Understanding the Genomics of Psychiatric Disorders: The Expanding Horizon

Basu Priyadrshi[1], Majumder Parthap P[2]

ABSTRACT:

Genetic factors play a major role in the etiologies of most psychiatric disorders. Psychiatric disorders caused by defects in a single gene that segregate within the family (following a Mendelian inheritance pattern) are easy to screen and hence used in molecular diagnosis routinely. However, a vast majority of psychiatric disorders are caused by the interaction of multiple genetic and environmental factors. The understanding and treatment of these complex psychiatric disorders pose many challenges, because of the clinical overlap of symptoms as well as genetic heterogeneity, which creates a problem in classification of these disorders. Advancements in DNA technologies have enabled scientists to study these disorders in increasing detail. As research progresses, there has been a recent reevaluation of diagnostic criteria and their usefulness in treatment and classification. This is based on the observation that there is more etiological overlap between psychiatric disorders than previously appreciated. As new information on genetic and epigenetic risk factors in psychiatry grows, this review takes a look at how genetic dissection of such disorders has evolved and progressed over the years.

Key words: *Genomics, Epigenetics, Complex disorders, Schizophrenia, Autism*

Introduction

It is now well established that genetic factors are important in the etiologies of most psychiatric disorders. However, the vast majority of psychiatric disorders do not follow simple patterns of inheritance within a family. This implies that psychiatric disorders are probably caused by the interaction of multiple genetic and environmental factors.

Advancements in DNA technologies have enabled scientists to study complex psychiatric disorders in increasing detail. Coupled with this, the identification and localization of DNA variants throughout the human genome has resulted in a rapid increase in molecular genetic investigations of major psychiatric disorders. Molecular genetics is concerned with the search for the DNA variants, which are responsible for a disorder or which influence its development or outcome.

There are over 300 identified psychiatric disorders. With continuing research, more psychiatric disorders are being identified each year, and many are being re-categorized/re-classified based on DNA and other evidence. It is beyond the scope of this review to cover the entire spectrum of research on psychiatric genetics. We have, therefore, restricted ourselves to such psychiatric disorders that have major genetic underpinnings. We have also discussed, in the following sections, how such genetic knowledge can be useful in diagnosis and in providing mechanistic insights into these disorders.

Molecular genomics of psychiatric disorders

Classical approaches to study genetic disorders

To investigate genetic contribution to the etiology of a disorder, classical approaches have used family and twin studies. In family studies, sets of related individuals are studied. The idea is that if a disorder has a genetic component, the relatives of the person with the condition (proband) are expected to have the disorder more frequently than the general population. Hence, morbidity risk among relatives increases with genetic proximity to the proband. For example, family studies have consistently demonstrated that schizophrenia runs within families. A first-degree relative (parents, offspring, siblings) of an affected individual has a 10% lifetime risk of developing schizophrenia in contrast to a risk of 1% in the general population.(1) Similarly, in such relatives of patients suffering from manic depression the risk is 8% compared to 0.5% in the general population.(2)

In twin studies, a pair of twins is said to be concordant for a condition if both members are affected, and discordant if only one member of the pair is affected. A genetic contribution is indicated if the concordance rate in monozygotic twins (MZ) is significantly greater than the concordance rate in dizygotic twins (DZ). For example, MZ and DZ concordance rates in schizophrenia are ~55% and 15% respectively, indicating a high genetic component.(3) Similarly, in manic depression, MZ twins show disease concordance of up to three times than DZ twins, which again indicates high genetic contribution.(2)

Simple monogenic psychiatric disorders

Genetic models are defined by the observed pattern of inheritance of a disorder or a trait within families. There are three such simple Mendelian models for inheritance. If the inheritance pattern is Autosomal Dominant (AD), only one copy of a mutation is required to express the disease. The risk is equal between sexes, with a morbidity risk of 0.5 in first-degree relatives of a proband and a morbidity risk of 0.25 in second-degree relatives. For example, Huntington's disease is caused by a mutation in one copy of a gene on chromosome 4.(4) If the inheritance pattern is Autosomal Recessive (AR), affected individuals require two copies of a mutation in the same gene, one from each parent. Individuals with one copy of the mutation are carriers. In AR inheritance, siblings have a morbidity risk of 0.25. In the X-linked Recessive model, a mutation on the X-chromosome causes disease in males, while females are usually protected by having two X chromosomes. An example is Fragile-X syndrome, where over 75% of males carrying the mutation have severe mental handicap compared to only 10-20% of females.(5) **Table 1** gives a list of some monogenic psychiatric disorders. Although in some cases, multiple mutations is the same gene might give rise to the disease phenotype, with the advent of modern technical advancements, it is relatively easier and cost-effective to screen larger stretches of DNA encompassing a single gene.

