Schizophrenia and the Question of Genetic Heterogeneity

by David L. Garver, Theodore Reich, Keith E. Isenberg, and C. Robert Cloninger

Abstract

Despite major advances in psychiatric diagnosis during the past 20 years, boundaries of the schizophrenic syndrome remain elusive. Moreover, in pedigrees containing cases of schizophrenia there are marked between-pedigree differences with respect to prognosis, familial patterns of psychiatric illness, drug response, and especially association of affected status with a specific chromosomal locus. Such between-pedigree differences suggest the syndrome may be made up of several different diseases. Linkage of affected status to specific loci may aid in resolving genetic heterogeneity. Large multigenerational informative pedigrees may permit the separation into those that do and do not link to a genomic locus of interest. Admixture analysis of smaller informative pedigrees may permit separation of linked and unlinked pedigrees on the basis of differences in the recombination fraction. Finally, biological "markers" can be used before the genetic analysis to separate putative linked and unlinked pedigrees. The combined study of genetic linkage and clinical heterogeneity will aid in the resolution of etiological heterogeneity of schizophrenia and the delineation of meaningful diagnostic boundaries.

Questions about the genetic and biological heterogeneity of schizophrenia begin with the persistent difficulty in defining what is and what is not schizophrenia. Though "schizophrenia" represents a relatively stable syndrome (Cloninger et al. 1985a), its boundaries are not distinct. Most diagnostic systems that attempt to define schizophrenia base the diagnosis primarily on phenomenological features of illness. A few diagnostic systems have extended diagnostic criteria to include certain aspects of course of illness. The three major diagnostic systems used in the Western World (Research Diagnostic Criteria [RDC; Feighner et al. 1972], Diagnostic and Statistical Manual of Mental Disorders Revised [DSM-III-R; American Psychiatric Association 1987], and the International Classification of Disease [ICD-9; World Health Organization 1978]) each have found cause to use somewhat different criteria in the diagnosis of "schizophrenia." Differences in diagnostic criteria result in different estimates of heritability of the syndrome (McGuffin et al. 1984).

While the boundaries of the syndrome itself are indistinct, the presence of subsyndromal forms further confounds validity. The adoption studies of Kety et al. (1975), reanalyzed by Kendler and Gruenberg (1984), found a greater occurrence of nonpsychotic forms of psychosocial morbidity in the biological relatives of schizophrenic patients than in adoptive relatives. These findings have been the basis of the concept of a spectrum of presentations of the same underlying disease. The "schizophrenia spectrum" designates a single disease for which the same underlying genetic process presents in a number of different symptomatic forms. Presently some authors operationally use the "spectrum" concept so broadly as to suggest that any psychosocial morbidity in any member of biological families of schizophrenic patients is related to...
the underlying genetic schizophrenic diathesis. Adding to the boundary problem caused by the different nosological systems, indiscriminate use of the expanded "spectrum" concept can easily make folly of any attempt to differentiate between psychiatric diseases on symptomatic or syndromal grounds. Since family members may manifest syndromal phenocopies as a result of other (nonschizophrenia) processes, the use of wider spectrum cases may confound linkage analysis (see below).

Adding to this confusion of what "schizophrenia" is and is not in its symptomatic or syndromal presentations, other investigators have suggested that several discrete diseases are responsible for similar symptomatic or syndromal presentations. Such investigators tend to see psychotic and "spectrum" symptoms as comparable to "fever": an observable end product or "final common pathway" activated by a host of fundamentally different pathological processes. Similarly, a host of psychiatric investigators now argue that in order to understand psychotic symptoms and other psychosocial morbidity found in certain families, one needs to uncover and diagnose several (as yet undetermined) diseases that underlie and are a necessary cause of schizophrenic (and spectrum) symptoms. Perhaps one of such diseases is a genetic disorder of hippocampal embryogenesis; another disease may be a genetic disorder of presynaptic dopamine autoregulation; a third disease may be a genetic abnormality of neuronal membrane phospholipid regulation; a fourth, a prenatal viral infection affecting neuronal cell migration, etc. Each of such diseases has a single critical common feature: though beginning with different pathological processes often at different sites within the central nervous system (CNS), each of the disease processes eventually converges upon neuronal circuitry whose disruption results in the subjective experience of hallucinations and delusions, and the thought disorder characteristic of the schizophrenias. It should be noted that while many of the diseases underlying schizophrenic and/or spectrum symptoms may be genetic, some of the disease processes may be the consequence of familial and other environmental factors (e.g., patterns of stress and characteristic defenses to cope with stress, high levels of "expressed emotion") as well as CNS viral infections, limbic system trauma with/without epileptoid disorders, etc.

