Genetic Principles and Methods in High-Risk Studies of Schizophrenia

by C. Robert Cloninger

Abstract

Recent advances in genetic epidemiology present excellent opportunities for future high-risk studies of schizophrenia. Improved methods are now available for specifying the natural boundaries of the schizophrenia spectrum and evaluating the mode of inheritance of schizophrenia and its biosocial risk factors. Path-analytic techniques permit the derivation of multifactor indices of both biological and social antecedents of schizophrenia. Powerful advances have been made in segregation analysis of pedigree data and in the power of linkage tests with DNA markers to confirm the presence of putative major loci that influence susceptibility to complex phenotypes like schizophrenia. The yield of information from high-risk samples is greatly increased when both longitudinal and pedigree analyses are combined.

Recent advances in genetic epidemiology provide methods that are useful in high-risk studies of schizophrenia. These advances include improved methods for (1) identifying etiological subtypes and the natural boundaries between discrete disorders using discriminant and admixture analysis (Cloninger et al. 1984, 1985a); (2) evaluating putative biosocial risk factors in longitudinal studies of families (Cloninger et al. 1980); (3) modeling the mode of inheritance of developmentally complex phenotypes (Cloninger et al. 1979a; Reich 1980; Risoh and Baron 1984); and (4) construction of linkage maps of the human genome with DNA markers (White et al. 1985).

Even with these improved techniques, the characterization of schizophrenia’s clinical boundaries, developmental course, and mode of inheritance presents many challenges. Although recent studies using rigorous sampling and assessment methods confirm that schizophrenia is familial, only a minority of schizophrenics have even one parent, sibling, or child who is also schizophrenic (Tsuang et al. 1982; Guze et al. 1983). Only rare cases associated with additional specific neuropsychiatric defects show mendelian patterns of inheritance (Francis 1979). Although there is substantial resemblance in type of psychosis within families, clinical variation alone has not permitted reliable separation of etiologically distinct subtypes (Ødegaard 1972; Gottesman and Shields 1982; Farmer et al. 1984) unless familial homotypy is used as a self-fulfilling criterion (Leonhard 1979).

Recent analyses of family data about schizophrenia permit rejection of the hypothesis that all schizophrenia is due to a single major-locus defect (O'Rourke et al. 1982). Single-locus inheritance can be rejected because model parameters that fit data about most nuclear families (in which neither parent or only one parent is schizophrenic) lead to falsely low predictions about the risk of schizophrenia in children of two schizophrenics as well as falsely low predictions about concordance for schizophrenia in monozygotic twins. It is not surprising that monogenic models of schizophrenia are inadequate because extensive experience in biochemical genetics shows that variation at a single gene locus rarely can account for a trait that is defined by clinical or physiological variables (Harris 1975;
Cloninger et al. 1985c). Simple mendelian inheritance is expected only for rare traits due to specific mutations.

Rejection of monogenic models of schizophrenia as a homogeneous unitary trait requires high-risk studies of schizophrenia to focus on alternative multifactorial hypotheses. These include the possibility that there are multiple loci each of which is sufficient to cause schizophrenic disorders: this situation is called genetic heterogeneity. A second possibility is that there is a complex developmental pathway from genotype to phenotype in which multiple genetic and environmental factors interact and no one factor is sufficient to cause schizophrenia; this is called complex development. Complex development includes the possibilities of strict polygenic inheritance, combined polygenic and cultural inheritance, "oligogenic" inheritance, and inheritance in which the effect of a single major gene locus is modified substantially by many other familial background variables (called the "mixed model").

In strict polygenic or multifactorial inheritance, the effect of any one factor is so small that its individual effects cannot be distinguished from those of many other factors. Strict multifactorial models are approximations that are useful for some statistical analyses, but breeding experiments with multifactorial traits in animals indicate that the individual effects of one or a few loci on a particular phenotype are usually much greater than the effects of other factors and are substantial enough to be individually distinguished through breeding experiments or linkage analysis when there are extensive genome maps (Wright 1968; Cloninger et al. 1985c). Accordingly, a more realistic model is the "mixed model," in which there is heritable multifactorial variation in the background of genotypes at a single gene locus.

In oligogenic inheritance, there are a few loci that each contribute substantially to risk of illness and that together account for a large portion of the genetic variability. For example, Vogel and Propping (1984) identified a dozen rare, recessive genetic disorders that are sometimes associated with symptoms like those considered characteristic of schizophrenia; they argue that susceptibility to schizophrenic disorders may increase with the number of loci that are heterozygous for these disorders. The heterozygotes would not show the full recessive disorder, but those with abnormal alleles at a few such loci might sometimes have schizophrenic symptoms. This model reminds us that all schizophrenic disorders may not have the same final common pathway; there may be more than one complex developmental pathway leading to schizophrenic disorders.