Table 1. List of some Mendelian psychiatric disorders with their causal genes

Disease	Inheritance pattern	Gene location	Phisnoty pe/ MIM#	Gene symbol	Symptoms	References
Huntington's Disease	AD	4p16.3	143100	#IT	chorea, dystonia, incoordination, cognitive and behavioral decline; The Huntington's Disease Collaborative Research Group 1993	
Epilepsy, X linked	X-linked recessive	Xp11.23	300401	SYN1	Epilepsy, with variable learning disabilities and behavior disorder	Garcia et al. 2004
Velocardiofacial syndrome/ Di George syndrome	AD	22q11.21	192430	TBX1	Cleft palate, cardiac anomalies, typical facies, and learning disabilities	Carelle-Calmels et al. 2009
Wolfram	AR	4p16.1	222300	WFS1	Diabetes mellitus, optic atrophy, diabetic insipidus, deafness; renal abnormalities, ataxia, dementia or mental retardation, and diverse psychiatric illnesses	Strom et al. 1998 syndrome
Metachromatic leukodystrophy	AR	22q13.31	250100	ARSA	Psychiatric and may lead to a diagnosis of schizophrenia	Berger et al. 1995
Myoclonic Dystonia	AD	7q21.3	159900	SGCE	Myoclonic jerks, Dystonia, psychiatric abnormalities	Zimprich 2001
Cerebral arteriopathy (CADASIL)	AD	19p13.12	125310	NOTCH3	Migraine, strokes, white matter lesions with resultant cognitive impairment	Joutel et al. 1996
Spinocerebellar ataxia 17	AD	6q27	607136	TBP	Ataxia, pyramidal and extrapyramidal signs, cognitive impairment, psychosis, and seizures	Gao et al. 2008
Infantile onset Spinocerebellar ataxia / SCAE	AR	10q24.31	271245	C10orf2	Hypotonia, ataxia, ophthalmoplegia, hearing loss, seizures, and sensory axonal neuropathy	Hakli et al. 2000
Frontotemporal Dementia	AD	17q21.31	600274	MAPT	Difficulties in social and personal conduct with loss of volition, executive dysfunction, loss of abstract thought, and decreased speech output	Hutton et al. 1998
Fragile X syndrome	X-linked recessive	Xq27.3	300623	FMR1	Progressive neurologic disorder with cerebellar ataxia and/or intention tremor, short-term memory loss, executive function deficits, cognitive decline, parkinsonism, peripheral neuropathy and autonomic dysfunction	Jacquemont et al. 2003

Complex psychiatric disorders

Understanding complex disorders

The understanding and treatment of complex neuropsychiatric disorders pose many challenges to medicine, since the most common clinical diagnoses are not defined on the basis of etiology but rather on the basis of clinical classification, behavior and cognition. In most common psychiatric disorders, it is usually rare to have a definite mode of genetic inheritance, because of genetic heterogeneity. In other words, while one gene may contribute nominally to several different disorders, one disorder may be caused by several different underlying genes as well. For example, variations in the brain-derived neurotrophic factor, BDNF, gene have been associated with schizophrenia, bipolar disorder, major depression, anorexia nervosa and bulimia nervosa.(15-19)