The possibility that multiple additive factors contribute to the expression of the schizophrenic syndrome has resulted in the development of a multifactorial model of disease transmission (Reich et al. 1975). In the multifactorial model, multiple genetic loci and multiple familial/environmental factors may contribute additively to the liability for expression of the schizophrenic syndrome. The syndrome is manifest when thresholds are exceeded. Multiple thresholds in the model permit differentiation of schizophrenia spectrum features at a lower threshold, and of narrower schizophrenia at a higher threshold. Unfortunately, the multiple threshold approach has not yet led to clarification of the mode of inheritance of the syndrome (Cloninger et al. 1985b).

There is growing suspicion that there is biological and genetic heterogeneity within the commonly delineated schizophrenia syndrome and/or spectrum. The suspicion is fueled by observations of between-pedigree differences in the course of psychiatric morbidity, in neurophysiological "markers," in differential drug response, and in initial linkage studies with human genomic DNA probes.

McCabe et al. (1971) provided evidence for two types of schizophrenic illnesses: "schizophrenia of good prognosis" and "schizophrenia of poor prognosis." Good prognosis probands had almost full recovery between episodes and a paucity of family history for deteriorating psychosis; in contrast, the poor prognosis schizophrenic patients of McCabe et al. had less recovery between psychotic exacerbations (or had steady psychotic features) and had significant numbers of family members with a similar persistent psychotic illness. Within their schizophrenic pedigrees both a familial/genetic and a nonfamilial form of psychoses were delineated. Familial/genetic transmission of deteriorating psychosis was found only in "poor prognosis schizophrenia." There was substantial affective disease in the families of "good prognosis schizophrenia" and little evidence for familial/genetic transmission of deteriorating psychosis.

Several investigators have noted that some schizophrenic patients, together with a considerable number of family members, show abnormalities of smooth pursuit eye tracking (Holzman et al. 1984), increased latency of the P300 evoked cortical potential following auditory or visual stimuli (Blackwood et al. 1987), and inability to discriminate (d' statistic) verbal cues on the continuous performance task (CPT) (Cornblatt and Erlenmeyer-Kimling 1985). Between 40 and 60 percent of schizophrenic patients display one or more such neuro-
physiological/psychophysiological patterns, while similar abnormalities in the general population fall below 10 percent.

Recent evidence also suggests that drug response in the schizophrenias may delineate at least two different familial and one nonfamilial form of schizophrenic illness (Garver et al. 1988). Mood-incongruent psychotics (DSM-III-R schizophrenia, schizophreniform disorder, and affective mood-incongruent psychotics) whose psychosis clears while treated with lithium alone show a virtual absence of psychosis in family members. A similar group of psychotic patients who, failing to respond to lithium, respond rapidly (within the first 7 days of treatment) during treatment with conventional (dopamine-blocking) antipsychotic drugs do have family loading for psychotic illness, but illnesses with minimum between-episode morbidity (good prognosis). A third group of psychotics, also nonresponsive to lithium, respond to conventional neuroleptics, but with a latency (several weeks) that is temporally unrelated to dopamine (D2) receptor blockade. Such “delayed responding” psychotics have family pedigrees with affected members whose psychosis is associated with marginal recovery, <70 on the Global Assessment Scale (GAS; Endicott et al. 1976), between episodes. Other investigators (Keefe et al. 1987) have described patients with so-called “Kraepelinian schizophrenia,” whose symptoms are virtually unchanged following systematic neuroleptic treatment and whose pedigrees are unusually enriched in psychotic illness. On the basis of differential drug response and differences in psychotic illness patterns in the pedigrees of the drug-response pro-

