication has been reported (Moises et al. 1995). Suggestive evidence has been found for a schizophrenia susceptibility locus on chromosome 22 (Coon et al. 1994), but nonreplications have been reported (Kalsi et al. 1995; Riley et al. 1996*a*). The results of a large post hoc analysis of multiple data sets, including the one in which suggestive evidence was obtained (Coon et al. 1994), failed to meet the criterion for suggestive linkage evidence (Gill et al. 1996). Potentially suggestive linkage evidence to 6q was reported in each of two independent samples (Cao et al. 1997).

In summary, the strongest linkage evidence to date supports the existence of schizophrenia susceptibility loci on chromosomes 6 and 8; however, the magnitude of the statistical evidence and the existence of nonreplication demonstrate that these are clearly not confirmed, convincing findings. The inability to obtain more compelling evidence may result from one of the following three explanations:

1. Genes on 6 and 8 confer susceptibility to schizophrenia, but they have such a small relative effect on dis-

ease risk that a very large sample is required for their detection; the failure to obtain such evidence in a large collaborative analysis of multiple data sets (Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 1996) reflects a loss of power attributable to methodological differences in diagnosis, ascertainment, or genotyping across studies.

2. Genes on 6 and 8 confer susceptibility to schizophrenia in a small number of families; failures to replicate reflect the confounding effects of genetic heterogeneity.

3. The reported positive results are due to chance.

Unfortunately, these three explanations are currently indistinguishable. Reported linkages to other chromosomes (3, 5, 9, 20, 22) are less compelling.

The inability to replicate findings convincingly thus far may reflect the loss of power afforded in small samples. Suarez et al. (1994) conducted simulations and found that, although detection of a locus of small relative effect for a disease influenced by n such loci is feasible (where $10 \geq n \geq 4$), replication required a sample about $n-1$ times larger than that required for initial linkage detection. Hauser et al. (1996) showed in simulations that at least 400 to 800 affected sib-pairs were required to detect, with reasonable power, gene effects of the magnitude likely to be found in schizophrenia.

The National Institute of Mental Health (NIMH) launched a Genetics Initiative in 1989 to collect family data for the linkage analysis of Alzheimer disease, schizophrenia, and bipolar disorder. The goal was to create a national resource of demographic, clinical, and diagnostic data, as well as DNA extracted from immortalized cell lines, that would be available for the scientific community. Schizophrenia family data have been distributed so far to nine research groups worldwide. As of September 1, 1997, clinical/diagnostic data and DNA samples are available on 624 affected and unaffected individuals from 89 families (16% of all families, including those collected for bipolar disorder and Alzheimer disease, available in the Initiative) that contain 97 affected sib-pairs; "affected" is defined as schizophrenia or schizoaffective disorder-depressive type in *DSM–III–R* (American Psychiatric Association 1987). Information about data access, as well as daily updated descriptive sample information, is available on the World Wide Web at http://www-grb.nimh.nih.gov/gi.html. The NIMH is currently considering options for greatly augmenting the samples.

Association Studies

Association studies offer a different strategy from linkage studies for finding susceptibility genes. The most likely explanations for disease-marker associations are as follows: a disease locus is physically very close to the marker studied, the marker interacts with a second locus that contributes to disease susceptibility, or the marker itself is involved in disease risk. The hope is that, rather than implicating a chromosomal region (as in linkage analysis), a specific gene involved in disease susceptibility can be identified. The traditional method—a population-based association study—involves contrasting the frequency of a marker in patients versus a control population. As discussed elsewhere (Crowe 1993; Gelernter et al. 1993; Kidd 1993), this particular type of association study offers little hope of clear results in the genetic analysis of mental disorders; major problems include the difficulties in choosing the proper controls and in determining the appropriate statistical significance level while maintaining an acceptably low false-positive rate.

However, the use of association studies for the detection of genes through linkage disequilibrium mapping is extremely valuable. An alternative method is the family-based association test (Spielman et al. 1993) in which the two parents of the affected individual (actually, the nontransmitted parental alleles) serve as controls. Risch and Merikangas (1996) recommend using this approach on a large scale to search for associations across the entire genome in future studies. They argue that successful detection of genes for complex diseases may occur with large-scale association analysis of all 50,000 to 100,000 human genes (currently, more than 16,000 have been identified); however, the technology to permit this analysis has not yet been developed.

