Review Article

Genetics in psychiatry

Shreekantiah Umesh, Shamshul Haque Nizamie[1]

Departments of Psychiatry, K.S. Mani Centre for Cognitive Neurosciences, and [1]Institute of Psychiatry, Kanke, Ranchi, Jharkhand, India

Today, psychiatrists are focusing on genetics aspects of various psychiatric disorders not only for a future classification of psychiatric disorders but also a notion that genetics would aid in the development of new medications to treat these disabling illnesses. This review therefore emphasizes on the basics of genetics in psychiatry as well as focuses on the emerging picture of genetics in psychiatry and their future implications.

Key words: Genetics, implications, psychiatry

Introduction

In the 21st century, psychiatrists are being invited to think about animal models of the illnesses they observe daily in human beings and to recognize that these models will aid in the development of new medications to treat mental illnesses. Psychiatrists are being challenged to learn about the new technologies and terminologies such as microarrays, haplotype maps, promotor regions and so on, as a consequence of the enormous progress that has occurred in the field of molecular biology. Most importantly, the tools of molecular biology are now being applied to improve understanding of both normal behavioral variations and also the mechanisms of a wide variety of complex disorders such as schizophrenia, mood disorders, substance abuse and so on. Although challenging because of their genetic complexity, mental illnesses are among the most important disorders to be studied with the tools of molecular biology as their effects are devastating to both patients and their families.

Access this article online	
Quick Response Code:	Website: www.ijhg.com
	DOI: 10.4103/0971-6866.142845

Subfields of Genetics

The scientific study of heredity, which arguably began with Mendel's work on peas in 1865, gradually developed into five major disciplines. Biochemical genetics is concerned with the biochemical reactions by which genetic determinants are replicated and produce their effects. Developmental genetics is the study of how the expression of normal genes controls growth and other developmental processes, often by the study of mutations that produce developmental abnormalities. Molecular genetics studies the structure and the functioning of genes at the molecular level. Cytogenetics deals with the chromosomes that carry those determinants. Population genetics, which deals with the mathematical properties of genetic transmission in families and populations, can be subdivided into the partially overlapping fields of evolutionary genetics, genetic demography, quantitative genetics, and genetic epidemiology.[1]

Study Designs for Genetic Research

- Traditional methods: Family study, Twin study, Adoption study
- Newer approaches: Linkage study, Association study etc.

Family study

It provides the first evidence that genes are involved in priming an illness alternatively; it can identify which

Address for correspondence: Dr. Shreekantiah Umesh, Central Institute of Psychiatry, Kanke, Ranchi - 834 006, Jharkhand, India.
E-mail: umesh.yes@hotmail.com

clinical entities are transmitted together in comparison to random transmission pattern (which is provided by control population). These studies are conducted with the hypothesis that illness should occur in the families of affected members at a higher rate than in appropriate control population. If this hypothesis is accepted, it favors familial aggregation which might be due to two possibilities, that is, shared diseased genes and shared environment which is subsequently analyzed.[2]

Twin study

Resemblance among relatives may be due to shared genes (nature) or shared environment (nurture). Twin study attempts to separate effect of gene from that of the environment. Twin studies are done with certain assumptions: Mono zygotic (MZ) twins share 100% of genome, dizygotic (DZ) twins share approximately 50% of genome, both MZ and DZ twins share the same environment, thus environment as a confounding variable can be controlled. These studies proceed with the hypothesis that if genetic factors are important in causing a disease, the monozygote concordance rate would be significantly higher than the dizygotic twins. Alternatively, if MZ concordance is <100%, this would rule out genes as a sole factor causing a disease.[3]

Adoption study

This kind of study attempts to clarify the role of genetic versus environmental factors in a disease by studying two kinds of informative relationship; individuals who are genetically related but do not share familial environmental factors and individuals who share familial environment factors but are not genetically related. The ability to draw an inference from adoption study is strongest when the adopted children are separated from their biological parents at birth. The study is conducted as:

