Recent and Future Molecular Genetic Research Into Schizophrenia

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Abstract

The difficulties anticipated in the application of molecular genetics to schizophrenia research have not prevented the first successful localization of a susceptibility gene for a subtype of schizophrenia. It is argued that this approach is the most useful of the possible molecular genetic strategies because it leads both to enhanced clinical genetic investigation and to further recombinant DNA research to clone and sequence schizophrenia susceptibility mutations. Future recombinant DNA research can now use long-range mapping and cloning techniques such as the chromosome walking/jumping approach and the strategy of cloning brain-specific cDNAs from brain mRNA. The identification of carriers for high-risk studies and the genetic validation of diagnosis appear to be the most promising clinical developments. Prenatal counseling will only become widely feasible when much more is known about the extent of heterogeneity of linkage in schizophrenia.

Schizophrenia has tended to occupy a special position in the genes versus environment debate over human behavior, and geneticists have often tended to be cautious with their hypotheses and claims concerning the genetics of schizophrenia. Quite recently, scientific articles were being written which put schizophrenia beyond the grasp of the methodology that linkage geneticists have been successfully using to detect single major gene effects in the classical Mendelian disorders. These authors claimed that the evidence for single major gene transmission for susceptibility to schizophrenia was untenable (O'Rourke et al. 1982; Sturt and McGuffin 1985; McGuffin and Sturt 1986). No such claims were ever made for certain medical disorders such as multiple endocrine neoplasia (MEN2a), which nevertheless show as much incomplete penetrance and apparent "polygenic" or uncertain inheritance as schizophrenia (Ponder et al. 1988).

Despite the superficial difficulties of working genetically with a disorder that, before successful linkage analysis, had never shown a consistent pattern of genetic transmission, it has nevertheless proved possible to identify a locus on chromosome 5 that confers susceptibility to the development of schizophrenia (Sherrington et al. 1988). The stage is now set to use recombinant DNA techniques to close the genetic gap between the linkage markers and the schizophrenia mutation itself.

A Successful Strategy for Studying Schizophrenia by Linkage

Schizophrenia is associated with reduced fertility, social isolation, and probably a greater than expected familial association with other nonschizophrenic psychiatric disorders. Therefore, it should not have been surprising that these factors could have masked or inhibited the recognition by segregation analysis of single gene susceptibility to schizophrenia. The susceptibility

For definitions of technical terms, see glossary on p 366.

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locus identified on chromosome 5 has been shown to be transmitted as an autosomal dominant gene with incomplete penetrance (Sherrington et al. 1988). Other types of schizophrenia could be recessive, polygenic, or environmental. The factors that contributed to the first successful localization of a schizophrenia susceptibility allele were not described in great detail at the time of publication. To make the design of the study more explicit, the various criteria that were used are listed below:

1. The United Kingdom/Icelandic study chose only to sample medium- to large-sized pedigrees with schizophrenia in at least three generations. In such families a lod score suggestive of linkage could be computed within a single family. The lod scores could therefore be analyzed using computer programs written by Ott (1985, 1986) and Risch (1988) to test the hypothesis that the sample of families was genetically homogeneous.

2. The study chose to select high-density pedigrees so that a suggestive lod score could be computed by considering affected schizophrenic individuals alone. This circumvented the problem of incomplete penetrance, which can rapidly lower the power of the linkage approach if there are many unaffected individuals who are in fact carriers of the susceptibility allele.

3. Careful attention was paid to selecting families without manic-depression (bipolar disorder) present. Families in which both schizophrenia and bipolar disorder (circular manic-depression) were present were in fact encountered. In each instance, however, it was established that there were two independent genetic sources of the two diseases present. This suggested that coexistence of the two disorders within a family was probably due to assortative mating by social homogamy. This was made possible by extensive pedigree-tracing work and showed up in the presence of schizophrenia on one side of a family and manic-depression on another (i.e., "marrying in" of the disorders).

