17

# BIOLOGICAL PSYCHIATRY

## MOLECULAR GENETICS AND PSYCHIATRY

### REVIEW OF RECENT DEVELOPMENTS

**P.N. SURESH KUMAR**

MD., DPM, D.N.B. (PSYCH.), MNAMS

LECTURER

DEPARTMENT OF PSYCHIATRY

MEDICAL COLLEGE

CALICUT

Young Dr. Suresh kumar, lecturer Calicut medical college is a promising star in the Kerala academic circle. In this exhaustive review on genealogy he has covered all the recent concepts save some.

*REPRINT REQUEST*

*Dr. P.N. SURESH KUMAR*
*M-26 (A) 62*
*Malaparamba Housing Colony*
*Calicut - 673 009*
*Kerala.*

"Once the gene or set of genes responsible for making people predisposed to mental ailments like schizophrenia is identified, it is going to revolutionise clinical psychiatry".

**Nobel Laureate James D Watson.**

## INTRODUCTION

Gregor Mendel an Austrian Monk began studies of inheritancee in 1856. Mendel proposed that inherited traits were transmitted through inherited factors that are now called as "genes" and the result of genetic expression could be predicted by a study of the characteristics of the of the parents. In 1906, Bateson named the new science of inheritance as "genetics".

## BASIC PRINCIPLES

One of the few clear leads in understanding the aetiology of the major psychiatric and neuropsychiatric illness is that a genetic component is involved. In major psychoses since there is no consistent pattern of mendelian transmission, they fall into a category of "complex genetic disorders" with interaction of small number of major genes (polygenic model) or require in addition environmental cofactors (a multifactorial model) (Walsh et al, 1991). The recent development of restriction fragment length polymorphism (RELPs) as genetic markers permits the study of genetic disorders whose underlying pathophysiological mechanisms are unknown. In the case of single gene disorders the power of "reverse genetics" has been clearly demonstrated by the recent identification of genes responsible for cystic fibrosis. By this method, it is now possible to locate, identify and characterize defects in a disease causing gene without necessarily knowing anything about the disease pathology.

The first phase of reverse genetic approach is to collect families with multiple affected numbers (multiplex fami-

lies) with a clearly defined disease phenotype. The mode of inheritance is then determined by segregation analysis. The next step is to determine the position of the disease gene on the chromosome. On occasions there will be clues from known pathological data suggesting a "candidate gene" (e.g..tyrosine hydroxylase gene, rate limiting step enzyme in the catecholamine metabolism is considered a candidtate gene in affective disorders) (Egeland et al, 1987); the co-occurrence of the disease with chromosomal anomaly (Alzheimer's disease(St.George-Hyslop et al, 1990) or direct linkage if the chromosome breakpoint in a translocation has directly interrupted the gene of interest. In the absence of such clues, it is possible to map the disease gene by looking sequentially a large number s of anonymous DNA markers mapped to particular chromosomal regions and following the segregation of these markers through the families. Since such co-segregation can occur by chance, statistical analysis is performed using LOD score method. This method calculates the odds ratio- the odds of the observed distribution of disease phenotypes and DNA marker alleles occuring assuming that the disease and the marker are genetically linked (i.e. are close together on the same chromosome) over the odds that this distribution could occur when the disease and the marker are unlinked (i.e. are located on different chromosomes). The logarithm of this ratio or LOD score is then calculated A LOD score of greater than 3 (an odds ratio 1000:1) is conventionally taker to infer genetic linkage whereas a LOD score of -2 infers non linkage The number of genetic recombinant events (when a cross over in meosis occurs between the disease gene and the genetic marker locus) gives an estimate of the genetic distance on the chromo some between DNA marker locus and disease locus (Ott, 1985). Once the genetic linkage is demonstrated, a pooling of all family data with known genetic markers in the disease region enable fine mapping to a small chromosomal region flanked by two known markers (Davies & Read, 1988).

While these techniques are successful with single gene disorders the problem with psychiatric disorders are

unclear definition of the phenotype, variable age of onset of psychiatric disorders, incomplete peneterance, gene environment interactions, multiple disease susceptible loci, epistasis (gene - gene interactions between different loci), inconsistent pattern of mendelian inheritance, diagnostic inconsistencies with lack of ability to corroboratte diagnosis by laboratory investigations, assortative mating and non-allelic genetic heterogeneity (several genes being able to each cause a similar clinical syndrome). Among these the most serious obstacle is genetic heterogeneity. Even moderate degrees of genetic heterogeneity may influence the LOD score with evidence of linkage in one family being offset by non linkage in another resulting in failure to detect linkage and to erroneous exclusion of a locus in a proportion of cases (Lander & Botstein 1986). By focusing on large pedigrees with a high density of a disorder, the likehood of detecting a single, highly penetrant gene is increased. However, for both schizophrenia and bipolar affective disorder such multiplex families are rare, and data from epidemiological studies do not support the role of a single major gene in either disorder (Mc Gue et al, 1986). The use of standardised criteria has led to improved reliability but the validity of such diagnoses remains uncertain (Gottesman & Shields, 1972). Phenotypic assignment is also complicated by non-genetic forms of schizophrenia and BPAD (Propping, 1983) and by the problem of incomplete peneterance. The existence of discordant MZ twin pairs in both disorders has also been considered evidence of non-genetic forms of psychosis.

A possible clue to the nature of genetic mutation predisposing to psychiatric disorders comes from studies of anticipation, a phenomenon whereby a disorder shows decreasing age of onset and/or increasing severity over generations. Several disorders including Huntington's disease and mytonic dystrophy exhibit this phenomenon and expansion of unstable trinucleotide repeat sequences (dynamic mutations) has been shown to provide a molecular mechanism for anticipation (Asherson et al, 1994).

# AFFECTIVE DISRODER

## I Linkage studies with DNA Markers

### Markers on X Chromosome

Data from family studies indicating a lack of father-to-son transmission and an excess of affected females led investigators to suggest an 'x' linked dominant transmission in BPAD showing close linkage with colour blindness (CB) and glucose-6- phosphate dehydrogenase (G6PD) deficiency (markers located in Xq 26-28 on the long arms of chromosome X) in large sample of families (Sevy & Mendlewics, 1993). However, more recently it has been shown diminshed support for linkage between BPAD and X-chromosome DNA markers (Xq 27-28 region) in BPAD pedigrees previously analysed with phenotypic markers in this region (Baron et, al, 1993). Moreover, evidence of male-to-male transmission and reports of no linkage to the same markers in this pedigrees made it clear that a y linked form of BPAD could account for no more than a subset of cases. Pooling data from a number of sources, Risch et al (1986) found significant evidence of linkage heterogeneity and estimated the proportion of bipolar population to carry this putative 'x' linked gene to be as high as 30%.

While studying other polymorphic D.N.A. markers, Mendlewics et a; (1987) reported loose linkage to the coagulation factor IX(F9) locus at Xq27 in nine Belgium pedigrees. The F9 locus is localised at a large distance of the CB and G6PD genes and this result could be explained by the presence of a second gene for BPAD in this region. In contrast, exclusion of linkage of BPAD to several X-chromosome DNA markers at Xq28 has been reported in nine American pedigrees (Barrettinin et al, 1990).

Taken together, the studies to date would seem to indicate that an X-linked variant of BPAD may exist but that such form of illness must be