At the outset, let me convey my sincere thanks to the honourable fellows of IPS for having given me this opportunity to serve the highest office of our beloved Society. It gives me an immense joy to recall my humble participation in our IPS during the last two and half decades, as I assume this august chair with your good wishes and blessings. As it is customary to deliver an oration on a personally preferred theme as the presidential address, several topics came to my mind. Ever since, my respected teacher Prof. A. Venkobarao introduced me to the field of Psychiatry, Prof. M. Saradha Menon and Prof. O. Somasundaram guided me in to the arena of research in Psychiatry, the foremost in my mind was to somehow contribute my little, towards the exploration of the etiologically elusive schizophrenia. In no small measure, the field of Psychiatric Genetics has attracted me, which I thought no small measure, the field of Psychiatric Genetics has attracted me, which I thought of this complex disorder of the brain. There are also some exciting preliminary findings on a possible genetic subtype of schizophrenia.

This oration summarizes the progress in this area, emphasizing findings of potential interest to clinicians and unfolding the scope for future research.

Classic Mendelian inheritance patterns are generally not observed in schizophrenia. Models proposed to explain the genetic complexity of schizophrenia include multifactorial inheritance (multiple genes with a nongenetic component) and epistasis (few genes acting jointly). In the general population there are likely to be several causal or susceptibility genes (genetic heterogeneity) and nongenetic causes (etiologic heterogeneity). Environmental components may also be minor factors in causing familial forms of schizophrenia. Results of studies of the offspring of discordant monozygotic twins are consistent with incomplete penetrance (some individuals carrying the genetic defect but not manifesting schizophrenia), variable expression (less severe manifestations of illness) and a low phenocopy rate ("sporadic" cases) in familial forms of schizophrenia.

Gene linkage and association studies are the principal research methods likely to localize genes. No single gene has yet been identified as causing or predisposing a person to schizophrenia. However, there are several promising findings with suggestive linkages, some of which have been replicated, providing evidence that genes related to schizophrenia may be present in several chromosomal areas.

A large number of early studies based on segregation analyses supported a genetic etiology underlying this disease. However, it was the development of restriction fragment length polymorphism (RFLP) as a mapping tool by Botstein et al. (1980) which provided markers that could be used to track the chromosomal region(s) of interest. A cytogenetic marker for the probable location of a schizophrenia gene came much later in 1980's when a balanced translocation was reported in a family with two males affected with schizophrenia, an uncle and a nephew. Both the males were found to be partially trisomic for chromosome 5q 11.2 - q 13.3 and carried an extra copy of this region translocated onto chromosome 1.

**FAMILY STUDIES**

Ever since Kallman (1938) reported on the empirical risks in the families of schizophrenics, several observers have reported on the prevalence of schizophrenia in the families of probands. According to these studies, the prevalence in the general population was about 1%, and in the child with one schizophrenic parent it was 12%, while in the child with two schizophrenia parents, the prevalence was around 40%. The prevalence in the non-twin sib of the patient was around 80%. Schizophrenia is aggregated in families because of underlying genetic factors.

High familial loading has been found to be associated with early onset of schizophrenia (Kendler & MacLean, 1990). Besides, larger periods of hospitalization and more severe social disability has also been noted in cases with familial loading (Verdoux et al, 1996).

Gottesman (1993), has pointed out that schizophrenia is more common in the children of patients (13%) than in their parents 6% or, siblings 9%, despite the fact that all of them are first degree relatives, and the genetic correlation is the same (r=0.50). Although this result may be more consistent with the environmental hypothesis according to which children learn psychotic behavior from their parents, still the possibility exists that the recently found mechanism of "anticipation" due to expansion of trinucleotide repeats in the genes involved may play a role in the inheritance of schizophrenia.
ADOPPTION STUDIES

The best known adoption study is the series of studies usually referred to as the Danish-American adoption study (Kety et al 1968, 1975; Roseenthal et al 1971, Wendt et al 1974, Kendell et al 1981 & 1994). The findings of this study have been regarded as the strongest evidence to date, for the heritability of schizophrenia. Schizophrenia and disorders approaching it (and included in the so-called schizophrenia spectrum) were found to be more common among adoptive children with schizophrenic biological mothers, or among their biological relatives, than in control groups consisting of other adoptive children or of biological relatives of the adoptive parents. However, the weakness of these studies is partly methodological and partly connected with findings which suggest a relatively strong element of heritability when a broad diagnostic criteria is used, but a relatively low heritability when a narrow criterion is applied.