4. Careful attention was paid to obtaining families in which there was only one possible source for a schizophrenia allele segregating into the kindred. This necessitated considerable knowledge about the past histories of the families that were sampled. In Iceland we were aided by the existence of genealogical information which was very extensive and which sometimes recorded the presence of mental illness even though the records were not specifically psychiatric in origin.

5. The study was carried out mainly on a population that has characteristics of a genetic isolate, and this increased the chance of obtaining a homogeneous sample with a single genetic subtype of schizophrenia.

Diagnostic Issues in Schizophrenia Genetics Research

Genetic linkage research is very sensitive to diagnostic error, especially to false-positive diagnosis of caseness. Failure to identify a true case has less severe consequences because such individuals will join the pool of individuals who are either showing recombination or who are nonpenetrant carriers. This group of individuals can receive special attention in the linkage analysis, unlike false-positive cases which will continue to have a hidden negative effect on all types of analysis.

An important element in coming to a valid decision about cases that are difficult to diagnose is the need to obtain information about the life history of the patient and the illness rather than using a single "snapshot" of the illness at one episode. Kraepelin, who coined the term dementia praecox to differentiate schizophrenia from manic-depressive psychosis (MDP), emphasized a deteriorating course, while Bleuler used diagnostic criteria emphasizing psychiatric phenomenology rather than prognosis. Schneider's (1959) attempt to use first-rank symptoms to increase reliability of diagnosis was of limited success (Taylor 1972; Wing and Nixon 1975), although influential in British psychiatry. Thus, there was increasing confusion in the early sixties and seventies as competing diagnostic ideologies led to researchers studying and describing very different populations (Cooper et al. 1982). Attempts to standardize diagnosis over the last 15 years have led to the introduction of Feighner criteria (Feighner et al. 1972) Research Diagnostic Criteria (RDC; Spitzer et al. 1978), and DSM-III criteria (American Psychiatric Association 1980), which are widely used and have narrower definition, greater reliability, and better prediction of prognosis (Brockington et al. 1978). Such diagnostic criteria are now routinely used in genetic linkage research with a resultant improvement in the comparability of findings. Fortunately some of the new diagnostic systems have been investigated in the identical cotwins of schizophrenic probands and the families of schizophrenic patients to give an idea of how sensitive they are for identifying psychopathology genetically related to schizophrenia. Gottesman and Shields (1972) found that very broad or very nar-
row definitions of schizophrenia reduced the ratio of monozygotic (MZ) to dizygotic (DZ) concordance in twins and suggested that the most genetic forms of the illness are found by using definitions of medium specificity. Pope et al. (1982) found that using DSM-III criteria gave low heritability in first-degree relatives of schizophrenic patients, and this suggests that DSM-III is too restrictive, perhaps because of an overemphasis on positive symptoms and recognition of the diagnostic importance of negative symptoms. McGuffin et al. (1984) tested six sets of operational criteria in MZ and DZ twins and found that RDC and Feighner definitions gave the highest concordance in schizophrenia, which would make these criteria the most useful for linkage research.

Schneiderian and Present State Examination (PSE; Wing et al. 1974) criteria gave very low scores indicating that they would be mainly of academic interest when used in genetic linkage studies. In an extension of this work, Farmer et al. (1987) found that the maximum difference in MZ/DZ concordance (i.e., the diagnostic criteria that detected the most heritable schizophrenic features) were for schizophrenia with mood incongruent delusions, schizotypal personality, and atypical psychosis. The effect of including paranoid disorder and all other affective disorders was a reduction in the concordance ratio, suggesting that they were not genetically related to schizophrenia.

