Review Article

MOLECULAR GENETICS IN MENTAL ILLNESS

**Col PK CHAKRABORTY*, Lt Col T VARGHESE+,
Sqn Ldr PL NARAYANA#**

MJAFI 1994; 50 : 211-214

KEY WORDS : Molecular genetics; Mental illness.

Introduction

More than one-fifth of the proteins, in each human being exist in a form that differs from the one present in the majority of the population. This remarkable genetic variability determines, among other body traits, the ability of each individual to meet the environmental challenges in a manner different from other. All human diseases, including psychiatric disorders, can be considered to result from an interaction between an individual's unique genetic makeup and the environment. The relative contribution of each may vary in a given disease.

The genetic basis of the psychiatric disorders has since long been presumed, because of the observations that they frequently occur in families and close blood relations. In some conditions, like the Huntington's disease, a single gene effect is strongly suggested by the pattern of inheritance. In others, like the psychoses, although there is no consistent pattern of Mendelian transmission, the evidence that the genetic factors play a major role is strong. For example, Rosenthal, reviewing the literature, states that the major cause for almost all the schizophrenia spectrum disorders is genetic [1]. Most of such psychiatric disorders fall into a category of complex genetic disorders, which may be explicable in terms of the interaction of small number of

genes (oligogenic model) or require the minor involvement of many genes (polygenic model) or require, in addition, environmental co-factors (multifactorial model). In spite of the strong presumptive evidence, the genetic basis of mental illness has not been firmly established. The recent advances in molecular biology have rejuvenated the psychiatric genetics and have renewed hope for the discovery of the disease-related genes.

Tools for Studying DNA

Molecular genetics is the study of the genes and the gene expression at the basic chemical level. The entire human genome contains about 3 billion base pairs of DNA and encodes 30,000 to 1,00,000 gene products. Each individual inherits two copies of this genome, and the DNA is packaged as 23 pairs of chromosomes. Each chromosome contains a single linear duplex DNA molecule, which is polymer composed of purine and pyrimidine bases. A gene represents the total sequence of a single polypeptide chain of a protein molecule. Thus the genes, through the proteins, determine the structure and function of the body.

In studying the DNA and the genes, the following tools are used in general :

1. *Restriction endonucleases* : These are bacterial enzymes, which cleave DNA only at locations at which specific

* Prof & Head; + Assoc Prof; Dept of Psychiatry, AFMC, Pune 411 040. # Graded Specialist (Psy), CH (SC), Pune 411 040.

nucleotide base pair sequences occur, thus giving a one - dimensional restriction map for that DNA.

2. *Recombinant DNA and gene cloning* : Recombinant DNA is a molecule with nucleotide sequences derived from more than one organism, made by inserting the foreign (e.g. human) DNA fragment into the genome of a vector (e.g. bacteriophage). By the multiplication of the vector these molecules or the genes can be cloned in abundant number
3. *Gene probes* : These are lengths of DNA constructed such that they have a nucleotide base sequence complementary to that of a given part of the genome. When used, these probes seek out complementary genomic DNA and hybridise with that.
4. *Southern blotting* : This is a technique of transferring DNA fragments to a nylon or nitrocellulose filter by overlaying the gel with the filter and overlaying the latter with paper towels and blotting a solution through the gel to the paper.
5. *Linkage analysis* : This is the most commonly used molecular genetic technique. Genes that are close to (i.e. linked to) one another on the same chromosome tend to be transmitted together from the parent to the child, whereas those that are far apart tend to be transmitted independently. Accordingly, it is possible to detect a susceptibility gene for a given disorder by demonstrating that it is transmitted together or is associated with the presence or absence of a known genetic marker like the RBC antigen or the restriction fragment length polymorphisms.

Specific Techniques as Applied to Psychiatric Disorders

In the case of the inherited psychiatric disorders with known genetic loci, there is little difficulty in identifying the molecular pathology by applying the above techniques.