The largest adoption study of schizophrenia is that of Tienari et al, 1992, 1993, 1994 (b), based on a sample including the adopted-away children of all of the women who had been in-patients in Finnish mental hospitals because of schizophrenia, between 1960 and 1979 and their matched controls.

The significance of genetic factors was confirmed among 136 early adopted away offspring of RCD/DSM III R diagnosed schizophrenic mothers. There were seven DSM III R schizophrenics, compared to two among the 185 control adoptees. The findings of the study also demonstrate that a healthy family environment can protect from disturbance even children whose biological mothers have had schizophrenia.

TWIN STUDIES

According to twin studies, the concordance for monozygotic twins varies between 15 and 58%, and that for dizygotic twins range between 4 and 27%, depending upon the diagnostic criteria used (Tienari, 1963; 1975, Gottesman & Shields, 1966, Krähenbühl, 1967). Nonetheless, the MZ twin concordance rate is substantially less than 100 percent, and thus (non Familial) environmental factors, be they prenatal, perinatal or sociocultural play a significant role in the etiology of at least some forms of schizophrenia.

Recent twin studies of schizophrenia have involved the offspring of discordant monozygotic twins. Gottesman and Bertelson, 1989, found no difference in the prevalence of schizophrenia in the children of the sick twin (16.8%) and in the offspring of the twin who remained healthy (17.4%). Krähenbühl and Cramer, 1989, on the other hand, reported a completely contradictory result. In their sample, 17.9% of the children of the sick twin were ill, compared to only 4.4% of the healthy twin. Although the difference did not reach the statistical level of significance, these contradictory findings again indicate the problems encountered in genetic studies of schizophrenia.

Stabenau and Pollin (1993), have pointed out that fewer than 50% of monozygotic twins are concordant, and that the twin with the lower birth weight, who usually remains the submissive twin in the pair, has a higher risk of becoming schizophrenic than the twin with the higher birth weight. However, differences of genomic DNA between monozygotic twins who are discordant for schizophrenia, by using restriction land mark genome scanning (RLGS) has been reported by Takahira Tsujita et al, 1998.

More recently, Klausing, 1999 reported that dizygotic twins are at increased risk of schizophrenia and he draws attention to the nature of dizygotic twinning. Twinning itself is reported to be familial, Boklage (1977), suggested that there is a relationship between handedness, twinning and schizophrenia. Is there something about this process that yields a clue to the origin of psychosis?

STUDIES IN MOLECULAR GENETICS

Linkage in molecular genetic studies refers to the fact that a gene is located near a specific DNA marker on the chromosome. Linkage analyses are based on family and pedigree studies, and their result is the so-called logarithm of odds (lod) score. (A lod score of 3 or more constitutes statistically significant proof of linkage, and a lod score of 2 or lower excludes linkage).

Association studies use unrelated affected individuals and appropriate control individuals. Therefore, they are case control studies. In reality, an association between a disorder and an allele is not possible without linkage between the disorder and the marker gene. Association studies are particularly effective, if the disease allele contributes only a small effect size, but given a gene with major or modest effect size, genetic markers have substantially less coverage in association studies than in linkage studies.

The first molecular genetic studies of schizophrenia involved the work of Bassett et al, 1988, who reported that schizophrenia appeared to be inherited with a translocation involving chromosome 5. However, other researchers were unable to confirm this finding (Kennedy et al, 1988, Kaufman et al, 1989, Mc Guffin et al, 1990, Aschauer et al, 1990, Chir et al, 1989). Also, a similar translocation involving chromosomes 2 and 18 had already been reported by Genest et al, 1976. A possible explanation for the accidental association of translocations with schizophrenia is that these chromosome mutations cause an imbalance in the whole genetic system, thus adding individual vulnerability to psychotic disturbance.