The inclusion of bipolar disorder and related schizoaffective illness in family studies of schizophrenia is an important issue. It is already known that schizoaffective disorder is found among pedigree samples of bipolar disorder showing linkage either to chromosome 11 or the X chromosome (Gurling et al. 1988). Schizoaffective disorder, therefore, has already been investigated sufficiently to know that it is sometimes part of manic-depression. Family studies also show that it occurs in association with schizophrenia (Baron et al. 1982). It is not certain whether the association between schizophrenia and schizoaffective disorder in some families is due to the marrying in of two disorders or the consequence of a separate type of psychosis. A further reason for the apparent coexistence of the two disorders within a family may be simple error in diagnosis because it is well known that young manic-depressive patients can receive a diagnosis of schizophrenia that is overturned after the passage of time. Because there are overlapping symptoms in schizoaffective bipolar disorder and schizoaffective schizophrenia, this does not mean that such individuals will share the same prognosis and etiology.

Recent proposals (Kendell and Brockington 1980; Crow 1984, 1986, 1988) for a unitary concept for both the functional psychoses now look increasingly inappropriate given that both the chromosome 11 and X chromosome linkages in manic-depression have been confirmed in two separate samples with total lod scores of above 9.00 for each of the subtypes (Mendlewicz et al. 1972, 1987; Baron et al. 1987; Egeland et al. 1987; Mendlewicz 1988). It seems that the weight of historical opinion, the evidence from MZ twin studies (Bertlesen et al. 1972), and the recent linkage studies of both schizophrenia and manic-depression show that the two disorders "breed true" and segregate independently. The most recent of these is the twin mating study carried out by Gottesman and Bertlesen (personal communication, 1988), which also shows that the two disorders are independent.

Until it is established that there is a true schizoaffective psychosis that is independent of schizophrenia and manic-depression (Baron et al. 1982), it seems illogical to include such cases in family studies of schizophrenia because they will introduce an avoidable source of heterogeneity of linkage for loci on chromosome 11 and the X chromosome.

**Diagnosis in the United Kingdom/Icelandic Study of Schizophrenia**

Before the advent of successful linkage studies, diagnosis has always been based on recurring clusters of clinical symptoms, and such a system may have little or no relation to etiology. Thus, the recent finding of the susceptibility locus for schizophrenia on chromosome 5 represents an opportunity to start an etiological classification based on genetic markers.

The United Kingdom/Icelandic study used the RDC system to study a sample of seven British and Icelandic families containing 104 individuals among which there were 39 individuals with schizophrenia (DOMS model\(^1\)) and 5 with schizoid personality with or without schizotypal features. These groups of patients were classified as schizophrenia spectrum disorders (DOMSS model\(^2\)), and their presence in the sample supports the concept (e.g., Kety 1983; Kendler 1984) of a continuum of schizo-
phrenia ranging from personality disorder to psychosis. There were other nonpsychotic or fringe disorders (DOMSSF model\(^3\)), some of which were rather atypical and required neuroleptic treatment.

The finding that all the traditional subtypes (i.e., paranoid, hebephrenic, catatonic, undifferentiated, and unspecified psychosis) were present in the same families within the sample suggests that one genotype can give rise to clinical diversity. This fact, together with the findings that hebephrenic schizophrenia may be more heritable than the paranoid variety (Winokur et al. 1974; McGuffin et al. 1984), lends some support to Tsuang and Winokur’s (1974) concept of a hebephrenic-paranoid continuum of illness, with the hebephrenic type being the most advanced and severe form.

The highest concordance for linkage was with the broadest definition of psychiatric disorder or case-ness including the fringe phenotypes (DOMSSF). The lod score for this model is now above 7.00. This analysis was planned before data collection, and therefore the lod was calculated with a prior hypothesis. This suggests that the schizophrenia genotype predisposes to other psychiatric conditions apart from schizophrenia, per se, and that these represent a subtle prepsychotic or “forme fruste” of schizophrenia. Such fringe cases may masquerade as a state that appears to be a “depression” or as other neurotic disorders. However, there was clear evidence from our clinical appraisal that there were additional psychological abnormalities present in the fringe cases that were related to schizophrenia.