To expand, a disease may be caused by one major defective gene with additional modulation by other minor genetic effects or environmental factors. However, in most cases no major gene effect is observed, and the disease is thus truly polygenic. Such traits are determined by a combination of effects from several genetic loci as well as many environmental factors with small, independent and additive effects. Thus, a fundamental question regarding allelic anatomy of complex disorders revolves around how big the effect of the mutation is. Usually, genetic variations that have very large effects on disease tend to be rare in the population. Conversely, common genetic variations associated with a disease tend to carry relatively small risks. Over the past decade, one of the leading theories regarding the allelic architecture of common disorders (affecting more than 1% of the population) is the "Common Disease, Common Variant" (CDCV) hypothesis.(20, 21) The CDCV hypothesis proposes that disease alleles for common diseases were common in our ancestral population, and disease alleles for rare diseases were rare. Due to rapid population expansion, common disease alleles massively increased in proportion. Rare disease alleles have also increased in proportion, but not as much as the commoner alleles, since they were rare in the original population. Another key aspect of the CDCV hypothesis is that new alleles are constantly introduced into the population, with the result that novel variations will substitute both rare and common disease alleles. However, the rate of introduction of new mutations is a relatively slow process. Thus, the fraction of new mutation in the population is predicted to be small compared to common variants, but may represent a considerable proportion of the disease burden for initially rare disorders.(20, 21)

Genetic Approaches for studying complex disorders

The Candidate Gene Approach: If there is an a priori reason to suggest the involvement of a gene in the pathophysiology of the disorder, it forms the basis of a candidate gene study. Once identified as a candidate gene, it is systematically studied to ascertain disease liability.

Linkage and Association Approach: Two different but related methods for investigating the relationship between candidate genetic markers and disease are association and linkage. Linkage is said to occur when two genetic traits are co-inherited rather than independently inherited as predicted by Mendel's second law. If the traits are encoded by genes that exist close together on the same chromosome, then recombination between them will occur very rarely during meiosis. Under these circumstances, the two genetic traits will be passed on to subsequent offspring simultaneously. Linkage analysis requires the study of families in which there are multiple affected individuals and its aim is to detect genes of major effect. Using modern technology, segregation of single nucleotide polymorphisms (SNPs; present throughout the human genome) in the DNA within a family can be determined and compared with their co-segregation with the disease. If they co-segregate, then the disease gene is located close to the polymorphic marker.

An alternative method is the genetic association study. This method looks for an association between one allele of a genetic polymorphism and the disease. For an association study, one requires a large number of unrelated patients and a large number of unrelated unaffected individuals. SNPs very close to the causal genetic mutation are unlikely to be separated because there is very little chance of recombination occurring between them. Thus certain alleles/SNPs will also occur more frequently in patients than in controls. Genetic association studies do not require any major assumption and is capable of detecting even minor susceptibility loci. Nowadays, with the appropriate statistical methods, genetic wide association studies (GWAS) can be used to screen for association of variants at the whole genome level.

Copy Number Variations (CNVs) in Psychiatric disorders

Chromosomal deletions and duplications or rearrangements (translocations, inversions, etc.) have been associated with psychiatric disorders, often caused due to genome instability. Deletion in chromosome 22 (22q11–12), often associated with psychotic and behavioural symptoms, is well-known in psychiatry.(22-24) Recently,

genomic hybridization arrays have allowed cytogeneticists to go beyond the microscopic level of resolution and to detect chromosomal alterations at the molecular level, termed as Copy Number Variations (CNVs). A CNV is a segment of DNA greater than 1000 base-pairs with variable copy number compared with the reference genome. CNV regions contained hundreds of genes, disease loci and functional elements. Some studies indicate that these variations are 2 to 3 times more important in scope than the SNPs that are used in genome-wide association studies.(25, 26) Interestingly, a large number of these submicroscopic CNVs were found to be widespread in the genome of otherwise healthy humans. The main challenge is to determine which of these CNVs are pathogenic. Usually, if a CNV co-segregates with the disease in the same family, it is very likely that this CNV is pathogenic. Reports of studies on many psychiatric disorders (e.g., autism, attention-deficit hyperactivity disorder, schizophrenia) support the possibility for a role of CNVs in these disorders.(27, 28)

Major findings from recent genetic studies

Although family-linkage and twin studies have indicated that genetic factors often play an important role in the development of psychiatric disorders, reliable identification of specific genetic susceptibility factors to particular disorders, through linkage or association studies, has proven difficult. This is possibly due to overlap of symptoms, inadequate clinical classification introducing biases, complexity of interactions between genes, environment and early development.(29) Recent research has increasingly focused on links between genes and endophenotypes, that is, specific traits like neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological characteristics, rather than disease categories.(30) We shall discuss the inherent vast variability in common psychiatric disorders in the light of modern genomic advances, particularly autism spectrum disorder (ASD) and schizophrenia. Some of the other complex psychiatric disorders are represented in **Table 2**.