bands, one might hypothesize four different psychotic “diseases,” three of which are familial/genetic psychoses, and one of which (lithium-responsive) is not.

Perhaps the most convincing and direct evidence for genetic heterogeneity of “schizophrenia” comes from recent molecular genetic investigations of pedigrees with “schizophrenia.” “Linkage” of chromosomal markers and phenotype was examined in a group of five Icelandic and two British pedigrees. Linkage was found to occur between the phenotype DSM-III (American Psychiatric Association 1980) schizophrenia and/or “spectrum disease” with a q11—13 locus on chromosome 5 (Sherrington et al. 1988). However, a very large and well-studied Scandinavian pedigree with poor prognosis psychotic members has been shown conclusively not to have a similar linkage of psychotic illness with the 5q11—13 locus (Kennedy et al. 1988). Several other unpublished investigations of pedigrees with psychoses and chromosome 5 have also failed to document linkage of psychosis to the 5q11—13 locus. These data indicate that at least one of the diseases which causes the schizophrenic syndrome is linked with a locus on chromosome 5. In other pedigrees, however, the 5q11—13 locus and its gene products have also failed to document linkage of psychosis to the 5q11—13 locus. These data indicate that at least one of the diseases which causes the schizophrenic syndrome is linked with a locus on chromosome 5. In other pedigrees, however, the 5q11—13 locus and its gene products are clearly not linked with psychotic disease. In the latter pedigrees, the disease process is either nongenetic or is associated with different “schizo-gene(s)” at different site(s) within the human genome.

These “first generation” molecular genetic studies of pedigrees with “schizophrenic” members suggests that one disease that results in the schizophrenic syndrome arises from a variation of a DNA locus on chromosome 5. Yet clearly not all disease processes that result in the schizophrenic syndrome are linked with this abnormality. In other pedigrees, the syndrome may be generated from different loci through different gene products. Or, barring demonstration of linked loci in other pedigrees, the syndrome may in some cases be familial but nongenetic: associated with environmental effects such as viral infections. Finally, sporadic, nonfamilial “schizophrenia” may result from isolated environmental effects on particular individuals.

Segregation and Linkage Analyses and Psychoses

Following familial transmission of a psychiatric disorder through a pedigree sometimes permits demonstration of an association or “linkage” of the affected state with some other feature, such as color blindness (Reich et al. 1969), blood groups (McGuffin et al. 1983), or specific restriction fragment length polymorphisms (RFLPs) (Egeland et al. 1987; Sherrington et al. 1988). In addition to the presence of such a feature which can be traced throughout a pedigree for comparison with affected status, other parameters must be known for linkage analysis to proceed. First, the mode of transmission of the disease must be established, that is, whether transmission is dependent on a single major locus, or whether transmission is polygenic (the result of several contributing genetic loci). Second, the mode of transmission needs to be established and/or estimated for the marker, that is, whether it is transmitted as a Mendelian dominant (homozygote [AA] displays the disease) or as a recessive disorder (only the affected homozygote [aa] displays the disease) or whether it is codominant.
Parameter estimates of penetrances and allele frequency need be specified (Suarez and Cox 1985).