\(^3\)Dominant gene transmission with schizophrenia, schizophrenia spectrum, and fringe cases counted as affected.

for which the RDC system had no adequate categorization. For example, a patient who appeared chronically and atypically depressed may have been suffering from the effect of a schizophrenia genotype that has manifested in blunted affect, anhedonia, and poverty of thought/speech found in the negative or type-2 form of schizophrenia (Crow 1980). Further evidence that these fringe phenotypes are indeed variant expressions of the same underlying mutation is needed because the elevation of the lod that occurred when they were included as cases for linkage was only about 2.00 (from 5.20 to 7.40 approximately), and this could have arisen by chance.

The lod score for schizophrenia, schizoid personality, and schizotypal disorders was significantly in favor of linkage (lod = 5.20) independently of the fringe cases, so that the evidence for linkage did not depend on the atypical cases.

**Comparison of the Chromosome 5 Linked Subtype With the Swedish and Other Schizophrenia Linkage Studies**

The proportion of schizophrenia that is related to the chromosome 5 mutation is as yet unknown. A similar study in a large Swedish pedigree (Kennedy et al. 1988) with a high density of schizophrenia failed to demonstrate chromosome 5 linkage, suggesting that the genetic factors underlying schizophrenia are heterogeneous. There were quite obvious differences in the way these two samples were ascertained. In the United Kingdom/Icelandic study whenever a sibship was found with affected individuals, then all normal individuals and all those with uncertain diagnoses within a sibship were systematically sampled. The Swedish study adopted a different approach by sampling only definite cases of schizophrenia. This therefore gave the impression that there were few schizophrenia spectrum or schizophrenia “fringe” phenotypes present in the Northern Swedish sample (Kennedy et al. 1988) when in fact the sampling procedure tended to exclude them (Wetterberg, personal communication, 1989). The two samples are not therefore comparable for rates and types of the nonpsychotic schizophrenia-related disorders but are comparable in terms of the schizophrenia subtypes (e.g., paranoid, catatonic, and hebephrenic) among the definite cases of schizophrenia. So far the Swedish sample has not been submitted to an investigation of RDC schizophrenia subtypes, but when this has been done, it will be possible to compare the two samples for any obvious differences in the distribution of subtypes.

Taking the United Kingdom/Icelandic and Swedish studies together, it seems that at least some genetic heterogeneity must exist for schizophrenia with some families being chromosome 5 linked and others not. The proportion which are linked cannot be estimated.

Ott and Risch have proposed formal mathematical tests to detect whether a group of families show linkage heterogeneity. Both tests use as data the lod scores for each family calculated at different recombination fractions and proceed to produce a maximum likelihood estimate of the true recombination fraction. Ott’s computer program, HOMOG, uses the A-test (for admixture test) to compare the hypothesis that all families are linked to the marker against the alternative hypothesis that some
families are linked but others are unlinked, whereas Risch's program (BTEST) is designed also to detect other types of heterogeneity—for example, some groups being more strongly linked than others—and to be less sensitive to variations in family size and recombination fraction. Quite a large amount of data may be necessary to detect heterogeneity when it exists. Ott calculates that one would need 10 phase-known double-backcross families with five meioses each to obtain a power of 67 percent to detect heterogeneity at a 5 percent level of significance.

When these homogeneity tests were carried out on the families from the United Kingdom/Icelandic study, the maximum likelihood estimate for the proportion of families to be linked to chromosome 5 was 100 percent so that not only could homogeneity not be rejected, it was actually the favored hypothesis over heterogeneity in those families. However, this does not necessarily mean that all the families were indeed chromosome 5 linked, and some had only weak positive lod scores. The power of these tests to reject homogeneity is, in fact, rather low, and it will be necessary to be able to incorporate further data from large numbers of other families in the future to detect heterogeneity and accurately assess its extent.

If, in fact, all seven of the United Kingdom/Icelandic families are linked to chromosome 5, then it is possible to use a simple binomial formula to provide a lower limit on the estimated proportion of all such families that are linked. Since 0.65 to the power of 7 is less than 0.05, it would be unlikely (within 95-percent confidence limits) to find seven families all linked if the actual proportion of linked families were anything less than 65 percent. It should be stressed, however, that this figure applies only to families which could have been ascertained with equal probability (i.e., families in the United Kingdom and Iceland with a high density of multiple cases of schizophrenia).