Autism Spectrum Disorders (ASD)

Autism is a of development disorder in children which includes deficiency in social functioning and language development, repetitive and ritualistic behavior, tantrums and aggressive behavior.(31) Autism is the most prevalent syndrome among a spectrum of disorders currently grouped under Autism Spectrum Disorders (ASD), including Rett's syndrome (0.006% prevalence), Asperger's syndrome (0.025%), Pervasive Developmental

Disorder Not Otherwise Specified (PDD-NOS, 0.15%), and Childhood Disintegrative Disorder (CDD, 0.001%).(32, 33) ASDs have a world-wide prevalence of approximately 0.1 percent. However, considering the entire spectrum of disorders, it may be as high as 1/150, which may be due to changes in modern diagnostic criteria.(32)

ASD is a common, highly heritable neuropsychiatric condition marked by genetic heterogeneity. It is one of the most familial of all psychiatric disorders, with approximately 90% heritability.(34) The risk to siblings of autistic individuals is at least 20 times higher than among the general population.(35) Over the past decade, large-scale gene discovery efforts have clearly shown that autism is not a simple/Mendelian disorder.(36) Thus it represents an etiologically heterogeneous disorder in which the various genetic or environmental risk factors affect common molecular pathways/ networks in the brain.(37-39) At the same time, despite very strong evidence for a genetic contribution(40, 41), the rate of progress in gene discovery has been slow. However, it is also the case that studies of the genetics of complex disorders, including ASD, have just begun to reach maturity. Over the last five years, with the rapid evolution of genomic tools and methodologies, a tremendous amount of data has been generated and recent findings are offering the first glimpses of the biology underlying common disease conditions.

While the CDCV hypothesis has been a leading school of thought, there are alternate views of genetic architecture of common psychiatric diseases, and autism in particular. The "Rare Variant Common Disease" (RVCD) approach supposes that common disease like ASD may be caused by multiple rare variations in the same gene (allelic heterogeneity) or multiple genes (locus heterogeneity), that lead to a common phenotype.(42, 43) Such variation could either be transmitted from generation-to-generation or de novo. With respect to ASD, gene discovery efforts have also included study of known rare monogenic syndromes that share features with ASD, like Fragile X syndrome, neurofibromatosis, and tuberous sclerosis which show phenotypic overlap with ASD. For example, mutations in MECP2, the Rett Syndrome gene, have been found among cases of idiopathic autism without the Rett phenotype.(44) Also, studies aimed at investigating extreme outlier or rare families that transmit the phenotype in a Mendelian fashion are of special interest.(45)

Rare microscopic chromosomal abnormalities occur at a mean rate of up to 7.4% in autism versus less than 1% in the general population, the most common of which are maternally inherited duplications at 15q11-13.(46-48)

De novo deletions or translocations have also been reported at Xp22.3.(49) A functional mutation at this region was reported in the gene NLGN4X, a neuronal adhesion molecule important for specifying excitatory versus inhibitory synapses.(50, 51) Genes coding for molecules that interact with NLGN4X, including SHANK3 and NRXN1 have both been strongly implicated in ASD. The convergence of findings showing multiple mutations in a relevant molecular pathway as opposed to just a single gene is important for confirmation of rare variant findings and autism.(52-55)

Candidate gene association studies have also aimed at identifying common alleles contributing to ASD. While potential flaws are found in many studies of ASD, several recent candidate gene investigations have been discovered. The genes EN2, MET and CNTNAP2 have emerged as relatively strong candidates from these recent single locus association studies. Of these, Contactin Associated Protein 2 (CNTNAP2), has emerged recently as a candidate for involvement in a range of developmental disorders including autism, language development, and seizure, based both on common and rare variant findings.(56-60)