Given the heterogeneity and developmental complexity of schizophrenic disorders, evaluation of the etiology and development of schizophrenia in high-risk studies requires attention to research problems at several levels. At the clinical phenotype level, there must be attention to (1) identification of subgroups that may be clinically and etiologically more homogeneous, (2) identification of components or symptom clusters (e.g., positive/negative symptom clusters), (3) characterization of the developmental antecedents of psychosis, and (4) identification of the range and boundaries in the spectrum of clinical expression of susceptibility to schizophrenic disorders. At the biosocial level, observations on multiple risk factors (e.g., abnormalities on continuous performance tasks, eye-tracking tasks, communication deviance, and birth and pregnancy complications) are needed to characterize individual and heritable differences in developmental pathway from genotype to phenotype. At the familial level, the pattern of familial transmission must be characterized by the mode of inheritance of the clinical phenotype and its biosocial risk factors. The steps in such studies are (1) specification of the phenotype, including its subtypes, components, and risk factors; (2) characterization of mode of inheritance; and (3) mapping relevant loci in the human genome and related sampling issues. The strengths and weaknesses of available approaches to problems at each level—clinical, biosocial, and genetic—are critically reviewed here with emphasis on their utility for high-risk studies.

**Specification of the Phenotype**

Alternative sets of diagnostic criteria for schizophrenia and its spectrum have proliferated to the point that it is difficult to compare results of different studies that use overlapping but different assessment procedures. Different diagnostic criteria define samples with different longitudinal courses and patterns of inheritance (McGuffin et al. 1984). Current DSM-III criteria (American Psychiatric Association 1980) are more restrictive than the criteria used in most European studies (Gottesman and Shields 1982). With criteria like those of DSM-III, the cumulative lifetime incidence of schizophrenia in first-degree relatives of schizophrenic probands is only about 5 percent or half the risk estimated in older European studies (Tsuang et al. 1982; Guze et al. 1983). However, nonaffective psy-
choses that do not fully satisfy modern criteria still aggregate with more strictly defined cases (Guze et al. 1983). Fortunately, procedures for identifying naturally occurring boundaries between disorders have been developed and applied to schizophrenia (Cloninger et al. 1984, 1985a).

The current status of the validation of schizophrenia as a disease is summarized in table 1. In a recent prospective followup and family study of 500 psychiatric outpatients (Cloninger et al. 1985a, 1985b), schizophrenia was shown to be a discrete disorder using a quantitative clinical scale that discriminated schizophrenics from other psychotic and nonpsychotic individuals. Discriminant analysis was used to identify the clinical features that made up this scale. Persecutory delusions, delusions of control, firmly fixed mood-incongruent delusions, and auditory hallucinations increased the probability of diagnosing schizophrenia in an independent, comprehensive clinical assessment 6–12 years later. These four variables were strongly correlated with one another, constituting a clinical syndrome that was stable over time. They had equal weight in distinguishing schizophrenics from others, with each variable contributing the value +1 to the total scale score if ever present. Spending sprees with marked elation decreased the probability of later diagnosing schizophrenia and had equal weight in the opposite direction (−1 if present). Scale scores were computed as the sum of the four symptoms with positive weights and the one symptom with negative weight (see table 2). More than 68 percent of schizophrenics had scores greater than +1, whereas this occurred in fewer than 2 percent of non-schizophrenics. These results are similar to those in the International Pilot Study of Schizophrenia (Bartko et al. 1974).

Two observations about the schizophrenia symptom scale indicated that schizophrenia is a discrete disorder. First, the distribution of scores was shown to be bimodal in admixture analyses of both the criterion sample and a replication sample: individuals were relatively rare who received scores of +1, which is intermediate to the higher scores of typical schizophrenics and to the lower scores of typical non-schizophrenics. Second, there was familial resemblance for the presence or absence of schizophrenia (i.e., for scores of +2 or higher) but no additional resemblance for number of schizophrenic symptoms. Nevertheless, scale scores were more informative than categorical diagnoses because they quantified the certainty of diagnosis and predicted outcome: individuals with higher scores were more likely to be chronically psychotic and diagnosed as schizophrenic at followup than those with lower scores. The followup results also raised questions about criteria for schizotypal personality.