Another recent study of families containing both bipolar disorder and schizophrenia from Edinburgh (St. Clair et al. 1989) has claimed negative results for the chromosome 5 markers found to be linked with schizophrenia in the United Kingdom/Icelandic study. This result needs to be interpreted with caution because of the fact that a substantial proportion of the cases for genetic analysis were bipolar or schizoaffective rather than schizophrenic individuals. Such a number of false-positive cases could easily obscure a positive linkage result.

Before the chromosome 5 schizophrenia result is accepted as being a confirmed linkage, a lod of above 3.85 (Lander, personal communication, 1988) needs to be obtained in two laboratories. This is slightly higher than the usual lod of 3.00 because both the recombination fraction and penetrance need to be estimated jointly. So far, the schizophrenia locus has been implicated in one laboratory. If there had been no prior hypothesis that the susceptibility locus was indeed on chromosome 5 because of the observation of the trisomy/translocation in association with schizophrenia (Bassett et al. 1988), then the evidence against the linkage having occurred by chance would have been slightly weaker.

An independent confirmation of this result, at an early stage, showing widespread involvement of the chromosome 5q11–q13 susceptibility locus would put the chromosome 5 molecular genetic approach to schizophrenia on a high priority. If the subtype of schizophrenia we have identified is rare, then it will serve as a useful model for other types of schizophrenia and may also help to unravel which brain systems are involved, even though different loci may be involved for each subtype.

**Future Clinical Genetic Research**

There are pitfalls for those trying to replicate the chromosome 5 linkage result, and these arise from the clinical characteristics of schizophrenia itself. These problems include variable penetrance and attenuated definitions of caseness for linkage analysis. However, once chromosome 5 linkage has been conclusively excluded in a sample of multiplex schizophrenia families, then there are three further ways of proceeding to find a linkage.

**Identifying Schizophrenia Susceptibility Loci.** The most productive method is likely to be the systematic investigation of loci that have some a priori reason to contain a genetic locus that is involved in schizophrenia. This strategy has already proved successful, and there are many more loci at which cytogenetic abnormalities have been reported in association with schizophrenia. A further method of choosing loci that may be involved is by the observation of an association at the clinical level between a genetic disorder and schizophrenia, where it is plausible that a dual pathology has been caused by the same cytogenetic abnormality. Two genetic diseases associated with schizophrenia are albinism (Baron 1976) and Marfan's syndrome (Romano and Linares 1987). Linkage markers at or near these loci
could be used to find linkage in nonchromosome 5 linked families. The second is the candidate gene approach in which genes with a plausible role in the etiology of schizophrenia are used as linkage markers on the assumption that mutant alleles at the same locus cause susceptibility to schizophrenia. A recently cloned neurotransmitter receptor gene, the D2 dopamine receptor, has yet to be investigated by the use of linkage genetics (Bunzow et al. 1988). The last approach is the random search, which has the advantage of the use of highly polymorphic linkage markers that are more or less guaranteed to provide linkage information in every family.

**Heterogeneity of Linkage and Family Size.** The difficulties that schizophrenia poses for the geneticist lie principally with the tendency for schizophrenic patients to have few children (especially schizophrenic fathers), thus making sibship size in schizophrenic pedigrees rather small in many cultures. Therefore, it is very difficult to prove chromosome 5 linkage in any given family unless there are at least five or six affected individuals in a sample of other like-sized families (Ott 1985, 1986). The sib-pair approach (the sampling of small nuclear families with or without parents) could in theory estimate the proportion of chromosome 5 linked pairs in a sample of sib pairs (Suarez et al. 1978) but cannot provide information about which specific sib pairs are linked as opposed to which sib pairs are unlinked. An accurate estimate of the recombination fraction (genetic distance) between any marker and schizophrenia would be impossible to obtain using the sib-pair approach if heterogeneity of linkage were present. If the goal of a research group was to obtain a sample suitable for accurate mapping of a schizophrenia-susceptibility locus with the eventual objective of cloning and sequencing alleles at that locus, then the sib-pair approach would be of little value. The one exception might be if the sample of sib pairs came from a genetic isolate where homogeneity was strongly suspected with prior linkage data in many families and where the proportion of sib pairs that were of the linked type was estimated to be maximal (i.e., complete linkage was present).