The first large-scale genome-wide association study (GWAS) showed significant association of ASD to an intergenic region on chromosome 5 – 5p14.1, mapping between the neuronal adhesion molecules Cadherin 9 and Cadherin 10.(40) In recent years, several studies have provided additional evidence for the role of rare variation and particularly Copy Number Variations (CNVs), in Contactin 4.(41, 61, 62) In general, contactins bind to contactin-associated proteins to mediate their functions, at least in the peripheral nervous system. CNTNAP2 was first and so far most convincingly tied to ASD.(63) Also, both de novo deletions and duplications at 16p11.2 have been identified in patients with ASD.(64, 65) Weiss et al. (2008) found these in ~1% of autism case samples compared to 0.1% in the general population.(65) Marshall et al. (2008), in addition to finding support for the 16p.11 locus, identified several new candidates, including DPP6 and DPP10.(66) It is of note that this deletion was observed in other psychiatric disorders including bipolar disorder (1/420), attention-deficit hyperactivity disorder (1/203), schizophrenia (1/648), dyslexia (1/748) and anxiety, panic, depression or addiction (1/3000).(28) Newly identified genes using this method include CNTN4, BZRAP1 at 17q22 and MDGA2 4at 14q21.3.(41, 67) Recently, a number of reports have been published reporting a spate of rare de novo and transmitted CNVs in ASDs.(68-70) Levy et al. (2011) studied a large cohort of families with a single affected child with at least one unaffected sibling

4

(multiplex families were excluded). Apart from rare deletions and duplications, they report role of inherited "ultrarare" duplications. They also report several hundred target loci causal to ASDs, which although point to a great diversity of genetic causes, but also suggests functional convergence of the pathophysiology of the disease.(68)

Morrow et al. (2008) conducted a large-scale homozygosity mapping study in consanguineous Middle Eastern families. They found several large, rare, inherited homozygous deletions that disrupted either the coding or potential regulatory regions of brain-expressed transcripts, including DIA1, NHE9, PCDH10 and CNTN3. They also found rare amino acid changes in NHE9 in nearly 6% of patients with both autism and epilepsy compared to 0.63% of controls. The results suggest that changes in activity-regulated gene expression during brain development may contribute to ASD.(71)

Since there is not a single gene or genetic test that definitively diagnoses autism, the diagnosis of autism remains largely a clinical/syndromic one. However, this does not preclude the usefulness of genetic testing in aiding in diagnosis, family planning or prognosis.(72) There are several institutional guidelines that provide recommendations regarding genetic testing in autism.

Schizophrenia

Schizophrenia is a psychotic disorder of severely inappropriate emotional responses, with patients suffering from delusions and hallucinations. There may be impairment of cognitive function, disordered thinking and concentration, as well as erratic behavior. Schizophrenia is a common disorder with a lifetime prevalence of approximately 1%.(73)

In 1988, Bassett et al. (1988) reported a Chinese family in which members with a diagnosis of schizophrenia had a partial trisomy of chromosome 5.(74) This finding was not replicated in subsequent studies. That genetic factors play a major role is evident from twin studies that show heritability for schizophrenia to be > 80%. However, identification of susceptibility genes has been slow, because of the lack of diagnostic biomarkers (physiological, biochemical, etc.) which can be used to define the parameters of the disorder. The uncertain relationship between diagnosis and underlying etiology has created difficulties for research. For example, while schizophrenia and bipolar disorder have been historically classified into non-overlapping categories with distinct etiologies, this separation is partially artificial.(29) Despite this, there have been a few notable successes in the identification of genetic risk factors. For a list of genes that have been associated with Schizophrenia as well as some common complex disorders, see **Table 2.**

Table 2. List of some complex psychiatric disorders showing association with multiple genes (data compiled from Online Mendelian Inheritance in Man)