Advances in Genomic Technology

The development of a new human genetic map (D. Wang et al. 1996) and high-density silicon DNA arrays for accessing genetic information (Chee et al. 1996) is leading rapidly to a new revolution in molecular genetic techniques. The DNA arrays, also referred to as microchips or GeneChips, are silicon chips the size of a thumbnail. Potentially hundreds of thousands of oligonucleotides, a linear sequence of the monomeric units from which DNA or ribonucleic acid (RNA) is constructed, can be synthesized on a single chip and then subjected to hybridization reactions. A fluorescent signal is then detected in a process that takes less than 30 minutes; the relative intensity of hybridization varies across different genomic locations. With current technologies, the complete human genome for one person could be represented on a mere 10 chips.

Microchip technologies greatly facilitate genotyping, DNA sequencing, and mutation analysis that can be

applied to the genetic analysis of schizophrenia. Recent work has demonstrated the utility of DNA microchip arrays in screening individuals for breast cancer gene mutations (Hacia et al. 1996) and in studying gene expression (DeRisi et al. 1996). Ultimately, such methods will permit highly rapid and efficient large-scale screening for linkage and for association. Francis Collins, M.D., Director of the National Human Genetic Research Institute at the National Institutes of Health, has commented in the lay press (Stipp 1977) about the building of silicon DNA arrays to analyze a whole range of disease genes: "You don't have to start all over when you want to study genes for schizophrenia or heart disease" (p. 38).

New robust statistical techniques that rapidly extract inheritance information provided by many genetic markers and permit estimation of disease gene location (Hauser et al. 1996; Kruglyak et al. 1996) offer enhanced power to detect linkage to complex diseases. These new methods rival or surpass the power of current analytical methods that use data from only two or three genetic markers, and they have just begun to be applied to the genetic analysis of schizophrenia (Kendler et al. 1996; Kruglyak et al. 1996).

Considerable media attention has been devoted to the report of the successful cloning of a lamb from the cells of an adult sheep (Wilmut et al. 1997). Although these current cloning techniques are quite inefficient (hundreds of attempts were required for success), this work may have profound implications for future genetic studies. Large numbers of identical copies of animals for genetic studies may be generated more efficiently and used to develop epigenetic and neurodevelopmental models of processes aberrant in schizophrenia (Barondes et al. 1997; Woolf 1997). Such models could encompass primate models of working memory, homeobox genes for neurodevelopment in lower organisms, and genes that control cell adhesion and cell migration.

Studies of Correlated Traits

The sole source of phenotypic data in the linkage studies discussed above is whether or not the person is affected with schizophrenia based on psychiatric diagnosis. Simulation studies indicate that individual loci with effect sizes likely to be found in schizophrenia may be detectable by employing multivariate genetic analyses (Moldin 1994, and in press; Moldin and Van Eerdewegh 1995). Linkages of two biological traits believed to be genetically related to schizophrenia, a neurophysiological deficit and eye-tracking dysfunction, have been reported on chromosomes 15 (Freedman et al. 1997) and 6 (Arolt et al. 1996), respectively. Unfortunately, multivariate methods to analyze the trait and schizophrenia simultaneously were not employed in either study; thus, if the results are valid, the putative loci identified as influencing the traits in question may exert no influence on schizophrenia.

Feasibility of Genetic Testing

Chromosomal localization is only the first step in the process of finding a disease gene. An identified region of 10 to 20 megabases is large enough to contain hundreds of genes. Although the application of molecular genetic methods to study simple monogenic diseases has resulted in the detection, isolation, cloning, and characterization of disease genes, the challenge is considerable. For example, the time from establishment of linkage to identification of the precise disease gene for Huntington disease was 10 years.

Although it is still premature to talk of identifiable susceptibility genes for schizophrenia, their ultimate identification will provide several benefits for clinical practice: (1) enhancement of diagnosis and risk of prediction in genetic counseling scenarios; (2) identification of gene products and elucidation of the biochemical and pathophysiological bases of diseases; (3) development of new medications and other therapeutic agents; and (4) implementation of gene-replacement therapy, although relatively unlikely at the present time, as a preventive intervention.

Realization of these benefits requires cloning the disease-promoting genes and developing a test to screen for alterations or mutations in those genes. The development and utilization of such a laboratory test for susceptibility gene detection in schizophrenia will require careful consideration of a variety of scientific and ethical issues: an identified susceptibility locus may be one of many and confer only a relatively small increase in risk, the influence of a particular susceptibility locus may be seen in only a small number of families, and environmental effects play an important role in influencing eventual phenotypic outcomes.