- Parent-as proband: Compares the rate of illness in the adopted offspring of ill and well persons. Support for a genetic component is obtained when the rates of illness is higher in the former. An important example could be the famous Danish adoption study
- Adoptee-as-proband: Compares the risk between biological relatives of ill probands with the adoptive relatives
- Cross-fostering approach: Compares rates of illness in two types of adoptee: Individuals with ill biological parents but fostered by healthy adoptive parents and individuals with healthy biological parents but fostered by ill adoptive parents. These approaches are only feasible in those countries where adoption register is strictly maintained.[4]

Molecular Genetics

Genetic information is coded along the length of a polymeric molecule composed of only four types of monomeric units. This polymeric molecule, DNA, is the chemical basis of heredity and is organized into genes, the fundamental units of genetic information. The basic information pathway has been the synthesis of RNA directed by DNA, which in turn directs protein synthesis. Genes do not function autonomously; their replication and function are controlled by various gene products, often in collaboration with components of various signal transduction pathways.

Genetic variation-normal and pathological

A position on a chromosome is termed a locus, a general term, which can refer to a gene or a segment of DNA with no known function. DNA sequences that differ at the same locus are termed allelic variants. Since we have two copies of each chromosome, by definition we have two alleles at each locus. If these alleles are identical the individual is said to be a homozygote at that locus; if they are different, the individual is a heterozygote. The number of alleles at any locus varies remarkably; at the most polymorphic loci, hundreds of alleles may be found.[5] Polymorphism in the human genome is important in a practical sense because it permits gene mapping, and hence disease gene identification.

There is a normal variation of DNA sequence just as is true of more obvious aspects of human structure. Variations of DNA sequence, polymorphisms, occur approximately once in every 500 nucleotides, or about 107 times per genome.[5] There are deletions and insertions of DNA as well as single-base substitutions. In healthy people, these alterations obviously occur in noncoding regions of DNA or at sites that cause no change in function of the encoded protein. This heritable polymorphism of DNA structure can be associated with

certain diseases and can be used to search for the specific gene involved.

Deletions, insertions and rearrangements of DNA

Studies of bacteria, viruses, yeasts, and fruit flies show that pieces of DNA can move from one place to another within a genome. The deletion of a critical piece of DNA, the rearrangement of DNA within a gene, or the insertion of a piece of DNA within a coding or regulatory region can all cause changes in gene expression resulting in disease.

Mutation

A mutation can be defined as any change in the primary nucleotide sequence of DNA regardless of its functional consequences. Some mutations may be lethal, others are less deleterious, and some may confer an evolutionary advantage. Mutations can occur in the germline (sperm or oocytes); these can be transmitted to progeny. Alternatively, mutations can occur during embryogenesis or in somatic tissues. If the DNA sequence change occurs in a coding region and alters an amino acid, it is called a missense mutation. Depending on the functional consequences of such a missense mutation, amino acid substitutions in different regions of the protein can lead to distinct phenotypes. Small nucleotide deletions or insertions cause a shift of the codon reading frame (frameshift). Most commonly, reading frame alterations result in an abnormal protein segment of variable length before termination of translation occurs at a stop codon (nonsense mutation). Mutations in intronic sequences or in exon junctions may destroy or create splice donor or splice acceptor sites. Mutations may also be found in the regulatory sequences of genes, resulting in reduced gene transcription. Alternatively, mutation in a single allele can result in haploinsufficiency, a situation in which one normal allele is not sufficient to maintain a normal phenotype.[5]

Gene mapping

Techniques involving cloned DNA are used to locate genes to specific regions of chromosomes, to identify the genes responsible for diseases, to study how faulty gene regulation causes a particular disease, to diagnose genetic diseases and increasingly to treat genetic diseases. The isolation of a specific gene from an entire genome requires a technique that will discriminate one part in a million.[6] Gene localizing thus can define a map of the human genome and there are two techniques used to accomplish gene localization, that is, somatic cell hybridization and *in situ* hybridization. In *in situ* hybridization, the simpler and more direct procedure, a radioactive probe is added to a metaphase spread of chromosomes on a glass slide. The exact area of hybridization is localized by layering photographic emulsion over the slide and after exposure, lining up the grains with some histologic identification of the chromosome.[7]