**Exploring Genetic Etiology in Relation to Known Abnormalities in Schizophrenia.** Unless chromosome 5 linkage can be unequivocally established within a certain family, then associated abnormalities in brain morphology and metabolism such as those found on computed tomography, electroencephalography, and positron emission tomography cannot be related to the underlying genotype.

Brain ventricular size is known to be abnormal in some schizophrenic patients (Johnstone et al. 1976; Turner et al. 1986). Although there is no firm consensus, this may be a marker for a less genetic form of the illness (Reveley et al. 1984), especially when associated with perinatal complications (Turner et al. 1986; Owen et al. 1988). This relationship also seems to hold for some familial cases, suggesting that the two etiological factors can operate in a cumulative way (Murray et al. 1988) and providing an example of how penetrance might be affected by environmental factors. The difficulty with much of the previous research that deals with antecedent factors such as birth and perinatal trauma is that it is often uncontrolled for simple demographic variables and is not up to the standard required for good epidemiological research. However, if simple hypotheses are tested with respect to a genetically defined population, the power of these studies can increase significantly in the same way that incorporation of specific indices of the environment can enhance path or variance component analysis of the genetic and environmental components of human behavior (Henderson 1982).

Other workers (Gruzelier 1987) feel that the fundamental feature underlying specific schizophrenia syndromes (positive/negative or type 1/type 2, see below) is the functional state of imbalance between the two cerebral hemispheres and that symptoms are an expression of the more activated hemisphere—the left in the activated syndrome and the right in the withdrawn syndrome. Eye-tracking movements are known to be abnormal in some schizophrenic patients (Holzman et al. 1974) and in some of their relatives (Matthysse et al. 1986), and these abnormalities may be a marker for a genetic subtype of schizophrenia as suggested by Holzman et al. (1988). The role of the electroencephalogram and evoked potentials is unclear, although it has been claimed (Blackwood et al. 1987) that the P300 component of the auditory evoked potential is characteristically abnormal in schizophrenia and manic-depression. It should be possible to determine whether all of the abnormalities described above are found in the chromosome 5 linked subtype of schizophrenia. This should lead to an enhanced ability for psychiatric researchers to pursue separate subtypes of schizophrenia in their own right. If these measures turn out to be weakly
specific to genetic subtypes of schizophrenia and present in other psychiatric disorders, then they may turn out to be epiphenomena of whole groups of mental illness without any specificity.

Advancing Accurate Diagnosis and Prognosis in Schizophrenia. Eventually molecular genetic methods may show that there are truly nongenetic environmentally caused subtypes of schizophrenia. Comparison between the genetic and nongenetic types may lead to a new etiological classification, and this avenue of research could lead to management and treatment advances even in the absence of further recombinant DNA research to clone and sequence the underlying genetic mutations. A more immediate advance that follows from successful linkage for schizophrenia is in the area of clinical variation. Crow (1980) has delineated two separate schizophrenia syndromes. Type 1 consists of positive symptoms and response to neuroleptics, and it is postulated to be due to abnormal brain dopaminergic function. Type 2 consists of negative features and tends not to respond to treatment. The two syndromes are not mutually exclusive, and the mixed type may be quite common and the pure type 2 unusual (Farmer et al. 1987). Twin studies (Dworkin and Lenzenweger 1984) have indicated that negative symptoms may be characteristic of the more strongly genetic form of schizophrenia, so this may be the type with the worst prognosis. Investigation in genotypically defined (i.e., linked) families should help resolve whether these supposed subtypes have any etiological validity.