Linkage between schizophrenia and the chromosome region 6 pter - p22 has been postulated by Wang et al, 1995; Straub et al, 1995. However this could not be confirmed by many (Mowry et al, 1995; Gurling et al, 1995; Antonoerakakis et al, 1995; Schwah et al, 1995).

Moises et al, 1995, using a new and powerful non-parametric linkage test, namely the weighted rank pair wise correlation statistic (WPRC) of Commeneges et al, 1994 and a narrow criteria for diagnosis of schizophrenia, found in a genome wide search, five different loci, one located on 6p and the others on 8p, 9, 20 and 22 which acting in concert, could cause susceptibility to this disease. Linkage with Chromosome 13 has been suggested by Lin, et al, 1995.

Two out of the 100 schizophrenic patients examined by Karayiorgou et al, 1995, carried micro deletion at the Chromosome region 22 q 11.
A maximal lod score of 1.9 in the region of chromosome 5 q 31, which is suggestive of linkage, was reported by Wildenauer et al., (1995).

More than one group has reported positive linkage results on chromosome 13q (Pulver et al 1996; Lin et al, 1995).

Report of a chromosome 18 to 1 translocation associated with schizophrenia (Smit et al, 1995) and one from Chromosome 11 to Chromosome 1 (Arveiler, 1997) require further confirmations.

A microdeletion on chromosome 22 q 11 has received much attention over the past few years since Pulver et al, 1994 reported a suggestion of linkage to schizophrenia distal to the region of this deletion on 22 q 12. Patients with Velocardiofacial syndrome (VCFS), which characterizes individuals with the deletion, are known to have an increased prevalence of schizophrenia, and some schizophrenic patients are known to have minor physical anomalies resembling those seen in VCFS, as well as microdeletion in this region (Gothelf et al, 1997).

**PSEUDOAUTOSOMAL LOCUS:**

The pseudoautosomal locus is located with the region of the short arms of both X and Y chromosomes where exchange of genetic material takes place in male meiosis. This region is not subject to X inactivation in the female. A pseudoautosomal gene inherited from a father will be passed above chance expectation either on the X chromosome to daughters or on the Y chromosome to sons. The pseudoautosomal hypothesis predicts that some sex concordance will be seen in paternally rather than maternally derived cases.

Based on both an excess of concordance by sex for schizophrenic siblings (Rosenthal, 1962) and a high frequency of cytogenetic abnormalities of the sex chromosomes in schizophrenia, a genetic locus for schizophrenia within the pseudoautosomal region of the sex chromosomes was proposed by Crow (1988). It is of relevance to note that a report on chromosomal patterns in schizophrenics (Chatterjee & Basu, 1980) found that out of the total sample of 287 cases, 5 showed abnormalities - 4 had XXY pattern and 1 showed XXY/XY mosaic pattern.

But, neither the linkage analysis (Asherson et al, 1992), nor the pedigree analysis (Ponnudurai, 1996) were supportive of this hypothesis.

**EXPANDED TRIPLET REPEATS:**

An interesting expansion probably related to a locus on chromosome 18q has been reported to be associated with schizophrenia in one Danish study, and new data in males with childhood onset schizophrenia implicate expansions in this region (Burgess et al, 1998). Unstable expansions of triplet repeats (specifically CAG which is translated into glutamine are now known to account for the process of genetic anticipation (successively worse illness with vertical transmission), have been found to be the mechanism behind gene defects in several neurodegenerative inherited diseases and the fragile X mental retardation syndrome. Thus, it has been reasonable to survey the genome for evidence of repeat expansion in patients with schizophrenia. One of the problems with this approach, however is that number of trinucleotide repeats present in genes are highly variable among normal and between populations.