Similar analyses are needed to val-

Table 1. Current status of schizophrenia as a disease concept

<table>
<thead>
<tr>
<th>Levels of disease concept</th>
<th>Criteria</th>
<th>Status of schizophrenia</th>
</tr>
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<tbody>
<tr>
<td>I. Clinical syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Distinct clinical features</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2. Correlated features</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3. Stable and homogeneous</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

II. Discrete clinical disorder

4. Explicit clinical criteria | Yes |
5. Predictable natural history | Yes |
6. Discrete natural boundaries | Yes |

III. Pathophysiological entity

7. Risk factors identified | Partially |
8. Pathophysiological explanations | Questionable |
9. Specific pathogenesis | No |


Table 2. Classification accuracy of schizophrenia symptom scale

<table>
<thead>
<tr>
<th>Scale score</th>
<th>Number of subjects</th>
<th>Schizophrenic diagnosis (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>1494</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+1</td>
<td>160</td>
<td>12</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>+2</td>
<td>55</td>
<td>53</td>
<td>69</td>
<td>98</td>
</tr>
<tr>
<td>&gt;2</td>
<td>40</td>
<td>80</td>
<td>36</td>
<td>99</td>
</tr>
</tbody>
</table>

The schizophrenia scale score is the sum of the following 5 variables at the time of last information: +1 if persecutory delusions are present, +1 if delusions of control, +1 if firmly fixed delusions, +1 if auditory hallucinations, and −1 if manic spending sprees have occurred.
idate criteria for schizotypal personality and to clarify its familial relationship with schizophrenia. Recent analyses indicate that the genetic overlap between strictly defined schizophrenia and less certain schizophrenia is not complete (McGue et al. 1983). The nature of the familial relationship between schizotypal personality and strictly defined schizophrenia is uncertain at present. Is progression from schizotypal personality to schizophrenia largely determined by non-genetic factors? Do nonpsychotic individuals within the schizophrenia spectrum have a quantitatively lower degree of predisposition (i.e., fewer susceptibility factors) than their psychotic relatives? Or are there qualitative differences among the antecedents of psychotic and nonpsychotic cases? Inclusion of nonpsychotic subjects with schizotypal features in the schizophrenia spectrum has a major impact on the analysis of familial transmission (Morton et al. 1979; Risch and Baron 1984), and yet the sensitivity and specificity of available criteria for the spectrum remain uncertain because of a lack of studies on general populations. More longitudinal studies of putative schizotypal traits in the general population, as well as in families of strictly defined schizophrenics, are needed to clarify the clinical boundaries and etiological relationships of subgroups of psychotic and nonpsychotic syndromes within the schizophrenia spectrum.

Much effort to identify subgroups of psychoses has failed to identify independent familial subtypes of schizophrenia. Cluster analyses have recently supported the clinical distinction between paranoid and hebephrenic syndromes, but family and genetic marker studies have not confirmed etiological differences (Farmer et al. 1984). The distinction between positive and negative symptom complexes has also failed to yield consistent familial differences. Prominent negative symptoms have been associated with a strong familial aggregation by some investigators (Dworkin and Lenzenweger 1984) and with weak familial aggregation by others (Nasrallah et al. 1982). Such inconsistency is not surprising with a complex heterogeneous disorder and emphasizes the fact that specifying phenotypes and characterizing underlying biosocial risk factors is an iterative process. We begin with imperfect clinical subdivisions, identify underlying risk factors, and then use the information about the association between clinical symptoms and risk factors to divide the phenotype into subgroups that are more homogeneous. This process is then repeated until the pathophysiological explanation of symptoms, syndromes, and longitudinal course becomes apparent.

**Biosocial Risk Factors for Complex Phenotypes**

In disorders like schizophrenia, in which there is etiological heterogeneity and/or complex development, the methods for validating putative biosocial risk factors (i.e., antecedents of illness) must take developmental complexity into account (Cloninger et al. 1980). When the disorder under study is a homogeneous unitary trait, robust criteria for validating a putative marker require both (1) that the frequency of the marker is greater in affected individuals than in well individuals at high risk (since only some at high risk will become affected), and (2) that the frequency of the marker is greater in well individuals at high risk than in low-risk controls (since there must be an association between the marker and risk for illness in the general population). However, when there is etiological heterogeneity and/or developmental complexity, the association between schizophrenia and its putative antecedents may be inconsistent because different cases have different antecedents. To deal with this, it is necessary to stratify probands into those with and without the putative marker (Cloninger et al. 1980). For complex phenotypes, robust criteria for validating putative biosocial risk factors are (1) that among the relatives of probands with the putative marker, the frequency of the marker is greater in affected relatives than in well relatives at high risk; (2) that the frequency of the marker is greater in well relatives of probands with the marker than in low-risk controls from the general population or relatives of normal controls; and (3) that the frequency of the marker is greater in well relatives of probands with the marker than in (affected or well) relatives of probands without the marker. The first two criteria demonstrate the association between the risk factor and clinical disorder; the third demonstrates etiological heterogeneity and/or developmental complexity. This has been described semiquantitatively in Cloninger et al. (1980).