The ambiguity of results will undoubtedly limit the utility of such a test. Comparable examples exist for simple monogenic diseases. Occasional Huntington disease patients may have had expansions of $\leq$ 35 cystosine-adenine-guanine repeats, and some individuals with 36 to 39 repeats may not develop the disease (Nance 1996). Although there is a strong association between the apolipoprotein E (APOE) ϵ4 allele and Alzheimer disease, Alzheimer disease develops in the absence of APOE ϵ4 and many persons with APOE ϵ4 escape disease; lack of sufficient specificity or sensitivity has led to the recommendation that APOE genotyping not be used for predictive genetic testing (National Institute on Aging/Alzheimer's Association Working Group 1996).

Likewise, the presence of modifying factors and the fact that the known mutations in the BRCA1 and BRCA2 genes do not account for more than a minority of all cases of disease make susceptibility testing for breast cancer an uncertain endeavor (Friend 1996). However, the recent availability of a $295 test for screening mutations in the BRCA1 gene demonstrates the entrepreneurial and commercial realities that will likely influence genetic testing for schizophrenia and other major mental disorders and that will likely precede a full understanding of the meaning of test results.

Psychiatric Genetic Counseling

Psychiatric genetic counseling is the process by which patients or relatives at risk of a mental disorder with a genetic component are advised of the consequences of the disorder, the probability of transmitting or developing it, and the ways in which the disorder may be prevented, avoided, or ameliorated. The goal is to provide individuals with the maximum amount of information to make their own informed decisions. Psychiatric genetic counseling provides the means to communicate complex genetic information to affected individuals and their relatives while providing the opportunity for individualized risk assessment and discussion of issues related to diagnosis, treatment, risk modification, identification of premorbid behaviors, and current genetic research (Gottesman and Moldin 1992; Moldin 1996). Research and practice in the field of psychiatric genetic counseling are only in the early stages of development. The need among consumers will likely increase when disease susceptibility genes are discovered, and the proactive biotechnology industry will undoubtedly ensure that these genetic findings will be rapidly translated into widely available test kits and diagnostic products—perhaps before full scientific understanding of such results is achieved.

Dangers of Genetic Discrimination

The future development of genetic testing to identify one or more disease susceptibility loci may set the stage for dramatic improvements in diagnosis and perhaps treatment. However, such advances may bring serious social problems that prevent genetics from realizing its true potential for good (Gottesman and Bertelsen 1996). *Genetic discrimination* is discrimination against an individual or his or her relatives because of real or perceived differences from the ideal genome. This definition does not apply to individuals who are affected at the time the discriminatory act occurs. Although the Americans with Disabilities Act of 1990 may play a role in proscribing genetic discrimination and regulating the use of genetic information by insurers, many have argued that discrimination on the basis of genotype should be considered as a separate category from other forms of discrimination. Several States (California, Wisconsin, Ohio, Oregon) have considered legislation specifically addressing the issue of genetic discrimination.

Distinguishing and classifying individuals at different levels of risk are the central activities of the commercial insurance industry. Although life insurance companies presently do not require genetic tests before underwriting policies, the lack of such a requirement is probably a reflection of high testing costs and the rarity of most genetic disorders for which testing is available. However, the development of presymptomatic tests for common mental disorders, together with the marked reductions in cost that will accompany multiple testing conducted on the same sample, may lead to a genetic testing requirement for medical or life insurance. Likewise, increased future accessibility of genetic information in the workplace poses societal risks that can have an impact on employment possibilities, health insurance, and privacy (Rothenberg et al. 1997). Given that schizophrenia is associated with high medical costs and increased mortality (Goodwin et al. 1993), it is possible that information generated from genetic testing will be used by insurance companies—if they are permitted access to it—to deny coverage to or lower the coverage of at-risk individuals.

Several ethical questions raised by the Ad Hoc Committee on Genetic Testing/Insurance Issues appointed by the American Society of Human Genetics (Ad Hoc Committee on Genetic Testing/Insurance Issues 1995) must also be raised in the genetic counseling of schizophrenia: How much should a patient be told about the potential future implications of genetic testing or counseling for insurance reimbursement or coverage? Should patients be advised to obtain life insurance before being counseled? Should genetic information be excluded from medical records before they are released to insurance companies? What are the legal and ethical responsibilities of the primary care physician who has knowledge of and access to genetic information? When is a patient competent to waive his or her right of confidentiality? The answers to these and other complex questions must evolve as the ethical, professional, and legal implications of genetic testing in schizophrenia are explored.