Segregation analyses on diverse phenotypes in relevant pedigrees have been able to reject the simple single-locus model (that all cases of schizophrenia have a common etiology and that no familial resemblance is environmentally determined) (O'Rourke et al. 1982) and the strict polygenic inheritance model (that the syndrome is caused solely by many additive genes) (Cloninger 1989). Unfortunately, such analyses have not been able to distinguish between several alternate multifactorial hypotheses of transmission including: (1) the possibility of multiple loci each of which is sufficient to cause schizophrenia (genetic heterogeneity) and (2) the possibility of a complex pathway from genotype to phenotype in which multiple genetic and/or environmental factors interact in such a manner that no single factor is sufficient to cause schizophrenia (complex development). Such complex multifactorial inheritance can involve: (a) oligogenic inheritance (a few loci each of which have a substantial effect on risk for schizophrenia though none is individually sufficient to cause the syndrome), (b) combined polygenic and cultural inheritance (social learning and other nongenetic influences) are transmitted in addition to polygenic factors from parent to child, and (c) mixed-multifactorial + single-locus inheritance (effect of major gene locus is substantially modified by many other familial background variables) (Cloninger 1989). McGue et al. (1983) found that a multifactorial model with polygenic inheritance (63 percent) and cultural inheritance (28 percent) was compatible with Western European family and twin data, but genetic heterogeneity and mixed-multifactorial + single-locus models have not been excluded.

Linkage analyses in the psychoses would come to a grinding halt were it not for the willingness of investigators to take a chance, to make an estimate of relevant parameters. The wisdom or folly of such estimates is born out subsequently as consistent or inconsistent linkage patterns emerge. Such estimates are "best guesses" and are reiterated again and again by the investigator in a manner not dissimilar to the traditional "maximum likelihood" method of the linkage programs themselves in achieving the closest "fit" of association (or nonassociation) of a critical feature with affected status.

Linkage analysis assigns to each pedigree a score that is relevant to the odds of linkage or association of the studied feature with the affected disease state. The commonly used measure of such linkage or association of feature and affected state is the "lod score," which is the logarithm of the odds of linkage (see glossary on p. 366). Assuming for the moment that a syndrome such as "schizophrenia" is the result of a single disease rather than several diseases (i.e., is homogeneous), the lod scores from each pedigree with schizophrenia are summed to achieve a total lod (likelihood) score for the linkage of the studied feature to schizophrenia. Traditionally, a lod score of +3 or greater has been evidence for linkage of a studied feature to the disease. A lod score of -2 or less is cause for rejection of linkage. A lod score of +3 is similar to rejecting the null hypothesis of no relationship between the studied feature and affected state with a p value of 0.001; while a -2 lod score is comparable to rejecting linkage at the p = 0.01 level. Very high probabilities are necessary because of the multiple comparisons that are at the heart of linkage analysis. Lod values between -2 and +3 are indeterminant, and require more or larger pedigrees and/or enhanced information carried in studied features. The method of linkage analysis that is generally used presupposes genetic homogeneity of the disease studied (Ott 1985).

Genetic Heterogeneity and Traditional Linkage Analysis

Earlier, the problem of genetic heterogeneity was raised by the rather convincing findings of linkage of schizophrenia to a chromosome 5 locus in seven Icelandic and British families (Sherrington et al. 1988) and the equally convincing finding that the same chromosome 5 locus could be rejected for linkage with schizophrenia in an extensively studied Scandinavian pedigree (Kennedy et al. 1988). Other as yet unpublished reports on multiple pedigrees containing cases of schizophrenia have also been unable to link 5q11-13 locus to schizophrenia. While it is always possible that problems relevant to the diagnosis of schizophrenia unwittingly led some of the investigators to include pedigrees outside of the schizophrenia spectrum, or that thousands of reiterations on poorly defined "spectrum" presentations and poorly anchored linkage program parameters finally resulted in a chance one-in-ten-thousand "significant" lod score for the apparent linkage of schizophrenia and a 5q11-13 locus, the most parsimonious explanation may be genetic heterogeneity of schizo-
phrenia and its consequences for linkage analysis.