For complex phenotypes, we must also change our expectations about the potential accuracy of any single risk factor because there is an inverse relationship between its potential sensitivity and specificity (Cloninger, in press). If there is genetic heterogeneity with many different factors that are each sufficient to cause a schizophrenic disorder, then each of these risk factors may be highly specific for schizophrenia (i.e., individuals with the factor are highly likely to develop schizophrenia), but the sensitivity will be reduced in proportion to the extent
of heterogeneity (i.e., many cases of schizophrenia will develop in individuals who have other sufficient causes). Likewise, if there is developmental complexity with many steps in the pathway from genotype to phenotype, the remote early steps in this chain of events (e.g., genotypic markers and primary gene products) are likely to be specific but not sensitive predictors of illness. Similarly, high sensitivity is unlikely to be obtained without consideration of nonspecific events that occur late in the developmental chain (e.g., environmental stressors like perinatal complications, communication deviance, and high expressed emotion in the home).

Thus, we cannot expect to find a single risk factor that will be both sensitive and specific for predicting schizophrenia. In all probability we need a profile of multiple risk factors, including some that are remote in the chain of events (proximal to primary gene products like DNA markers, enzymes, and protein defects) and some that are late in the chain of events leading to clinical dysfunction (nonspecific psychosocial and environmental antecedents; Cloninger, in press). A full appreciation of the developmental pathway and accurate prediction of risk are unlikely to be achieved without attention and measurement of factors at multiple levels in the chain of events. This is a major strength of the design of studies in the high-risk consortium—longitudinal analysis of multiple indices of several variable domains, including clinical, psychosocial, and neurophysiological factors.

**Evaluation of Mode of Inheritance**

Despite rejection of simple monogenic models of the inheritance of schizophrenia (O’Rourke et al. 1982), much more work is required to clarify its pattern of inheritance. Recent work on pedigree analysis has considered generalized multifactorial models allowing for both polygenic and cultural inheritance (Rao et al. 1981; McGue et al. 1983); mixed models, including both a major diallelic locus and polygenic background (Risch and Baron 1984); and oligogenic models (Böök et al. 1978; DeBray et al. 1978).

A path diagram depicting the causes of resemblance between strict multifactorial phenotypes of full siblings reared in nuclear families is shown in figure 1. The major variables are the phenotypes (P), additive polygenic factors (A), sociocultural factors transmitted between generations (B), and other relevant environmental factors that are not transmitted between generations (E). The subscripts denote the mother (M), father (F), and two offspring (O and O’). It is desirable to measure some observable index of environmental influences (I). There may be assortative mating, denoted by the copath between the phenotypes of mates (Cloninger 1980). The noninherited environments of siblings may be correlated (denoted by the correlation c) due to their being reared together at a particular time and place. The correlations between family members have been derived using this basic model (Cloninger et al. 1979a; Cloninger 1980) and for extensions incorporating variable family structures, as seen in extended or broken homes (Cloninger et al. 1979b) and mixed phenotypic and social homogamy (Cloninger 1980).

The assumptions, historical development, and utility of such strict multifactorial models have been discussed in Cloninger et al. (1983a), and this general multifactorial model has been applied to a summary of

![Figure 1. A multifactorial path model of complex inheritance](image-url)

*Variables are defined in text.*
European data on multiple classes of relatives (Rao et al. 1981; McGue et al. 1983). Although these data are not based on explicit diagnostic criteria, they have the advantage that recent operational criteria are overly restrictive and the pattern of results using these broader criteria is supported by methodologically rigorous, modern studies (Guze et al. 1983). The analysis leads to high estimates of polygenic heritability (71 percent) and evidence for substantial transmission from parent to offspring of relevant sociocultural influences (i.e., cultural heritability is 20 percent). No direct indices of these putative sociocultural factors were available for this analysis, so the detection of sociocultural inheritance was based on the transmission probability of sociocultural factors being nonmendelian. In fact, the cultural transmission probability was estimated as only about 0.28 instead of the 0.5 expected with autosomal diploid inheritance. This means that to the extent that some sociocultural factors are transmitted with the same probability as autosomal genes (0.5), the estimate of polygenic influences is inflated. This should encourage studies of both genetic and cultural inheritance in schizophrenic families. The resolution of biological and cultural inheritance will be much more precise when indices of these latent heritable factors are used. In other words, future studies in which both phenotypes and biosocial risk factors are measured should be more informative than pedigree analysis of phenotypic data alone.