For the disorders caused by gross chromo-

somal lesions, the restriction maps will identify the lesions because of the changes in the size of the appropriate DNA fragments detected by the gene probes. To identify the molecular pathology of those disorders caused by point mutation, the oligonucleotide probes can be used. But the genetic loci are not yet known for the majority of the psychiatric disorders with a genetic component. In such cases even the biochemical defects are often not known. It is in these cases that the linkage analysis is proving to be a powerful investigative tool. For this purpose, large multigenerational pedigrees are used preferentially as they contain more genetic information than nuclear families. The availability of the large sibships reduces the number of families needed to reveal linkage and also overcomes the problems of heterogeneity of linkage.

Another method is using the candidate genes, when there is reason to believe that the protein coded by a particular gene may be defective in the disorder. For example, if complementary DNAs for the subunits of a given neurotransmitter receptor are available and if there is psychopharmacological evidence that this neurotransmitter may be involved in a certain psychiatric disorder, then those complementary DNAs can be used as the candidate genes in the investigation of the genetic causation of that disorder.

Yet another method is to concentrate on a particular part of the genome because of some information which indicates its relevance to a disorder of unknown genetic locus. An example is the known link between the neuropathology of the Down's syndrome, resulting from trisomy 21, and that of the Alzheimer's disease. Because of this association, effort was concentrated on chromosome 21 in the search for the inherited defect in the Alzheimer's disease [2].

Recent Advances

I. The Psychoses

Schizophrenia : Bassett *et al* reported the cosegregation of partial trisomy of

chromosome 5 with schizophrenia in an Indian family in Canada [3]. Later some workers have reported a linkage between a region on the long arm of chromosome 5 (5^{q11-13}) and schizophrenia in Icelandic and British families. But the same could not be replicated by others [4]. A candidate gene of major interest in schizophrenia is the dopamine D2 receptor gene (DRD2). The DRD2 gene has recently been mapped to the q^{22-23} region of chromosome 11. This and the identification of a linked RFLP now facilitate the testing of the dopamine hypothesis of schizophrenia at a molecular level.

Affective Disorder : Following their investigation of a relatively large American Old Order Amish pedigree, Egeland *et al* reported linkage between a locus on the short arm of chromosome 11 and bipolar mood disorder [5]. Medlewicz *et al* and Baron *et al* reported a linkage between bipolar mood disorder and a region of the long arm of X chromosome close to the locus for the fragile X syndrome [6,7]. It is now felt that an X-linked variant or subtype of bipolar mood disorder may exist and the failure to replicate this X linkage by some other workers may be due to the aetiological heterogeneity of this disorder [2].

It is of interest that the gene encoding the alpha-3 GABA receptor has recently been mapped to Xq^{28} , close to the G6PD gene. The possible involvement of GABA receptors in affective disorders and the reports of linkage to the nearby G6PD locus makes this a candidate gene for attention.

Possible nature of the psychosis gene : Neurotransmitter-related genes (coding for monoamine synthetic enzymes or receptors) or the critical genes that control the brain growth are considered as candidates for a psychosis gene. The findings of Crow *et al* indicate that the psychosis gene itself may be a component of the genetic determinants of cerebral asymmetry located on the X and Y chromosomes [8].

A problem for any genetic hypothesis of psychosis is to explain the age of onset of the illness and its episodicity. It is said that a

sybiotic relationship between the cerebral dominance gene and the viro gene (retroviral sequence inside a human genome) develops early in man's evolution from the other primates and this gene complex (viro gene + cerebral dominance gene) includes a component that is subject to significant variation between individuals. This component is responsible for variations in expression including those that lead to psychosis [9].

II. Dementias

Huntington's Disease : The gene for this is localised to the most distal band of the short arm of chromosome 4 using loci very tightly linked to the disease locus and mapping. This HD-gene is expected soon to be cloned and characterised.

Transmissible spongiform encephalopathies : The abnormal isoform of the otherwise normal intracellular prion protein, which accumulates as the amyloid plaques in Gerstmann-Straussler syndrome and familial Creutzfeldt-Jakob disease is traced to the point mutation in the prion protein gene (pr p gene) on the short arm of chromosome 20 [9].

Alzheimer's Disease : The amyloid protein core of the neuritic plaques of AD pathology is traced by some studies to the mutation in the B-amyloid precursor protein gene (B-APP gene) located on the proximal part of the long arm of chromosome 21. [9].