Linkage study

There are two distinct but related paradigms for identifying genes or regions that confer disease risk: Linkage analysis and association analysis. The traditional approach for locating a disease gene in humans is linkage analysis, which tests the association between DNA polymorphic markers and affected status within families. After linkage is detected with an initial marker, many other markers nearby may also be examined. Markers showing the strongest correlation with disease in families are assumed to be closest to the disease locus. Linkage analysis uses DNA sequences with high variability (i.e., polymorphisms) in order to increase the power to identify markers that are associated with a disease within families. Historically, different methodological approaches have been applied. Earlier linkage studies employed restriction fragment length polymorphisms, whereas subsequent studies examined short tandem repeat markers, or “microsatellites” DNA sequences that show considerable variability among people, but that have no functional consequences. More recently, linkage and association studies have examined single nucleotide polymorphisms (SNPs) to track diseases in families.

Markers in the candidate region identified by linkage analysis can be used to narrow the location of the disease gene through linkage disequilibrium analysis. Linkage disequilibrium is a population association between two alleles at different loci; it occurs when the same founder mutation exists in a large proportion of affected subjects in the population studied. Usually, the

closer the marker is to the disease locus, the greater proportion of affected subjects who carry the identical allele at the marker. However, in measuring the strength of linkage disequilibrium for a given marker, it is also important to select unaffected control subjects from the same population, since an allele shared among affected subjects may also be common in the general population and thus shared by chance rather than due to proximity to the disease locus.

For complex human diseases, a simple mode of genetic inheritance is not apparent, and indeed, multiple contributing genetic loci are likely to be involved. Study designs that do not depend on the particular mode of inheritance are required for linkage analysis. Since affected relatives provide most of information for such analyses, studies that focus on searching for increased sharing of marker alleles above chance expectation among affected relatives may be employed. The simplest of such studies involves affected sibships, where allele sharing in excess of 50% (the expectation when there is no linkage) is sought.[8]

Genetic markers used in linkage analysis are typically duplications or SNPs. Traditionally, a set of approximately 400 duplication polymorphisms (microsatellites) were used. These polymorphisms are highly informative, because there can be 10-20 different alleles at one locus, but these had lower resolution that limited them. More recently, SNPs have been used for linkage analyses; a standard set of approximately 6000 SNPs for linkage analyses are available, although any subset of independent SNPs from a genome wide SNP panel could be used.[9] Although individual SNPs are less informative (only two alleles per locus) increased density of SNP panels allows greater resolution than previous microsatellite panels.

Association study

Genetic linkage studies have been successful in mapping genes involved in Mendelian disorders that have high relative risks in families. These studies, however, have been less successful in mapping complex disorders. Genetic association studies, which are more similar to traditional epidemiologic studies that test for an association between an exposure and an outcome, offer an alternative to linkage studies, although the two are conceptually related. Association studies are commonly used in cases of psychiatric disorders due to the complexity of the disorder. A typical association study design compares the frequency of marker genotypes in cases with an appropriate control group. There are two common approaches to association studies, case-control designs and family-based designs, which typically investigate trios (mother, father, and an affected offspring). In a case-control study, allele frequencies are compared between a group of unrelated affected individuals and a matched control sample. This design is generally more powerful than a family-based design, as large samples of cases and controls are easier to collect than trios and are less expensive as they require the genotyping of fewer individuals. Case-control samples may be the only practical design for traits with a late age of onset (such as Alzheimer's disease [AD]) for which parents of affected individuals are typically unavailable. The main drawback of the case-control approach is the potential problem of population stratification; if the cases and controls are not carefully matched demographically, then they may display substantial differences in allele frequency that reflect population differences rather than associations to the disease.