Minimizing Misconceptions

Given that millions of individuals are affected with schizophrenia or related to someone with schizophrenia, and

given the spectacular successes that have occurred in the genetic analysis of simpler genetic disorders such as Huntington disease and cystic fibrosis, there is considerable interest among the general public, the wider scientific community, and the media regarding genetic research in schizophrenia.

A false step in the path of discovery occurred in 1988 with the chromosome 5 linkage report (Sherrington et al. 1988). Similar false-positive reports may be prevented in the future by (1) initial application of linkage analysis using multiple markers in a given chromosomal region; (2) deliverance of diagnostic, pedigree, and genotyping into the public scientific domain as rapidly as possible from the time of the initial linkage report; (3) continued renewed maintenance of replication as the standard for declaring a linkage report "confirmed"; and (4) healthy skepticism about initial linkage reports.

The chromosome 5 finding (Sherrington et al. 1988) was welcomed with considerable optimism and insufficient scientific criticism not only because hopes were raised of identifying a factor that could finally provide clues to pathophysiology and ultimately new treatments, but also because localization of a locus was "confirmation" that schizophrenia was in fact a "biological" and not a "psychosocial" disorder. The long history of stigma associated with schizophrenia further reinforces the desire to see schizophrenia as a genetic or medical condition. Any findings that confirm this expectation are gratifying to many, and thus there is a frequent rush among the public and some members of the scientific community to accept uncritically tentative or preliminary findings as definitive facts.

There are several potential solutions to this problem. First, circumspect presentation and minimal publicity by scientists, their universities, and funding agencies should be given initial linkage reports. Second, to determine the statistical significance of a reported linkage, there should be careful documentation in scientific reports regarding how may different markers were analyzed and how many diagnostic models were employed. Likewise, interpretation in reference to genome-wide p values must be strongly encouraged. The rationale for including or excluding phenotypes as affected also must be explicitly stated. Third, rigorous peer review in high-quality journals of linkage reports to schizophrenia must continue (sole dissemination of findings through undocumented conference reports must be strongly discouraged). Finally, ongoing tutorials about linkage analysis, psychiatric genetics, and findings from prior epidemiological studies must be provided to science writers and other individuals who disseminate information about genetic research to the public and to lawmakers in order to provide them with the knowledge to become informed consumers and critics.

Common Misconceptions and Current Realities

Because of the barrage of information and misinformation that has been reported over the past 10 or so years, the public and many scientists outside the field of psychiatric genetics hold several misconceptions about the genetics of schizophrenia. These misconceptions are listed below, along with appropriate correct information.

- *One gene causes most cases of schizophrenia.* Although a rare gene may be responsible for some cases of schizophrenia around the world, most cases are unlikely to result from a single gene alone. Multiple genes, perhaps in interaction, are responsible.
- *A gene for schizophrenia has been identified.* As discussed above, promising regions of the genome have been targeted as potentially containing a susceptibility locus for schizophrenia. However, convincing replication in independent samples have not been forthcoming. In addition, no specific gene in any of the regions has been identified, let alone one identified with a specific neurochemical defect.
- *The environment is not important in the etiology of schizophrenia.* Environmental factors are clearly of importance in the etiology of schizophrenia. Unfortunately, no specific factor has been found to trigger schizophrenia in many or most cases. Our best leading candidates (e.g., obstetrical complications, illicit drug abuse) are nonspecific and idiosyncratic. These factors are more likely to be implicated in the course of illness, rather than its distal etiology.
- *Genetic testing is available for schizophrenia.* Given that a specific gene has not been identified and cloned, it is not currently possible to do genetic testing for schizophrenia. Given the likely involvement of multiple genes of small relative effect as well as the role of nongenetic factors in etiology, the interpretation of genetic testing that may be developed in the future will likely be fraught with ambiguities and uncertainties.
- *Since there is no gene for schizophrenia on chromosome 5 and strong replication has not occurred for the other loci recently reported, schizophrenia is not a genetic disorder.* The false-positive linkage report involving chromosome 5 markers (Sherrington et al. 1988), as well as recent inconsistencies and the inability to replicate convincingly any of the linkage reports within the past 2 years, does not in any way weaken the considerable evidence gathered over the past three decades that genetic factors contribute to the etiology of schizophrenia. Rather, the lesson is that schizophrenia is a highly complex disorder that is only very slowly yielding its secrets under more and more intensive scientific investigation.