III. Mental Retardation

A fragile site on the X chromosome localised to $Xq 27$ occurs in the inherited form of mental retardation known as Fragile X syndrome. Close linkage has been found between the fragile site and the coagulation factor IX locus in that region of the X chromosome [2].

Uses of Molecular Genetics

The techniques of molecular genetics have made it conceptually possible to diagnose, prevent and treat mental disorders at this most basic molecular level [10]. However, it is not yet possible to use them widely in day to day clinical practice.

1. Using these techniques the genes for psychiatric disorders can be identified which leads to greater insight into their aetiology and to sound ways of classifying them.
2. Knowledge of the genes location enhances the precision of diagnosis. This allows screening in prenatal or presymptomatic stages, which will be useful in accurate genetic counselling.
3. When the defective gene is isolated and its product identified, definitive prevention and treatment measures could be devised.

Limitations and Problems

While the molecular genetic techniques have proved spectacularly successful with the single gene disorders, the major psychiatric diseases present significant problems, because the definition of their phenotype is unclear, the age of their onset is variable and their diagnoses uncertain. These diseases are incompletely penetrant and the modes of their inheritance do not fit Mendelian models. Nonallelic genetic heterogeneity (several genes each being able to cause a similar clinical syndrome) is a possible aetiological factor. Families may therefore have several disease genes segregating and interacting. Thus the linkage findings of many studies, relating a particular gene to a specific psychiatric disorder could not be replicated.

Conclusions

The application of molecular genetics to the problems of psychiatric diseases has made significant progress in a number of areas, though there have also been some false positive findings. The pitfalls of these studies, as have been pointed out by many, can be avoided and their validity and reliability improved if decisions concerning the models and the phenotype definitions are made beforehand; if due consideration is given to the age of onset and to the effects of cohort, of

multiple testing and of the assorted mating; if the diagnostic determinants are made blind to the genetic marker data; and if large and dense pedigrees are selected for the study [11].

However daunting the enormous size of the human genome, the process of sequencing and mapping all these genes including the psychiatric disease related genes on this is likely to be a reality soon, given the modern-day sophisticated molecular genetic techniques.

REFERENCES

1. Rosenthal D. Genetic aspects of schizophrenia. In : Van Praag HM, Lader MH, Rafaelsen OJ, Sachar EJ, eds. *Handbook of Biological Psychiatry*. New York : Marcel Dekker Inc, 1980; 3 : 31-2.
2. Puri BK, Tyrer PJ. Genetics. In : *Sciences Basic to Psychiatry*. New York : Churchill Livingstone, 1992; 143-75.
3. Bassett AS, Jones BD, Mc Gillivray BC, *et al*. Partial trisomy chromosome 5 cosegregating with schizophrenia. *Lancet* 1988; i : 799-801.
4. Kaufman CA, Delisi LE, Lehner T, *et al*. Physical mapping and linkage analysis of a putative schizophrenia locus on chromosome 5q. *Schizophrenia Bulletin* 1989; 15 : 441-52.
5. Egeland J, Gerhard DS, Pauls DL, *et al*. Bipolar affective disorders linked to DNA markers on chromosome 11. *Nature* 1987; 325 : 783-7.
6. Mendlewicz J, Simon P, Sevy S, *et al*. Polymorphic DNA marker on X chromosome and mania-depression. *Lancet* 1987; i : 1230-2.
7. Baron M, Risch N, Hamburger R. Genetic linkage between X chromosome markers and bipolar affective illness. *Nature* 1987; 326 : 289-92.
8. Crow TJ. Temporal lobe asymmetries as the key to the aetiology of schizophrenia. *Schizophrenia Bulletin* 1990; 16(3) : 433-43.
9. Walsch C, Collinge J, Crow TJ. Molecular and clinical genetics in relation to psychiatric disease. In : Granville-Grossman K, ed. *Recent Advances in Clinical Psychiatry*. New York : Churchill-Livingstone, 1991; 7 : 119-34.
10. Grebb JA. Neural Science. In : Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*. Baltimore : Williams and Wilkins, 1989; 5-6.
11. Baron M, Endicott J, Ott J. Genetic linkage in mental illness - Limitations and prospects. *Br J Psychiatr* 1990; 157 : 645-55.