Disorder	Phenotype MIM#	Symptoms	Affected/Associated Genes
Schizophrenia SCZD1	181500	Psychotic disorder, inappropriate emotional responses, delusions and hallucinations, impairment of cognitive function, disordered thinking and concentration, erratic behavior.	SCZD12, MTHFR, CHDL1, DISC1, DISC2, SYN2, DRD3, SCZD3, DTNBP1, SCZD5, SCZD6, SCZD11, GPR49, SCZD2, DAO, HTR2A, SCZD7, DAOA, AKT1, SCZD10, SCZD8, COMT, RTN4R, APOLA, APOL2
Obsessive-compulsive disorder (OCD)	164230	Recurring obsessions and/or compulsions	BDNF, COMT, HTR2A, SLC6A4, HTT, NTRK3
Bipolar affective disorder / Major Affective disorder/ Manic Depressive Psychosis	125480	Episodes of dysphoria, episodes of mania (bipolar I) or hypomania (bipolar II) interspersed with periods of depression	SLC8A3, HTR4, ABCA13, DRD4, BDNF, CUX2, SLC6A4, BCR, COMT, XBP1, TRPM2, MTND1, TPH2
Anorexia nervosa	606788	Eating disorder, obsessive fear of weight gain, low body weight	COMT, BDNF, MAOA-uVNTR, 5-HTTLPR
Autism Spectrum Disorders (ASD)	209850	Deficiency in social functioning and language development, repetitive and ritualistic behavior, tantrums, aggressive behaviour	NLGN4X, SHANK3, NRXN1, EN2, MET, CNTNAP2, CONTACTIN4, DPP6, DPP10, CNTN4, BZRAP1, MDGA2, DIA1, NHE9, PCDH10, CNTN3
Attention Deficit-Hyperactivity Disorder (ADHD)	143465	Childhood-onset behavioral disorder, persistent inattention and/or hyperactive-impulsive behavior results in impaired social and/or academic functioning.	DRD5, SLC6A3, HTR1B, ADRA2A, DRD4, SCN8A, SNAP25, COMT
Major depressive disorder (MDD)	608516	Major depressive episodes, changes in appetite, weight, sleep, and psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty thinking, concentrating, or making decisions, recurrent thoughts of death or suicidal attempts, impaired social functioning.	MTHFR, CREB1, FKBP5, TPH1, TPH2, HTR2A, MDD1, MDD2, CHRM2, TOR1A, DRD4, SLC6A4, BCR

Role of Epigenetics in psychiatric disorders

In recent years, there have been a large number of studies indicating the importance of the effect of the environment on genome regulation through epigenetic processes, resulting in the silencing of key regulatory genes as well as re-expression of key genes. The term Epigenetics, which literally means "in addition to genetics", has evolved to include any process that alters gene activity without changing the DNA sequence, and leads to modifications that can be transmitted to daughter cells. However, unlike genetic mutations, epigenetic changes

are potentially reversible and therefore hold the promise of being treatable or preventable through drugs, diets/ supplements and other environmental influences.

Also, since epigenetic changes may precede pre-symptomatic stages of many diseases, such changes, if detectable, can serve as important biomarkers for early disease detection and prognosis. Although DNA methylation, histone modification and small regulatory RNA (eg. microRNA) mediated regulation of gene expression are three major epigenetic mechanisms identified, most technological advancements have been achieved in the DNA methylation field. Aberrant DNA methylation (hyper/ hypomethylation) is an epigenetic change that involves the addition/removal of methyl groups to cytosine residues in the context of a CpG dinucleotide. This usually occurs in the promoter region of a gene, which contains a high density of CpG dinucleotides, termed CpG islands. The methyl group addition interferes with binding of transcriptional proteins to the gene promoter (regulatory region of a gene) resulting in long-term silencing of that gene. On the other hand, promoter hypo-methylation may result in re-expression of key genes.

In recent years there has been an explosion of data indicating the importance of the effect of environment on the genome regulation through epigenetic processes, especially in the development of cancers, systemic lupus erythematosus, cardiovascular disease (atherosclerosis, homocysteinemia), psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder), chronic obstructive pulmonary disease, reproductive dysfunction and aging.(75-81)