• *The social environment is the cause of schizophrenia.* No consistent evidence exists that the social environment, or any specific nongenetic factor, will induce schizophrenia in individuals who are not genetically predisposed to this condition.

• *Individuals with schizophrenia should not reproduce; prevention of reproduction will lead to the eradication of schizophrenia.* Given that there is an imperfect relationship between genotype and phenotype, with multiple genetic and nongenetic factors intervening to augment or decrease one's risk of developing schizophrenia, there is unlikely to be a way to predict with great certainty who will or will not become affected with schizophrenia. There is absolutely no indication that prevention of reproduction in many or most individuals with schizophrenia will result in a decrease in the population incidence. Many (if not all) of the genes involved may not in themselves confer abnormal phenotypic characteristics; thus, many individuals who are psychiatrically normal, productive members of society may pass along genes predisposing to schizophrenia. In fact, some mutations may confer a selective advantage; for example, some studies report reduced risks of rheumatoid arthritis and cancer for individuals with schizophrenia, but the findings are inconsistent (Jeste et al. 1996). When an individual inherits enough of these predisposing factors and when the environment is sufficiently unfavorable (for a variety of idiosyncratic reasons), illness results.

• *Presymptomatic screening for schizophrenia will soon be possible.* Given our inability to convincingly identify a chromosomal region, much less identify and clone a specific gene, genetic testing or screening is not possible. Presymptomatic screening will always be a highly problematic enterprise because multiple genes and nongenetic factors act together to trigger illness. Thus, it is unlikely that the presence of any one genetic factor will predict clinical illness with acceptably high certainty to make presymptomatic screening beneficial. A case in point can be observed in identical cotwins of individuals with schizophrenia who remain well throughout their lives (Gottesman and Bertelsen 1989; Torrey et al. 1994).

• *Prenatal screening will decrease the incidence of schizophrenia.* Detection of a susceptibility locus for schizophrenia in a fetus will have little practical value because it is highly unlikely that any one genetic factor will predict clinical illness with acceptably high certainty.

• *Population screening can be used to prevent schizophrenia.* At the present time, there is no therapeutic intervention that can prevent the occurrence of schizophrenia. Thus, even if it were possible to predict with great certainty who was going to develop schizophrenia, there is no known drug or other therapy that would prevent illness expression.

A Blueprint for Genetic Research on Schizophrenia

We have made considerable advances in the genetic investigation of schizophrenia. These advances go hand in hand with the development of increasingly more powerful quantitative methods for the statistical analysis of human linkage data, efficient genotyping methods and technologies, and denser maps of the human genome. Genetic research on schizophrenia in the next decade will likely benefit from the following actions:

1. Collection of a sufficiently large sample of pedigrees in which replication can be attempted with sufficient power is warranted. The NIMH Schizophrenia Genetics Initiative now available to qualified scientific investigators offers additional families that have not yet been analyzed, and options are being considered to significantly augment the sample by several hundred families.

2. Independent confirmation by at least one independent group of investigators remains the standard to establish the validity of an initial linkage report. The linkage evidence in at least one report needs to be significant (Lander and Kruglyak 1995) and must remain after sample augmentation (i.e., more families or more subjects per family are added).

3. The true mode of transmission of schizophrenia must be carefully considered and is likely to be as follows: A very small number of cases of schizophrenia are attributable to rare genes, a small number of cases are induced primarily by environmental effects, and most cases are induced by the interactive and coactive effects of multiple genes and nongenetic factors (Gottesman 1994; Sing et al. 1996). A market basket of different models, all multifactorial, are most likely required to fit the family data.

4. Resolution of genetic heterogeneity requires further work on phenotypic classification in order to identify clinical characteristics that can delineate genetically distinct subgroups. Such efforts have resulted in the successful mapping of genes for genetically heterogeneous disorders (e.g., Alzheimer disease, coronary artery disease, and Type I diabetes).

5. Strict blindness on a project must be maintained as clinicians gather pedigree and diagnostic data and laboratory personnel establish genotypes. Maintaining blindness necessitates close collaborative relationships among mental health clinicians, human biologists, genetic epidemiologists, and molecular geneticists in future large-scale schizophrenia projects.