Mixed models that allow for a possible major locus as well as multifactorial inheritance of the background variation permit formal tests of the hypothesis that there is no major locus effect or that there is no multifactorial inheritance of the background variation. Risch and Baron (1984) have described this approach to segregation analysis in detail and presented an application to data about the parents and siblings of 79 schizophrenics. Schizophrenia was diagnosed using Research Diagnostic Criteria (Spitzer et al. 1978) that are even more restrictive than DSM-III criteria according to the authors. Using data about restrictively defined schizophrenia, they were unable to discriminate among alternative models with confidence because the small number of affected relatives gave little information. It is unfortunate that a broader definition of schizophrenic psychoses comparable to that in older European studies was not also evaluated. They did evaluate a much broader definition, including schizotypal personality. The simple polygenic model could not be rejected in their segregation analysis, and its predictions were in reasonable agreement with the observed mating type distribution, incidence of schizotypal personality and schizophrenia in the general population, and the concordance in monozygotic twins. They also found that their data were consistent with a single recessive locus making a large contribution to liability to the spectrum. However, their putative recessive gene has the dubious property of occurring in over 60 percent of the general population and having a penetrance for schizophrenia that is barely 1 percent higher than the predicted general population incidence (1.7 vs. 0.6 percent). The dependence of these results on the classification scheme emphasize how critical it is to identify the natural boundaries of schizophrenia and clarify the familial relationship of schizotypal traits to schizophrenic psychoses.

Another approach is to consider oligogenic models, as in recent analyses by DeBray et al. (1978), who concluded that data about 25 large French pedigrees were most consistent with single-locus, two-locus, and four-locus models from among 12 alternative models they considered. The major difficulty with oligogenic models is that they require so many arbitrary assumptions about genotypic frequencies and penetrances, unless prior information is available about the parameters of each locus and their interaction with each other in relation to liability to schizophrenia. Hence, most evaluations of multifactorial hypotheses are more likely to be based on path-analytic multifactorial models and/or on mixed models.

Despite the inadequacies of past applications of the mixed model, the method itself has great potential to guide investigators in the identification of pedigrees that provide the most evidence for a segregating major locus. This is exemplified by a recent analysis of Tourette's syndrome (Comings et al. 1984). Rapid advances are being made in the mapping of the human genome (White et al. 1985), so it is now likely that a major locus effect can be confirmed if it is truly present.

Gene Mapping of Complex Phenotypes

Extensive maps of the human genome are a powerful and valuable tool for analysis of complex phenotypes, but they are not a panacea (Cloninger et al. 1983b; Sturt and McGuffin, in press). Careful attention to the specification of the phenotype, measurement of antecedent biosocial risk factors that may allow detection of well individuals, and evaluation of mode of inheritance are critical aspects of the problem. A
major issue that has not been ade-
quately discussed is the utility of
high-risk projects in testing the va-
lidity and generalizability of reports
of linkage between genetic markers
and putative susceptibility loci for
complex phenotypes.

In the presence of genetic hetero-
geneity and/or complex develop-
ment, the interpretation of reports
of linkage is not as straightforward
as with rare discrete disorders like
Wilson's disease or Huntington's
disease. Many geneticists are
emphasizing the identification of
large, multigenerational pedigrees
with many affected individuals,
then testing a large number of ran-
domly selected markers against
many alternative disease classifica-
tions. Such a procedure has several
inherent dangers that may confound
meaningful interpretation.

First, large pedigrees with many
affected individuals may not be rep-
resentative of the disease under
study. For example, schizophrenia is
associated with reduced fertility, so
that families with large sibships may
yield an atypical sample. Likewise,
most schizophrenics do not have
multiple affected relatives, so the
pedigrees that are most informative
for linkage analysis cannot be read-
ily generalized. This difficulty is
compounded unless informative
pedigrees are ascertained using a
specific criterion from systematic se-
ries of patients; without a definite
sampling frame, no generalization at
all is justified. No matter how stri-
k ing the strength of association in a
particular pedigree from an un-
defined sampling frame, it must be
considered an anecdotal observation
or case report.