**PORPHOBILINOGEN DEAMINASE:**

Increase in urinary porphobilinogen in psychotic patients had already been shown in an earlier Indian study (Golechha, 1980). An association between the gene for porphobilinogen deaminase and schizophrenia was shown by Sanders et al, 1992; but others were unable to confirm it (Owen et al, 1992; Nimgaonkar, et al., 1992).

**INTERLEUKIN RECEPTOR**

Another candidate gene for schizophrenia is the gene for the interleukin receptor located on chromosome 22. However, Pulver et al, (1993) was unable to demonstrate a linkage with schizophrenia.

**HLA**

An association with schizophrenia has also been suggested in the case of the HLA gene complex, but, in the final analysis, the suspected association remains doubtful (Ponnudurai, 1989; Owen & Mc Guffin, 1991).

**NEUROTROPHIN 3 GENE**

In the Japanese population, it was observed (Nanko et al, 1994; Jonsson et al, 1997) that schizophrenia is associated with A3 allele of the neurotrophin 3 gene, a possible candidate gene for schizophrenia.

**SMOOTH PURSUIT EYE TRACKING**

Abnormal smooth pursuit eye tracking that has been reported, may be an indicator for genetic liability for schizophrenia. Such an abnormality has been noted in schizophrenics in India also (Ram Sharon et al 1990). Litman et al, 1997 have also suggested regarding the use of this trait for that the smooth pursuit eye movements may not be genetically determined, but rather an expression of the illness itself or a consequence (De Lisi, 1999). This trait maps to 6p 22-24 (Arnlit, 1996).

**EVENT-RELATED BRAIN POTENTIALS**

W100, P300, P50 and P3 can be particularly useful as quantitative trait loci for linkage studies, although only Freedman et al, 1997 has reported a linkage to P50 (decrease in normal inhibition of P50 auditory evoked potential response). The genetic marker is 0.5 CM distant from d-7 nicotinic-cholinergic receptor gene.

**BRAIN MORPHOLOGIC ANOMALIES**

Ventricular size has been hypothesised to be associated with the genetic susceptibility.
Preliminary reports on regional cortical, subcortical grey and white matter and cerebral asymmetries have also emerged (Seidman et al, 1997; De Lisi et al 1997).

**APOLIPOPROTEIN E4**

Given that this allele is clearly associated with late onset Alzheimer's disease, and schizophrenia is known to be characterized by changes in cognition, its locus would seem to be a candidate. But, no study has shown a positive association of apolipoprotein E4 with schizophrenia.

**SYNAPTOPHYSIN GENE EXPRESSION**

Synaptophysin, a 38-kilodalton synaptic vesicle protein, mRNA was decreased in Broadman area 17 (occipital) and in BA 22 (superior temporal) in the women with schizophrenia (Eastwood et al, 2000).

**GENETIC TESTS OF THE Dopamine THEORY OF SCHIZOPHRENIA**

The locations for the genes for all dopamine receptors in the genome are known and these genes have been isolated and cloned (Seeman et al, 1993; Crow, T.J, 1994). The chromosomal locations of the dopamine receptor genes are as follows: D1: 5q 35.1; D2: 11q 22.5; D3: 3q 13.3; D4: 11p 15.5; D5: 4p 15.2 (Civelli et al, 1991).

With regard to the genetics of schizophrenia, the crucial question is whether a linkage or association exists between schizophrenia and the genes for dopamine receptors.

Jensen et al, 1993; were unable to demonstrate any linkage between schizophrenia and the gene for D receptor. Similar was the report for D2 receptor by Verhey et al, 1989; Gill et al, 1993; Gershon et al, 1992; Moses et al, 1991; Wang et al, 1993.

Although an association between schizophrenia and a certain type of D3 receptor gene homozygosity has been observed (Croco et al, 1992; Mint et al 1994; Birongkar et al, 1993), contradictory reports have also been reported (Johnson et al, 1993; Nanko et al, 1993; Notnen et al, 1993; Sabate et al, 1994; Yang et al, 1993).