Let us suppose that, as in poly-cystic kidney disease (Kimberling et al. 1988) and retinitis pigmentosa (Wirth et al. 1988), such genetic heterogeneity of schizophrenia is common: that there are several different diseases that make up the schizophrenic spectrum, but that the diseases are phenomenologically similar to one another and have not been distinguished from one another. For the sake of the argument, let us suppose further that 20 percent of schizophrenic patients have a disease associated with chromosome 2, 35 percent with chromosome 5, 30 percent with chromosome 17, and an additional 15 percent are phenocopies associated with prenatal and perinatal events. Despite such presumed linkage between chromosome 5 and schizophrenia, only 35 percent of pedigrees with schizophrenia who have informative markers for a chromosome 5 locus would have positive lod scores; 65 percent of pedigrees with schizophrenia who have informative markers for a chromosome 5 locus would have negative lod scores. Thus, simply summing lod scores of the multiple pedigrees, as in the traditional method of linkage analysis, could be expected repeatedly to result in a negative, perhaps significantly negative (lod < -2), total lod score for linkage of chromosome 5 to schizophrenia—nonlinkage despite about one-third of the pedigrees having linkage and demonstrating positive lod scores.

If schizophrenia arises independently from such multiple genetic loci, linkage for a locus on chromosome 5 with schizophrenia would not be expected from usual linkage analysis unless pedigrees were selected from a relatively isolated population in which the chromosome 5 moiety was much more frequent. To be detected by traditional linkage analysis, the chromosome 5 moiety of schizophrenia must be the primary contributor to the total (summed) lod score.

**Strategies to Detect Genetic Diseases Making Up Schizophrenia**

There are at least three different basic strategies that can be used to detect separate diseases within a presumably heterogeneous syndrome such as schizophrenia. They are: (1) intensive multigenerational study of single large pedigrees, (2) distributional analyses of the recombination fraction in large numbers of pedigrees, and (3) use of independent measures (external to the linkage distribution) to separate families that are and are not linked to a particular locus. Each of these strategies will be discussed in some detail.

Single large pedigrees with many members afflicted with schizophrenia as well as large numbers of unaffected members can be very informative for genetic studies. The key advantage of such pedigrees is that the sheer numbers of affected and unaffected members may permit computation of a single significant (> +3 for linkage and < -2 for rejection of linkage) lod score for the entire pedigree. The single pedigree is less likely than multiple pedigrees to be contaminated by a mixture of other schizophrenia-like diseases which do not transmit through the locus of interest. In such a large multigenerational pedigree, the mode of transmission can be assessed more easily, and the parameters of transmission can be estimated more accurately. If the associated feature being studied for linkage is a highly informative genomic probe close to the locus of interest, a highly significant lod score (well above +3) can be generated by a single pedigree. Conversely, single large pedigrees and informative probes can be used convincingly to reject specific linkage patterns, at least within that single pedigree. Rejection of linkage in a single pedigree simply confirms that “not all do,” while confirmation by one pedigree affirms that “some do.” To keep the possibility of chance occurrence of linkage to a minimum, similar linkage to the same locus should be replicated in at least one other pedigree before the level of confidence in the linkage is moved from “possible” to “probable.”

An extension of the single pedigree method is the study of a relatively isolated (inbred) population. Such an isolated population is also much more likely to have a single genetic form of illness than found in the general population. The Amish studies of affective disorder took advantage of this extended pedigree method in determining cosegregation of affective illness and a locus on chromosome 11 (Edland et al. 1987). Similarly, isolation of Icelandic and some British populations may have provided pedigrees enriched in the chromosome 5 moiety of schizophrenia, permitting demonstration of linkage to schizophrenia with usual linkage methods (Sherrington et al. 1988). Linkage might not have been detected with traditional linkage analysis if studied in less isolated populations with greater admixture of genetically discrete diseases.
respectively).