Family-based association studies are designed to ameliorate the problem of population stratification. In this design, the nontransmitted chromosomes (the copy of each chromosome that is not passed from parent to the child) are used as control chromosomes, and differences between allele frequencies in the transmitted and nontransmitted chromosomes are examined, eliminating the problem of stratification, as the comparison group is by definition genetically similar to the case group. Although more robust to population stratification than a case-control study, family-based studies are only about two-thirds as powerful using the same number of affected individuals, as noted previously.

Until recently, it was not practical to conduct association studies on a genome-wide basis, as relatively few SNPs were available. Therefore, association studies focused on testing one or a few markers in candidate genes chosen on the basis of their hypothesized function in relation to a given disease. Recently, however, as a result of international efforts that have identified millions of SNPs distributed relatively evenly across the genome and that

have developed technology for genotyping them relatively inexpensively, genome-wide association (GWA) studies are now a reality. Such studies hold much promise for the identification of common variants contributing to various common diseases.[2]

Epigenetics

The term epigenetics refers to "changes in the genetic material that leads to phenotypic changes without altering the DNA sequence." Epigenetic changes mainly include the methylation of DNA and modifications of chromatin, such as methylation and acetylation of the histones, the DNA's packaging material. Epigenetic changes are acquired during the life of an organism and they are important for gene regulation, with big differences observed in epigenetic marks across different tissues. Environmental factors can also influence epigenetic marks through life, before they are reprogrammed in gametogenesis. Occasionally epigenetic changes can escape reprogramming and be vertically transmitted across generations and as a result, an acquired epigenetic state can persist in the next generation. Multiple tools now available enable the assessment of epigenetic variation across the genome. These tools employ methods using a modification of methylated DNA or chromatin immuno-precipitation and microarray hybridization, the latter now being replaced by modern sequencing methods. It is postulated that epigenetic variation can be causally linked to complex diseases, including psychiatric disease, and recognizing the interplay between epigenetics and genetics might help us discover complex disease genes.[2]

Genetic Architectures of Psychiatric Disorders: The Emerging Picture and its Implications

Alzheimer's disease

Before 2007, rare autosomal dominant mutations in amyloid-beta precursor protein (APP), presenilin 1 (PSEN1) and PSEN2 were known to cause early-onset familial AD.[10] These loci have atypically large effect sizes, thereby facilitating identification using "past generation" technologies, such as a candidate gene association and genome-wide linkage studies. Recently a rare structural variation duplication containing APP have been associated with AD.[11] Approximately, ten loci have been identified to date that accounts for ~ 33% of the risk attributable to genetic effects, with the major contribution being from APOE in AD.[12] Intriguingly, pathway analyses (based on the assumption that risk variants for a disease will converge on sets of genes with functions that are more closely related to each other than to random sets of genes) of AD have implicated cholesterol metabolism and the innate immune response whereas GWA study have found a significant association toward immune and inflammatory processes (clusterin [CLU] and CR1), lipid processing (APOE, CLU and ABCA7) and endocytosis (phosphatidylinositol-binding clathrin assembly protein, bridging integrator 1, CD2-associated protein and CD33). Altered immune function and lipid metabolism had previously been proposed as AD risk factors, but whether these represented causation or reverse causation was unclear in the past. The current genetic findings now strongly point to reverse causation. It is unclear how the above findings relate to accumulation of β-amyloid in AD pathogenesis, but some relationship seems likely.[13]

