Development of an Infrastructure for Molecular Genetic Analysis in Psychiatry

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Clinical Material

Molecular genetic studies in psychiatry are dependent upon the development of repositories of clinical information and genetic material derived from a large number of families in which there are family members with clinically and biologically characterized psychiatric illness. It seems likely that major psychiatric illness is caused by a series of different genes which may exert their effects singly or, in some instances, together. It is therefore particularly important that material be obtained from a large number of families to address questions of genetic heterogeneity. Ideally, families for genetic studies should be derived from population groups from various parts of the world, since the various genes involved in determining susceptibility to development of psychiatric illness may have different frequencies in different populations.

Family Size and Structure

Although much progress has been made in genetic linkage analysis through the utilization of large pedigrees in which a particular genetic disease occurs in a large number of individuals, for example, Huntington's chorea (Gusella et al. 1983), it is important to be aware that, if only high-density families are utilized, we may in the case of certain diseases be selecting for particular subtypes of an illness. If small families are utilized, perhaps the minimum informative structure is an affected proband with one unaffected sib and both parents available.

Diagnostic Criteria

Ideally, a number of different classification systems should be used for defining psychiatric illness in families to be included in genetic linkage studies. It is critically important that comprehensive descriptions be available regarding the classification systems and thresholds used.

Development of Comprehensive Data Bases

Progress in delineating the molecular basis of psychiatric illness will be expedited by the development of comprehensive data bases which include not only clinical diagnostic information and results of genetic marker analysis but also neurophysiological, neuroendocrine, and neurochemical indices and neuropharmacological information.

Aspects of linkage Analysis

In carrying out linkage analysis in psychiatric illness it will most likely be important to utilize models based on several different modes of inheritance and various different degrees of penetrance. Particular emphasis may need to be placed on affected individuals within one family. Since the development of overt psychiatric disease may require the predisposing gene and additional factors (e.g., age-related factors, inducers), unaffected family members may provide less information. Ongoing exchange of ideas between clinicians and statisticians will be valuable to devise better models for linkage analysis in psychiatric illness.

Studies in Special Populations

There are a number of examples in the literature in which mapping of genetic disease genes was greatly facilitated by the identification of individuals in whom genetic disease was cosegregating with a cytogenetically detectable structural chromosomal aberration. One example of this is the deletion on the X chromosome which facilitated mapping of the Duchenne muscular dystrophy disease gene (Franke et al. 1985). Detection in particular families of the cosegregation of psychiatric illness and chromosomal rearrangements could greatly facilitate identification of chromosomal regions which are important in the causation of such illnesses.

It is therefore important to obtain a careful family history to identify those families with mental illness and a history of multiple miscarriages or developmental abnormalities present in immediate or extended family. If such families are identified, chromosome analyses should be carried to search, for example, for balanced and unbalanced chromosome translocation carriers.

Collection and Handling of Samples

Wherever possible, efforts should be made to obtain blood samples suitable for establishing lymphoblastoid cell lines. Such cell lines not only serve as a resource for preparation of DNA but can be utilized subsequently for analysis of large fragments of DNA, e.g., utilizing pulse-field gel electrophoresis.

In situations in which it is not possible to establish cell lines, alternate procedures may be used, e.g., obtaining white blood cell samples for DNA preparation,

freezing of white blood cells or whole blood in DMSO for subsequent culture, or freezing of white cells for subsequent DNA isolation. In collecting samples for linkage analysis it is important to store red cells and plasma/serum since protein markers may be valuable.

Possibilities for Various Centers to Participate in Different Phases of Molecular Genetic Analyses in Psychiatric Disorders

In establishing an infrastructure for molecular genetic studies in psychiatry it is important to note that there are different phases of the projects, including clinical evaluation, laboratory analyses, and statistical analyses.

Centers may participate in one or more of the following phases:

1. Identification of families and patient groups of interest.
2. Obtaining blood samples for storage or for establishing cell lines. In phases 1 and 2 investigators will need to be aware of sociocultural factors which may affect the obtaining of information about family structure or obtaining blood samples.
3. Karyotypic analysis in special groups of patients.
4. Analysis of polymorphic DNA markers. Centers involved in such studies will need to have available a large series of informative polymorphic DNA probes.
5. Linkage analysis. Centers involved in linkage analysis will need to have available programs for two-point and multipoint linkage analysis and facilities for maintaining comprehensive data bases for information gathered in families submitted for linkage analysis.
6. Derivation of new probes in specific chromosomal regions which appear to be important in psychiatric illness, based on the results of linkage analyses.
7. Analysis of large fragments of DNA through pulse-field gel or CHEF gel electrophoresis to define the presence, at a molecular genetic level, of possible deletions or rearrangements.
8. mRNA analysis. Having identified chromosomal regions which are closely linked to specific psychiatric disorders, it will be advantageous to have available tissue banks containing brain tissue, so that mRNA can be prepared and subsequently screened for detection of expressed sequences.
9. Analysis of DNA sequence.

References

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