High-Risk Studies and Incomplete Penetrance. In the United Kingdom/Icelandic study (Sherrington et al. 1988), the best estimate of penetrance was 71 percent for schizophrenia rising to 76 percent for the DOMSS and 86 percent for the DOMSSF models. This implies that for all definitions of genetic case-ness there were a number of individuals with the disease genotype who were clinically normal and did not develop the full syndrome. The Icelandic families studied were genetically isolated and had a high density of illness, so they were selected for high penetrance. The factors influencing penetrance are likely to be a productive research area in the future with implications for preventive psychiatry. The true penetrance for genetic cases of schizophrenia as a whole must be much lower than that observed in the recent linkage studies. Eliot Slater (1972) calculated that if all of schizophrenia was genetic, then the gene frequency would need to be 3.00 percent and the penetrance approximately 15 percent with a dominant pattern of transmission. The corollary of this is that it is unwise to assume that an individual who does not have a family history of schizophrenia has a nongenetic type of the illness. If the penetrance really is as low as 15 percent, then most schizophrenic patients will have inherited the susceptibility from normal parents and will also have unaffected siblings. The cause of the low or variable penetrance of schizophrenia could be environmental, biological, or genetic. There may be evolutionarily determined mechanisms specific to the brain that compensate for mutations affecting behavior so that most individuals with the susceptibility never develop the illness. Polygenic background effects are just as likely to contribute to the variable penetrance as are specific environmental factors such as stressful psychological experiences. However, if clear evidence of environmental precipitants for schizophrenia could be identified acting jointly with the genetic susceptibility, this could lead to dramatic and simple methods of prevention.

Cloning a Schizophrenia Susceptibility Gene. Using classical genetic linkage analysis with affected families as described previously may make it possible to identify a chromosomal region of 1 to 5 centimorgans containing the schizophrenia susceptibility gene. This would require a hundred or more informative meioses in pedigrees linked to chromosome 5, preferably from affected individuals only, as this would be more robust to the problems of incomplete penetrance. The observed heterogeneity (Kennedy et al. 1988) may make this difficult. However, the advantage of the deleted chromosome 5 (Bassett et al. 1988) is that it should be possible to produce a long-range restriction map, including the schizophrenia locus, of ordered but nonoverlapping clones. These maps will provide information on the spatial arrangement of Hpa II, tiny fragment islands that will indicate the presence of possible candidate genes. The selection of specific clones where physical distances match the genetic distance from a known tightly linked marker may enable us to identify candidate loci by chromosome walking and/or jumping. Confirmation of the fact that the gene is expressed in the brain can be carried out by hybridization with brain specific cDNAs to the genomic locus and to northern blots of brain mRNA. The identi-
fication of markers in strong linkage disequilibrium with the schizophrenia susceptibility locus will greatly facilitate the cloning of the affected gene.

The problems of heterogeneity for the establishment of linkage disequilibrium may be overcome in several ways. One way, for example, is to collect a large number of affected individuals, each from a chromosome 5 linked family. Alternatively, by obtaining a large sample of affected individuals from many families, it may be possible to identify linkage disequilibrium with a particular subtype showing through the “noise” of unlinked subtypes. The success of this latter approach depends on the degree of heterogeneity in schizophrenia and the proportion caused by the chromosome 5 locus. The proportion affected could be increased by studying a genetically isolated population that has been subject to genetic drift. The search for linkage disequilibrium could be facilitated by the identification of a particular clinical marker associated with the chromosome 5 linked disorder. It is possible that schizophrenia linked to chromosome 5 may be caused by more than one mutation at the same locus. This would make the search for linkage disequilibrium more difficult. This does not present an insurmountable obstacle to successful cloning of the gene, as such problems were present in the search for the retinoblastoma gene (Dryja 1986).

The rapidly moving field of molecular genetics and the ingenuity of molecular biologists may ultimately enable the cloning of genes conferring a susceptibility to schizophrenia. This would provide fundamental knowledge of the biochemistry of the disease pathway. Consequently, new and more appropriate therapies will be developed.

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