Psychotic disorders

Unfortunately, unlike the case for AD, no Mendelian forms of bipolar disorder and schizophrenia have been identified however, rare but potent structural variants (copy number variants) have a role in a small proportion of cases with schizophrenia. None is fully penetrant, and nearly all appear to be nonspecific, as risk is often increased for schizophrenia, autism spectrum disorder (ASD), developmental delay, intellectual disability, epilepsy, somatic dimorphism and extremes of body mass and head size. Most of these structural variation regions are fairly large (hundreds of kilobases to hundreds of megabases) and generally center on structural variation hotspots. Two rare structural variants affect single genes (namely, neurexin 1 and vasoactive intestinal peptide receptor 2), offering opportunities for downstream functional studies. Pathway analyses of genes that are intersected by rare structural variants suggest enrichment for neuronal processes of plausible etiological relevance (Schizophrenia Psychiatric GWA Study Consortium, 2011). The strongest association

is also extended to major histocompatibility complex region (MHC region; chr6: 27-33 Mb) and it could be speculated that neuro-developmental abnormalities due intra-uterine infection, auto-immunity, synaptic pruning may be asserted to MHC. A novel association for schizophrenia is in Ensembl gene, which encodes the primary transcript for the microRNA-137 (MIR-137). MIR-137 is a key regulator of neuronal development with roles in neurogenesis and maturation and is highly expressed at synapses in the cortex and hippocampus (Kwon *et al*., 2013).[14] Future studies of networks regulated by miR-137 offer the possibility of insights into schizophrenia pathophysiology.

In bipolar disorders, the genome-wide significant association is at voltage dependent calcium channel L type, alpha 1C subunit (CACNA1C). Calcium channels are a treatment for bipolar disorders and regulate neuronal excitability and multiple brain functions, including long-term potentiation and synaptic plasticity. Combined analysis of the bipolar disorders and schizophrenia samples strengthened the association in the CACNA1C region. Further, researches also implicate neurogranin, which may act as a calcium sensor. Therefore, a detailed investigation of brain calcium biology is warranted for both bipolar disorders and schizophrenia (Zhong *et al*., 2009).[15]

Autism spectrum disorder

For ASD, karyotyping studies suggest that on the order of 5% of ASD cases have one of a large number of rare but fairly gross chromosomal abnormalities. In addition, ASD has been noted as a co-morbid feature of >100 single-gene Mendelian medical genetic syndromes, although the penetrance and confidence of the clinical associations are variable. Indeed, ASD mutations with a high penetrance are exceptional (that is, Rett's syndrome mutations in methyl-CpG-binding protein 2 and cyclin-dependent kinase-like 5) and Mendelian diseases with ASD have far less than complete penetrance (for example, fragile X syndrome and tuberous sclerosis).[16] Recent researchers have identified roles for de novo exonic mutations in sodium channel protein type 2 subunit alpha, katanin p60 subunit A-like-2 and chromodomain helicase DNA-binding protein 8 in the pathogenesis of ASD (Sanders *et al*., 2012).[17]

Alcohol and tobacco dependence

Published genomic studies for alcohol dependence are small and no large-scale meta-analysis has been conducted (Bierut *et al*., 2010). For alcohol consumption, genomic studies on East Asian samples confirmed the role of aldehyde dehydro-genase 2 and autism susceptibility candidate 2 has been implicated in alcohol consumption in European subjects.

For nicotine dependence, there is a paucity of meta-analysis but large meta-analyses have been conducted for smoking behavior (Tobacco and Genetics Consortium, 2010). The strongest finding is an association is associated with a cluster of nicotinic receptor genes (CHRNA5–CHRNA3–CHRNB4) with an effect size that corresponds to one cigarette per day. Associations to this region have also been reported for lung cancer.[18]

Major depressive disorder

The genomic analysis of 9240 major depressive disorder (MDD) cases and 9519 has revealed no findings of genome-wide significance (Major Depressive Disorder Working Group of the PGC, 2012). The most likely reasons for these results are particularly high heterogeneity. A risk for MDD might be influenced by a gene-environment interaction with genetic variation near the serotonin transporter.[19]