Second, the significance of ob-
served associations is uncertain
when multiple criteria for defining
the phenotype are considered. So
many markers and criteria can be
considered that it is likely that some
disease definition will be correlated
with some genetic marker by
chance. Unfortunately, in the pres-
ence of heterogeneity, such isolated
reports of linkage in a particular
large pedigree cannot be falsified. If
another investigator does not con-
firm an earlier linkage claim, this
can be explained as consistent with
gene heterogeneity.

To be able to falsify and generalize
from linkage trials in large ped-
igrees, it is necessary that they be
drawn systematically from well-de-
finite samples, such as those under
investigation in high-risk studies of
schizophrenia. Many of these fam-
ilies have no secondary cases of
schizophrenia and would be unin-
formative in linkage analysis of sus-
ceptibility to narrowly defined
schizophrenia. However, if linkage
is a finding of practical clinical im-
portance, there will be some ped-
igrees in every series that are
informative. Once linkage is found
between a marker and some cases of
schizophrenia in multiplex ped-
igrees from two or more series, ge-
netic heterogeneity and linkage can
be considered confirmed. Then the
association between the genetic
marker and other behavioral abnor-
malities can be explored to clarify
the range of clinical expression in
the schizophrenia spectrum. To do
this, of course, blood samples must
be obtained to extract DNA from
white blood cells and to preserve
other cells and plasma.

Recommendations

The risk of schizophrenia in children
of schizophrenic parents varies
widely depending on additional in-
formation about psychopathology
and biosocial risk factors in other
family members. Segregation and
path-analysis methods permit effi-
cient quantitative prediction of risk
using both clinical and biosocial
pedigree data. These methods also
permit tests of mode of inheritance
and etiological heterogeneity. To
take optimal advantage of these re-
cent advances in genetic epidemiol-
ogy, several steps must be taken in
future high-risk studies:

1. Descriptive information about
probands and their extended fam-
ilies must be recorded in a standard-
ized way to facilitate comparison of
different samples. Pedigree sum-
maries including at least first and
second degree relatives of probands
need to be prepared for pedigree
analysis to evaluate mode of inher-
itance and quantify risk.

2. Multiple clinical, physiological,
and social variables about each fam-
ily member are desirable to charac-
terize heterogeneity, to identify
antecedents of later clinical distur-
bances, and to permit evaluation of
the inheritance of different clinical
and biosocial variables associated
with the schizophrenia spectrum.
More emphasis is needed on profiles
or sets of multiple indicators rather
than on individual biosocial
markers, because no one antecedent
of schizophrenia is likely to be both
a sensitive and specific indicator.

3. Evaluation of the relationship
between schizotypal traits and nar-
rowly defined schizophrenia needs
to be carried out in longitudinal
studies in the general population as
well as in families at high risk for
schizophrenia. This will clarify the
specificity of available measures of
schizotypal traits and the bound-
daries and range of behaviors in the
schizophrenia spectrum. Accurate
quantitative predictions of risk can-
not be made from pedigree data
without precise specification of both
psychotic and nonpsychotic cases.
within the spectrum, so the need for this work is urgent.

4. Segregation analysis of families with large sibships can be used to identify families that provide the strongest evidence for major gene effects. These families should be informative in linkage studies that can be carried out in collaboration with others. More attention to sampling issues that may confound the generalization and falsifiability of linkage trials is needed. The sampling frame of families selected for linkage analysis must be well defined.

5. Blood samples should be obtained from available subjects in high-risk studies to extract and preserve DNA and other materials for later genetic analysis. Ten milliliters of venous blood contains sufficient nucleated white blood cells to yield 200 to 300 micrograms of DNA in most cases. This can be cryopreserved for later analysis. If such material is not preserved now, it will not be possible to relate the current studies to future advances in the genetics of schizophrenia. When heterogeneous series of schizophrenia can be subdivided according to genetic and biological markers, the findings about developmental course obtained in current longitudinal studies will remain informative only if DNA and other relevant biological material has been preserved.

References


**Acknowledgments**

Preparation of this report was supported in part by NIMH grants MH-31301 and Research Scientist Development Award MH-00048, and by the MacArthur Foundation Network on Risk and Protective Factors in Major Mental Disorders.

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