A linkage between schizophrenia and the D4 receptor gene has been excluded by several groups (Mayer et al, 1994; Sheikh et al, 1994). Also, Coon et al, 1993; and Sunahara et al, 1993; studied linkage between schizophrenia and all of the dopamine receptor genes and obtained negative results in all cases.

On the whole, it seems that molecular genetic studies lend only minor support to the dopamine theory of schizophrenia.

**GENETIC TESTS FOR OTHER RECEPTORS OF NEUROTRANSMITTERS**

A linkage between the gene for GABA receptor and schizophrenia could not be established (Asherson et al, 1991; Coon et al, 1993). However, Akbarian et al, 1995; have suggested that hyperactive prefrontal cortex of schizophrenia could be associated with down regulation of gene expression for GAD.

**SEROTONIN TRANSPORTER GENE:**

Some have noted association of alleles for this gene with schizophrenia (Malhotra et al, 1997) and a specific allele has been shown to be associated with clozapine response (Arranz et al, 1997). These results are all considered preliminary.

**CATECHOL-O-METHYL TRANSFERASE:**

Whether alleles of COMT predispose to aspects of behavior or expression of schizophrenia is unresolved and of interest because COMT maps to the Velocardiofacial syndrome (VCFS) region of Chromosome 22, and VCFS patients are frequently known to have schizophrenia - like illness. Lachman et al, 1998; reported that one allele for low activity is associated with violent behavior in schizophrenia.

**α-7 NICOTINIC ACETYLCHOLINE RECEPTOR IN SCHIZOPHRENIA:**

The hypothesis that a defect in this gene could be associated with schizophrenia stems from the Freedman et al, 1997; report of a linkage of the schizophrenia associated p50 abnormality to Chromosome 15q, which is very close to the location of this receptor. These investigators noted the unusual smoking cravings of patients with schizophrenia and thus concluded that α-7 nicotinic receptor was a candidate gene.

**DERMATOGLYPHICS**

There have been noteworthy observations such as reduction in total finger ridge counts (Mellor, 1968); altered frequency of patterns (Srinivasa Murthy & Wig 1977; Ponnudurai, 1981; Jhingan & Munjal, 1990) and differences in a-b-c-d ridge counts in schizophrenia. Relevance of positive family history has also been noted by Srinivasa Murthy, & Wig, 1977. Fluctuating asymmetry of this trait has also been reported (Mellor, 1992; Ponnudurai et al 1997). At any rate, although dermatoglyphics is a genetically determined trait, its role as a genetic marker is yet to be established.

**GENE MODELS**

A prominent historically first hypothesis (Rosanoff and Orr, 1911; Rudin 1916) was that schizophrenia is due to a single gene defect (Book, 1953; Slater and Cowie, 1971). However, the generalized single locus (GSL) model has repeatedly failed to account for the observed pattern of familial risk in schizophrenia (Elston and Campbell, 1970; Tsuang et al, 1986; Mc Gue et al, 1986).

The two most widely applied multiple gene models for schizophrenia are, multifactorial threshold (MET) and mixed
models. Under the MFT models, genetic factors are assumed to be polygenic, such a polygenic model has been proposed by Gottesman & Shields (1967), Miron Baron (1980), and also by an Indian study (Ponnudurai, 1989). However, Meehl (1972) suggested that both a major gene and polygenes (Mixed model) play a role in the etiology of schizophrenia.

Many geneticists favor an oligogenic hypothesis, according to which, two or three genes together lead to the predisposition to schizophrenia (Owen & McGuffin, 1993).

However, it seems more likely that underlying the susceptibility to schizophrenic disorder are many non-specific minor genes, which act together. Hence, new strategies are needed if it becomes apparent that most cases of schizophrenia result from combined effect of multiple genes.

**CONCLUSION**

The genomic era has already begun to alter the course of schizophrenia research. However, there is also possibly a neurodevelopmental component to schizophrenia. Hence, combined epidemiological, neurobiological, genetic and functional genomic analyses are needed to provide real answers to this intractable and destructive medical history.

"Real failure comes only when we forget our ideals, objectives and principles and begin to wander away from the road which leads to their realisation.

Jawaharlal Nehru

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