Panic disorder

Several family studies have detected a higher rate of panic disorder in the relatives of affected probands than in the relatives of control subjects. The relative risk to first-degree relatives of panic disorder probands ranged between 2.6- and 20-fold, with a median value of 7.8-fold. Panic disorder has also been the subject of a reasonable number of molecular genetic studies, though by current standards most sample sizes were relatively small and genotyping was of only a moderate density. Regions of interest have been found in chromosome 7, chromosome 15 (near the γ-aminobutyric acid [GABA] receptor subunit genes), chromosome 12, chromosome 9. Candidate gene studies of panic disorder present a similar picture. A variety of studies have been reported with the choice of genes ranging from those implicated by the efficacy

of pharmacological agents (e.g. serotonin receptors or GABA genes related to benzodiazepine drug effects), symptoms (e.g. monoamine oxidase A [MAOA] or catecholamine methyl transferase [COMT]) and etiological theories such as (cholecystokinin B receptor CCK2R and adenosine receptor ADORA2A). While there are a number of positive studies, none has been consistently replicated, and in many cases even the positive studies vary as to which allele is associated with panic disorder.

Obsessive-compulsive disorder

The first genome scan of obsessive-compulsive disorder (OCD) included seven families (56 individuals) studied with 349 microsatellite markers (average intermarker distance 11.2 cM) and found a maximum lod score of 2.25 on chromosome 9p24 (D9S288). Significant associations between OCD in men and one gene, SCL1A1 has been shown. SLC1A1 codes for an amino acid transporter that is involved in both maintenance of normal extracellular glutamate levels and shutdown of excitatory glutamate activity. Given the specific treatment response of OCD patients to selective serotonin reuptake inhibitors many of these studies have focused on serotonin-system-related genes (e.g. 5-HT1B, 5-HT2A, and SLC6A4). Other selections are related to the hypothesized role of certain neurotransmitters, neural circuits, or structures in this disorder (e.g. glutamate, cortico-striato-thalamo-cortical circuitry, or brain white matter). No consistently replicated findings or functional variants that have been shown to have a causal role in OCD or related behaviors.

Posttraumatic stress disorder

There are no linkage studies or other genome scans of posttraumatic stress disorder (PTSD). A small number of candidate gene studies have been reported, mostly involving dopamine-related genes. Sample sizes have been relatively small, and results to date are inconsistent.

Generalized anxiety disorder

There are no published linkage studies or genome scans of generalized anxiety disorder. Some relatively small-sample candidate gene studies have been reported, but as yet there are no consistent results.

Eating disorders

Population studies suggest that genetic factors may, overall, contribute approximately 50% or more to the appearance of anorexia nervosa and bulimia nervosa. Genetically interesting loci and polymorphisms have been associated with genes for the 5-hydroxytryptamine types 1B (5-HT1B), 1D (5-HT1D), 2A (5-HT2A), and 2C (5-HT2C) receptors, norepinephrine transporter, dopamine receptor, MAOA, deltoid opioid receptor, cannabinoid receptor, brain derived neurotropic factor, preproghrelin, CLOCK (endogenous oscillator) system, uncoupling proteins 2 (UCP2) and 3 (UCP3), beta-type estrogen receptor, hSKCa3 potassium channel, and human agouti protein. In a study the presence of the short allele on the serotonin transporter gene was shown to be a significant risk factor for anorexia nervosa. A polymorphism in the coding region of the gene for the 5-HT2C receptor subtype, resulting in a cysteine to serine substitution, has been reported in 23.7% of adolescent girls reporting weight loss compared to 7.7% of normal weight girls. In studies of the human agouti-related protein gene (related to an orexigenic neuropeptide), two alleles have been found to be in complete linkage disequilibrium and are significantly enriched in anorectic patients (11%; $P = 0.015$) compared with controls (4.5%). Several large-scale linkage and association studies are under way.