In summary, the single pedigree model and its extension to pedigrees from isolated populations aid in the identification of a genetically homogeneous disease by taking advantage of reduced degrees of genetic heterogeneity in such pedigrees/populations. Use of such pedigrees reduces the often overwhelming distractions which affect traditional linkage analysis to focus on a single disease. The disadvantages of such a strategy is that the analysis may identify a unique gene(s) limited to one large (or extended) pedigree and therefore lack generalizability to the population of people with schizophrenia. Nonreplication of findings in other samples does not permit discrimination between the possibility of chance findings or true genetic heterogeneity.

Admixture analyses of multiple pedigrees which are genetically mixed provide a second avenue toward resolution of genetic heterogeneity in the schizophrenias. The concept is that of multiple pedigrees which are a mixture of two types: those with linkage of affected state to a specific genomic site of interest, and those whose affected state does not appear to link to that particular site of interest.

Lod scores at multiple recombination fractions ("distances" between loci of interest) are calculated using the maximum likelihood method for each pedigree. Lod scores at various recombination fractions on all pedigrees are used to estimate the true recombination fraction of the pedigrees of the linked type, and to estimate the proportion of pedigrees distributed within that recombination fraction (Ott 1983). HOMOG, a published computer program (Ott 1985), carries out these procedures and provides test statistics concerning the two "null" hypotheses (none of the pedigrees show linkage or all of the pedigrees show linkage). Finally the HOMOG program provides posterior probability of linkage for each of the pedigrees and provides information about the percentage of pedigrees genetically homogeneous due to marker linkage.

This type of analysis has been described for the separation of two phenotypically identical genetic forms of Charcot-Marie-Tooth disease, one of which links with the Duffy blood group locus. An early analysis was based on the contrasts of two pedigrees, a pedigree with 200 members across five generations and a pedigree of 8 members across three generations. The former pedigree was clearly not linked, with lod scores of $(-)\infty$ at 0.00 recombination fraction and -10.93 at 0.01 recombination fraction, while the smaller linked pedigree had a lod score of 1.204 at 0.00 and +1.19 at 0.01 recombination fraction (Dyck et al. 1983). Subsequent analysis was based on the findings in seven pedigrees, with an estimated 65 percent linked at a recombination fraction of 0.05. Four of the pedigrees had a posterior probability of linkage above 0.92; the fifth, at 0.67; and the two remaining, at 0.00 (Ott 1985). It should be noted that as the percentage of linked pedigrees declines and/or the recombination fraction becomes larger, a considerably greater number of comparably informative pedigrees are required to estimate the recombination fraction with similar precision: 10 times as many pedigrees are needed to estimate the recombination fraction when 50 percent of the pedigrees are linked as needed when all pedigrees demonstrate linkage. Clearly the major limitation of admixture analysis for psychiatric disorders is the requirement of either a large number of large pedigrees or huge numbers of smaller pedigrees, or a mixture of large and small pedigrees with the necessity of correcting for variable pedigree size and information content. Ott (1986) showed that with only 10 families and 4 offspring each, one would never have a power of 80 percent to detect heterogeneity, no matter how much heterogeneity existed; the same is true for 30 families when the recombination fraction is 0.10 or larger. At recombination of 0.01, 20 percent of unlinked families can be detected with 20 families; 10 percent of unlinked families can be detected with 30 families (Ott 1986). Similar tests of linkage heterogeneity have been devised and appear to have power similar to that of HOMOG. Comparisons between methods of testing for genetic heterogeneity, such as devised by Morton (1956), K-test; Ott (1985), A-test; and Risch (1988), B-test, are found in Risch (1988).