The correlation between psychiatric disorders and the states of genomic methylation has been under extensive investigation for a long time.(81, 82) Initially, several studies pointed to abnormal methylation of the promoter of the reelin gene (RELN) and glutamic acid decarboxylase gene (GAD67) in schizophrenia and bipolar illness.(83-87) The reelin protein is necessary for neuronal migration and synaptogenesis during brain development. Another group found three fold higher methylation in the serotonin 5-HT1A gene promoter in schizophrenic or depressed patients than in controls.(88) Mill et al. (2008) studied DNA methylation changes in the frontal cortex and germline tissues associated with schizophrenia and bipolar disorder in microarrays of gene promoters.(89) Psychosis-associated DNA methylation changes were identified in numerous genes involved in glutamatergic and GABAergic neurotransmission, brain development, and other processes functionally linked to disease etiology, and corresponded

to reported changes of steady-state mRNA levels associated with psychosis (eg. BDNF).(89) Other genes that have abnormal DNA methylation patterns in schizophrenic patients include COMT, SOX10 and syt11.(90-92)

McGowan et al. (2008) studied the rRNA gene that encode ribosomal RNA in the genome of brain tissue of suicide subjects, and found hypermethylation throughout the promoter and regulatory regions, consistent with reduced rRNA expression in the hippocampus.(93) Poulter et al. (2008) demonstrated that DNMT3b gene (DNMTs; the enzymes which catalyze the addition of the methyl group on CpG sites) expression is increased in suicide subjects compared with control subjects in the brain cortex, linked with female bias, and consistent with the observation that Major Depression Disorder (MDD) is twice as prevalent in women.(94)

However, epigenetic changes being stable but reversible, there is a possibility to use suitable drugs that can amend epigenomic defects by therapy.(95) DNA methyltransferase inhibitors and histone deacetylase inhibitors are being explored for epigenomic therapy, and two types of DNA methylation inhibitors, azacitidine and decitabine, have generated much interest in cancer therapies.(75, 96)

Conclusion

Modern technical advances have accelerated progress in psychiatric genetics. Single gene Mendelian disorders are easy to screen and used in molecular diagnosis routinely. For complex disorders, the collection of large cohorts via international collaborations, together with array-based DNA technologies permitting genome-wide interrogation of variation, have resulted in major advances. More progress is expected with data coming from massively parallel sequencing (Next gen sequencing) of partial and whole genomes. Although such experiments are gradually becoming routine, interpretation of results, particularly in the context of diverse and overlapping phenotype data (as is presented in psychiatric disorders), will require major computational infrastructure and possibly new computational methods.

As etiological research into psychiatric disorders progresses, there has been a recent reevaluation of diagnostic criteria and their usefulness in treatment and classification. This is based on the observation that there is more etiological overlap between psychiatric disorders than thought previously. In fact, they might better be described as domains of disorder-related traits rather than separate categories. The view that many complex

psychiatric disorders are not separate entities but are intervals in a continuous spectrum, is supported by evidence coming from epidemiology and genetics. Also, gene-environment interactions that affect the genetic and epigenetic status of an individual are being highlighted to influence psychological traits. Such interactions may be the cause of development of certain personality and psychiatric traits. Recent epidemiological studies have revealed that the development of some traits common to psychiatric disorders, such as antisocial behavior or depression, can result from environmental insults that may have occurred prior to the onset of illness in some children that carry certain genomic variants that sensitizes them to these insults.(97)

As the list of new information on genetic risk factors in psychiatry grows, the most challenging aspect will be to understand the manner by which these changes affect the development and function of regions in the brain. It is probable that instead of looking at individual genes, genetic circuits and pathways that are disrupted by variations and are affected in disease will be targeted for therapy. With these rapidly occurring changes, it is vital for clinicians and counselors to keep abreast of these new developments. Moreover, it is important to keep in mind that many of the formal diagnostic criteria and analyses were developed prior to the recent explosion of genetic data, and consequently tend to underestimate the now-demonstrated value of these approaches. Current literature recommends that there is increased need for genetic testing with a decreasing threshold for obtaining such tests. This is well justified as more is learned about the genetic causes of psychiatric disorders and as tests become more accurate and less expensive.

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Authors

1. Priyadarshi Basu, Phd.
   Astt. Professor
   National Institute of Biomechical Genomics.
   P.O.- NSS, 2nd floor
   Kalyani 741251, West Bengal
   E- mail : pb1@niibmg.ac.in

2. Partha P. Majumder Phd.
   Professor and Director
   National Institute of Biomechical Genomics.
   P.O.- NSS, 2nd floor
   Kalyani 741251, West Bengal
   E- mail : ppm1@niibmg.ac.in

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