6. Diagnostic models and hierarchies, as well as a justification for classifying specific genotypes as "affected," must be specified clearly *before* statistical

genetic analyses are undertaken. Consistency with prior epidemiological work is expected, but over time phenotypic classification will change with improvements in our ability to identify who has a schizophrenia genotype.

7. Diagnostic and genotyping data should be rapidly placed in the public scientific domain. Inclusion of actual DNA samples in repositories available to the wider scientific community will permit typings of new markers for multipoint analyses. Similar arguments have been made for making available primary data from genetic studies of bipolar disorder (Risch and Botstein 1996). Because of the sensitivity of such information, all personal identifiers must be unlinked from DNA samples to create anonymous samples that are unlinked to their sources, and subjects must be informed that these samples will be used only for specific genetic research (Board of Directors of the American Society of Human Genetics 1996).

8. State-of-the-art techniques for molecular and quantitative analysis must be rapidly applied to the genetic analysis of schizophrenia. New nonparametric methods for multipoint linkage analysis (Hauser et al. 1996; Kruglyak et al. 1996), advances in high throughput genotyping, the development and application of microchip DNA arrays (Chee et al. 1996; DeRisi et al. 1996; Hacia et al. 1996), and the generation of new DNA markers (D. Wang et al. 1996) will revolutionalize the genetic analysis of complex diseases within the next few years. Rapid integration and utilization of these methods in the search for schizophrenia susceptibility genes will further necessitate the development of close collaborative relationships between mental health clinicians and human geneticists.

9. Family-based association tests (Spielman et al. 1993) should be conducted and there should not be an exclusive reliance on candidate gene approaches, which have been shown to be of limited use in the genetic analysis of mental disorders. Future large-scale family-based association analysis across the whole genome (Risch and Merikangas 1996) may greatly facilitate the detection of schizophrenia susceptibility genes.

10. The research on and practice of psychiatric genetic counseling must continue to evolve. Education and counseling will become essential once susceptibility loci are identified and genetic tests are developed. The level of misinformation among the general population regarding the meaning of these developments is likely to be very high. For example, one study found that many well-educated individuals with a family history of breast–ovarian cancer, despite having participated in prior genetic studies and having received information about the genetics of cancer, continued to hold incorrect beliefs: 26 percent thought that a woman without an altered BRCA1 gene cannot get cancer, 40 percent thought that all women with an altered BRCA1 gene will get cancer, and 83 percent thought that the BRCA1 gene causes about half of all breast cancers (Lerman et al. 1996). Likewise, 56 percent of women who tested negative for a limited number of mutant cystic fibrosis alleles did not understand that they could still have an affected child (Loader et al. 1996).

Summary

It is highly likely that multiple genes and random environmental factors are involved in the transmission of schizophrenia; psychosocial factors that may be relevant to course or outcome are not yet implicated in the distal etiologies. The application of rapidly evolving genetic technologies has resulted in the implication of several chromosomal locations as harboring susceptibility genes. The strongest candidate regions to date are on chromosomes 6 and 8, but convincing replications have not occurred. The identification of genetic risk factors, elucidation of gene-environment interaction, exploration of the feasibility of genetic testing, greater sophistication in the clinical practice of psychiatric genetic counseling, and the ongoing elaboration of the dangers of genetic discrimination are essential goals for psychiatric geneticists and interested observers over the next decade.

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The Authors

Steven O. Moldin, Ph.D., is Acting Chief, Genetics Research Branch, Division of Basic and Clinical Neuroscience Research, National Institute of Mental Health, National Institutes of Health, Rockville, MD, and Assistant Professor, Department of Psychiatry, Georgetown University Medical Center, Washington, DC. Irving I. Gottesman, Ph.D., Hon. FRCPsych., is a Sherrell J. Aston Professor of Psychology and Professor of Pediatrics (Medical Genetics), University of Virginia, Charlottesville, VA.

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Providing a forum for a lively exchange of ideas ranks high among the *Schizophrenia Bulletin*'s objectives. In the section **At Issue**, readers are asked to comment on specific controversial subjects that merit wide discussion. But remarks need not be confined to the issues we have identified. **At Issue** is open to any schizophrenia-related topic that needs airing. It is a place for readers to discuss articles that appear in the *Bulletin* or elsewhere in the professional literature, to report informally on experiences in the clinic, laboratory, or community, and to share ideas—including those that might seem to be radical notions. We welcome all comments.—*The Editors.*

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Office of Scientific Information
National Institute of Mental Health
5600 Fishers Lane, Rm. 10-85
Rockville, MD 20857