When sufficient numbers of informative pedigrees are found to be linked to a locus of interest, the admixture assessment permits separation of pedigrees for the purpose of both reevaluating nosologic (diagnostic) criteria, and of focusing investigations of biopathology of major psychotic illness. In the case of Charcot-Marie-Tooth disease, the form not linked to the Duffy locus on chromosome 1 was found to have less slowing of motor nerve conduction velocities and less prominent onion bulb change evident on sural nerve biopsy than the linked form, suggesting revision of diagnostic criteria for the disorders (Dyck et al. 1983). The isolation of pedigrees with a single disease from a mixture of pedigrees having
similar appearing diseases permits focus on the single disease’s underlying biopathology. Identification and description of the abnormal (and normal) gene underlying the disorder can be performed using DNA from affected pedigree members. The abnormal (and normal) protein can be sequenced and the presence of the abnormal protein in the CNS of afflicted individuals confirmed. The effects of the abnormal protein on induced pathophysiology/chemistry can be delineated. Finally, specific therapeutic interventions can be designed to circumvent such effects and their clinical consequences. This process of “reverse genetics,” which gives promise of providing a solution to the major form of muscular dystrophy in the next few years (Hoffman et al. 1988), can be applied whenever one homogeneous disease which contributes to a syndrome can be genetically isolated for focused study. Its application to the schizophrenias will provide investigators with a powerful tool with which to unravel many of the underlying biopathologies.

Independent external measures may be useful in separating pedigrees for linkage analysis on the basis of additional information which is entirely external to the linkage parameters themselves. When such an important piece of outside information such as a “marker” can be brought into linkage analysis, pedigrees can be grouped on the basis of presence or absence of the marker. The lod scores of the marker-positive group can be tallied and contrasted with the total lod scores of the marker-negative group. For example, if muscle chemists long ago had found abnormal or absent “dystrophin” (Hoffman et al. 1988) in muscle biopsies of some dystrophic patients and not in others, the abnormal or absent dystrophin in muscle could have served as a “marker” to separate pedigrees containing dystrophic members for linkage analysis at an Xp21 locus. Lod scores from pedigrees containing dystrophic members with normal dystrophin could be tallied separately from pedigrees where dystrophin was abnormal. Pedigrees with abnormal dystrophin would be found to have significant (> +3) total lod scores; pedigrees with normal dystrophin would be found not to have linkage (< -2). Heterogeneity of dystrophic disease would have been demonstrated.

In fact, as noted above, dystrophin was not discovered until long after linkage to Xp21 was demonstrated in Duchenne’s and Becker’s dystrophy; the example above, however, illustrates that heterogeneity reduction can proceed in either direction: from isolation of pedigrees as a consequence of recombination distributions or from the use of external “markers” to separate groups of pedigrees for subsequent tallying of lod scores. Provided that the “marker” is closely related to the effect of the locus of interest, pedigree groups defined by markers should be virtually identical to (and have identical recombination fractions) the linked pedigrees defined by admixture analysis. The statistical significance of pedigree separations using “marker” methods needs correction for multiple marker comparisons.

Criteria for promising “markers” in heterogeneity analyses (as soon as linkage of affected status with a genomic locus of interest can be demonstrated) include markers which segregate in pedigrees, which are present in a relatively high proportion of pedigrees, and which are relatively unaffected by clinical state at the time of examination.

Three neurophysiological “markers” that appear to meet these criteria and are presently the focus of studies on the heterogeneity of schizophrenia are: smooth pursuit eye tracking dysfunction (Holzman et al. 1984), P300 latency (Blackwood et al. 1987), and the CPT when analyzed by the d’ statistic (Cornblatt and Erlenmeyer-Kimling 1985). Each has been found to be transmitted in pedigrees. Each is relatively stable despite change in state. Each is found in only about 50 percent of syndromically diagnosed schizophrenic patients. Whether such “markers” alone or in combination will be useful in separating pedigrees of schizophrenic patients linked/not linked to a particular genomic locus of interest awaits the outcome of ongoing studies.

Other potential markers are as yet less well developed. Differences in antipsychotic drug response that appear to be associated with differing prognosis in both patient and affected pedigree members (Garver et al. 1988) may be another marker of heterogeneity worth pursuing in the context of linkage/nonlinkage to a genomic locus of interest.