Attention deficit hyperactivity disorder

There has been increasing interest in attempting to identify the specific genes and the abnormalities associated with their variance that may be implicated in patients with attention deficit hyperactivity disorder (ADHD). Early molecular genetic studies showed that mutation of the thyroid receptor B gene, which causes resistance to thyroid hormone, was associated with high rates (61%) of hyperactivity and impulsivity (but not inattention) in affected children and adults. Only 1 of 2500 patients with ADHD had this thyroid abnormality. Thus, this gene could not be a major cause of ADHD. Dopamine Type D2 receptor gene was not specific to ADHD (46.2%), but was also seen with increasing frequency in autism (54.5%), alcoholism (42.3%), and PTSD (45.7%) versus normal controls (24.5%). Dopamine transporter gene (DAT)

is associated between ADHD and the DAT1 with 480-base pair allele has been shown in few studies, but inconsistent. Although both family-based and population studies have shown a positive association between the dopamine 4 receptor seven-repeat allele gene (DRD4) and ADHD, it is inconsistent. Like the dopamine transport gene, the DRD4 receptor gene holds some promise in clarifying the genetic basis of ADHD. However, these genes may exert their influence in ADHD in combination with other genes and in conjunction with other neurotransmitter systems. Genes that code for dopamine β-hydroxylase, the dopamine 5 receptor, COMT, androgen receptors, and factors in immune function and regulation have been reported to correlate with ADHD symptoms, but only have been examined in single studies that require replication.

Implications of Genetic Architecture in Psychiatry

A comprehensive portrait of genetic architecture does not now exist for any psychiatric disorder in the current era. However, gaining a more complete knowledge of each disorder, that is, the specific loci that are etiologically involved, the identity, frequency and impact of genetic variation at each locus would be of exceptional importance. Such an enumeration would catalyze an array of specific, targeted and nuanced scientific studies. For example, such studies might lead to the elucidation of biological mechanisms between the genotype and psychiatric phenotype, enablement of cell-based chemical biology and pharmacological screening, evaluation of gene action over developmental time, addressing the important roles of gene-gene and gene-environment interactions, understanding the part played by epigenetic modifications, evaluation of disease prediction models, and hence forth. The genetic variation could be used to redefine the disorders, replacing the current diagnostic system, which has no evident biological basis. In this regard, it is worth noting that the syndromes defined by genotype may have much different boundaries than what we have tried to craft with diagnostic manuals based on presenting symptoms. It is also possible that some genotypes will link to a much broader phenotype than what we have identified diagnostically till date.

Future of Psychiatric Genetics

As we enter the new millennium, the field of psychiatric genetics is experiencing a paradigm shift. Linkage analyses continue to be largely disappointing – even though some loci can be confirmed, positional cloning is considered an unlikely route to identify genes involved in most psychiatric disorders. Co-morbidity and diagnostic uncertainties continue to plague the field. The realization that many susceptibility alleles will be common variants rather than rare mutations makes necessary new approaches to the design, analysis and interpretation of psychiatric genetic studies. Two new directions emerge from these facts: (i) The genetic study of endophenotypes, that is, phenotypes associated with a psychiatric illness that are more quantifiable, more common and often associated across a wider spectrum of disorders; and (ii) genetic studies that are candidate gene driven rather than disorder driven. Candidate genes are surveyed for variants, and when a promising gene variant is identified that is both biologically relevant and has proven functional significance, it is tested across the whole spectrum of psychiatric-illnesses, endophenotypes and mainly for psychopharmaco-genetic relevance. With new emerging techniques such as SNP analysis on DNA chips, these types of studies are predicted to increase. Although in this review we have barely touched on recent advances in statistical analyses, they are the lenses through which we examine heredity-behavior relationships. The inclusion of covariates and the examination of interactions, both gene-gene and gene-environment, will be necessary in the development of a more complete understanding of the etiology of psychiatric disorders. Although there is a tremendous amount of work ahead, we remain cautiously optimistic that genetic studies will clarify the complex roles of genes and environment in the etiology of psychiatric disorders.