Summary
A series of observations have suggested that the mood-incongruent psychoses, generally diagnosed as “schizophrenia,” are not a single disease, but are a mixture of several diseases. Some are both familial and genetic, some may be only familial, and others may be sporadic and related to environmental effects. Though segregation analysis has not yet satisfactorily determined the mode of inheritance of the
genetic forms of the syndrome, most investigators tentatively and perhaps heuristically have adopted the single major locus model to pilot investigations of linkage. Investigations of linkage may often be confounded by this very mixture of pedigrees with different diseases (heterogeneity), with only one of the diseases linked to a particular genomic locus of interest.

Linkage studies in schizophrenia must therefore be alert to the potential for between-pedigree genetic heterogeneity. Wide variance in pedigree lod scores, which reflect linkage/nonlinkage of affected status to locus of interest in each pedigree, can be associated with such heterogeneity in a syndrome such as schizophrenia or can be simply chance findings. Admixture analysis performs formal tests of homogeneity on such multi-pedigree data. When homogeneity is rejected, admixture analysis also indicates the likelihood of each pedigree being linked to the locus of interest. Investigation of single large pedigrees with informative probes can often demonstrate linkage (lod > +3) or rejection of linkage (lod < -2) within the pedigree: linkage in one large pedigree and rejection of linkage in another large pedigree can indicate either heterogeneity or chance findings. Replication of linkage in at least one additional pedigree increases confidence in linkage rather than chance findings. Finally, neurophysiological or neurochemical “markers” such as smooth eye pursuit or CPT performance or “markers” such as differential drug response may be used as additional external information to separate pedigrees a priori for evaluation of linkage.

The tools of molecular genetics and linkage analysis can be expected to aid in the resolution of the question of genetic and biological heterogeneity in schizophrenia(s). Resolution of heterogeneity by clear separation of the diseases that make up the schizophrenic syndrome may be the critical step toward focused progress in the unraveling, understanding, and intervening in specific psychotic disorders.

References


The Authors

David L. Garver, M.D., is Professor and Chairman, Department of Psychiatry, University of Alabama.
School of Medicine at Birmingham, AL; Keith E. Isenberg, M.D., is Assistant Professor of Psychiatry, and Theodore Reich, M.D., is Professor of Psychiatry and Genetics, The Jewish Hospital of St. Louis, Washington University School of Medicine; and C. Robert Cloninger, M.D., is Professor and Chairman, Department of Psychiatry, and Professor of Genetics, Washington University School of Medicine, St. Louis, MO.

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The American Psychiatric Association takes pleasure in inviting submissions for the Thirteenth Annual Foundations’ Fund Prize for Research in Psychiatry.

Candidates for this prize should be citizens of the United States or Canada and should be nominated by a sponsor. Sponsors should be members of the American Psychiatric Association. Members of the Prize Board are excluded from submitting nominations.

The sponsor should submit a supporting letter setting out in detail justification for the nomination and summarizing the research accomplishments of the nominee in a specific area or with a coherent theme.

The nominee should submit:

• A book or paper, or a group of representative and thematically linked, books or papers published (or accepted for publication) in English and dated within 10 years before the deadline of submission.

• A summary statement written by the nominee, emphasizing the principal theme (or themes) running through the work, its internal cohesiveness and consistency, and scientific implications.

• An up-to-date curriculum vitae.

• An up-to-date bibliography.

All entries must be submitted in six copies (including six copies each of the sponsor’s letter, curriculum vitae, bibliography, and summary statement) and sent to Ira D. Glick, M.D., Chairman, Foundations’ Fund Prize Board for Research in Psychiatry, American Psychiatric Association, 1400 K Street, NW., Washington, DC 20005. Entries will be acknowledged, but cannot be returned. The prize is based on a yearly competition and resubmission is encouraged. The award will be presented at the Convocation of Fellows at the Association’s Annual Meeting in May of 1990.

The deadline for submission is November 1, 1989.