Conclusion

With the continued excitement of the publication of the human genome, scientists will no doubt continue to uncover the functions of specific genes. These discoveries will be augmented by connecting major

avenues of genetic research across disciplines, using different approaches that bridge animal models with human behavior and evolving imaging methods with genetic technologies. These approaches will provide a more unified understanding of neural mechanisms involved in human behavior and its disruption in psychopathologies. Such an approach may open up new avenues for therapeutic intervention for clinical populations at the pharmacological, genetic and behavioral levels and identify windows of development that may be most optimal to treatment.

References

1. Kingston HM. ABC of Clinical Genetics. 3rd ed. London: BMJ Books; 2002. p. 1-10.
2. Prathikanti S, Weinberger DR. Psychiatric genetics – The new era: Genetic research and some clinical implications. Br Med Bull 2005;73-74:107-22.
3. Tsuang M. Schizophrenia: Genes and environment. Biol Psychiatry 2000;47:210-20.
4. Moldin SO, Gottesman II. At issue: Genes, experience, and chance in schizophrenia – positioning for the 21st century. Schizophr Bull 1997;23:547-61.
5. Flint J, Munafò MR. Forum: Interactions between gene and environment. Curr Opin Psychiatry 2008;21:315-7.
6. Schwab SG, Albus M, Hallmayer J, Hönig S, Borrmann M, Lichtermann D, *et al.* Evaluation of a susceptibility gene for schizophrenia on chromosome 6p by multipoint affected sib-pair linkage analysis. Nat Genet 1995;11:325-7.
7. Asherson PJ, Curran S. Approaches to gene mapping in complex disorders and their application in child psychiatry and psychology. Br J Psychiatry 2001;179:122-8.
8. Risch N. A note on multiple testing procedures in linkage analysis. Am J Hum Genet 1991;48:1058-64.
9. Burmeister M, Bryda EC, Bureau JF, Noben-Trauth K. Mouse chromosome 10. Mamm Genome 1999;10:950-1.
10. Schaffer BA, Bertram L, Miller BL, Mullin K, Weintraub S, Johnson N, *et al.* Association of GSK3B with Alzheimer disease and frontotemporal dementia. Arch Neurol 2008;65:1368-74.
11. McNaughton D, Knight W, Guerreiro R, Ryan N, Lowe J, Poulter M, *et al.* Duplication of amyloid precursor protein (APP), but not prion protein (PRNP) gene is a significant cause of early onset dementia in a large UK series. Neurobiol Aging 2012;33:426.e13-21.
12. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: The emerging picture and its implications. Nat Rev Genet 2012;13:537-51.
13. Guerreiro RJ, Lohmann E, Kinsella E, Brás JM, Luu N, Gurunlian N, *et al.* Exome sequencing reveals an unexpected genetic cause of disease: NOTCH3 mutation in a Turkish family with Alzheimer's disease. Neurobiol Aging 2012;33:1008.e17-23.
14. Kwon E, Wang W, Tsai LH. Validation of schizophrenia-associated genes CSMD1, C10orf26, CACNA1C and TCF4 as miR-137 targets. Mol Psychiatry 2013;18:11-2.
15. Zhong L, Cherry T, Bies CE, Florence MA, Gerges NZ. Neurogranin enhances synaptic strength throughits interaction with calmodulin. EMBO J 2009;28:3027-39.
16. Folstein SE, Rosen-Sheidley B. Genetics of autism: Complex aetiology for a heterogeneous disorder. Nat Rev Genet 2001;2:943-55.
17. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, *et al.* De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 2012;485:237-41.
18. Thorgeirsson TE, Gudbjartsson DF, Surakka I, Vink JM, Amin N, Geller F, *et al.* Sequence variants at CHRNB3-CHRNA6 and CYP2A6 affect smoking behavior. Nat Genet 2010;42:448-53.
19. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, *et al.* Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.

Cite this article as: Umesh S, Nizamie SH. Genetics in psychiatry. Indian J Hum Genet 2014;20:120-8.

Source of Support: Nil, **Conflict of Interest:** None declared.