Review Paper:

Epigenomics: the interplay of genetic and epigenetic factors behind Psychological disorders

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Abstract

The sequence of the human genome encodes the genetic instructions for different physiological processes. In the last two decades, an attempt has been taken to establish linkage between human genome sequence data and different psychological disorders after the completion of human genome project. Advanced technology such as Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP) microarrays allow rapid inspection of coding and non-coding sequences leading to early detection, additional precision and eventual application of the generated data in population studies.

Anxiety, depression, bipolar disorder and Schizophrenia show genetic, epigenetic and environmental control. In this review paper, a total of 10 valuable genes, 7 crucial SNPs, role of micro-RNAs (mi-RNAs), structural chromosomal variants, contribution of tandem repeat of sequences, significance of integrated pathogens were thoroughly analysed along with different microdeletions and microduplications in genomic hotspots. The role of differential methylation leading to epigenetic reprogramming and pathophysiology of several psychotic candidate genes were explored in this current study.

Keywords: Genetic, Epigenetic factors, Psychological disorders, Allelism, Micro- RNA, Single Nucleotide Polymorphism, Structural chromosomal variants, Tandem repeat sequences, Pathogens.

Introduction

The cracking of the euchromatic human genome sequences leads to a remarkable leap in the health and medical industry. The use of haploid human genome as reference and invention of novel, cheaper and faster sequencing technologies unravelled the opportunity to determine genetic influences in mental disorders and conversion of a long thought myth into reality. The explosive activity of comparing genome sequencing data of ethnic traditional races along with modern urban personalised diploid human data led to the identification of genes related to abnormal mental traits. Diverse DNA sequence data is the key to search for individual genetic variation from single nucleotide polymorphism to easily detectable structural variants[5]. Translation of genome-scale variation into medically useful information, however, is in its infancy. The utilization of human genome sequence data for identifying the cause of genetic diseases may focus on targeted treatment strategies. The application of molecular genetics approaches for understanding different types of mental illness is changing the nature of medical research throughout the world.

Although our knowledge of the human genome is far from sufficient, still the available inventory of limited genomic understanding could help in early diagnosis of disorders and prompt focus on clinical monitoring and lifestyle changes. Clinicians all over the world are currently embracing genome sequence variants as more comprehensive in search of diagnosed diseases as they are heritable and more reliable. Though it is more complicated in case of rare and complex polygenic mental diseases, multiple gene variants are responsible for the development and progression of the mental disease[1].

This review summarizes the available molecular-genetic data for some of the synoptic disorders such as Schizophrenia, Bipolar Disorder, Depression, Obsessive Compulsive Disorder (OCD) and other anxiety disorders. The related genes, primers, probes and other markers were identified to suggest adjuvant therapies and medication. Better analysis tools and a deeper understanding of the biology of the human genome are necessary in order to decipher, interpret and optimize clinical utility of genetic variation. Personal genome sequencing may play a crucial role in medical practices providing information that assists in the formulation of a differential diagnosis and prescription of novel personalised treatment processes. The application of dry laboratory information of the human genome for mental illness treatment, along with suggestions and avenues for future studies in this newly emerged dynamic field is discussed in this study.

Review on psychological disorders: Mental illnesses profoundly affect an individual's ability of thinking, feeling and response to a particular situation. Although mental disorders were recognized as illnesses in the mid-18th century, suspicion and fear often overshadowed understanding. Gradually, trepidation has been replaced by knowledge as the fields of psychiatry, behavioural science, neuroscience, biology and genetics have progressed. This mental illness can affect the social, cultural and professional

performance of a country. The diagnosis, treatment and prevention of mental illnesses continue to be crucial to improve the quality of life of affected individuals, as well as to reduce health care costs.

The causal relationship between complex traits and diseases could be accomplished if the genetic correlation between them could be properly analysed. The World Health Organization [17] estimated that mental and behavioural disorders account for about 12 percent of the global burden of diseases. The Mental Health Statistical data estimated that 792 million in 2017 lived with a mental health disorder. This is slightly more than one in ten people globally (10.7%) [17, 19, 20].

In India, the burden of mental and behavioural disorders ranged from 95 to 102 per 1000 population. Several factors are related to the epidemiological development of different mental disorders. Biological factors affecting mental disorders are genetic origin, abnormal physiology and congenital defect. Seven percent (7%) of the total Indian population suffers from severe mental illnesses. [17, 19, 20]

Despite strong evidence for genetic susceptibility, no specific gene has been unambiguously identified for common forms of mental disorders. Many researchers believe that this is due, in part, to the critical role that the environment plays in modulating genetic susceptibility in mental disorders. Both genetic and environmental factors have been shown to be important in mediating mental disorders. Though most of the mental diseases show polygenic inheritance patterns, searching and validating linked hereditary markers may assist in the early diagnosis of the disorder with effective treatment as a part of primary health care.

Table 1
The Global Picture of Psychological Disorder and Substance Abuse in 2017

Disorder	Share of global population with disorder (2017)	Number of people with the disorder (2017)	Share of males: females with disorder (2017)
Any mental health disorder	10.7%	792 million	9.3% males 11.9% females
Depression	3.4% [2-6%]	264 million	2.7% males 4.1% females
Anxiety disorders	3.8% [2.5-7%]	284 million	2.8% males 4.7% females
Bipolar disorder	0.6% [0.3-1.2%]	46 million	0.55% males 0.65% females
*Eating disorders (clinical anorexia & bulimia)	0.2% [0.1-1%]	16 million	0.13% males 0.29% females
Schizophrenia	0.3% [0.2-0.4%]	20 million	0.26% males 0.25% females
*Any mental or substance use disorder	13% [11-18%]	970 million	12.6% males 13.3% females
*Alcohol use disorder	1.4% [0.5-5%]	107 million	2% males 0.8% females
*Drug use disorder (excluding alcohol)	0.9% [0.4-3.5%]	71 million	1.3% males 0.6% females

*****disorders not described in details in the current study

Table 2
The Percentage (%) of Indian Population Affected by Psychological Disorder and Substance Abuse in 1990, 2000, 2010 and 2017

Year	Schizophrenia (%)	Bipolar disorder (%)	* Eating disorders (%)	Anxiety disorders (%)	*Drug use disorders (%)	Depression (%)	*Alcohol use disorders (%)
1990	0.262	0.552	0.106	3.324	0.487	3.759	1.372
2000	0.262	0.552	0.115	3.282	0.504	3.921	1.514
2010	0.264	0.555	0.137	3.285	0.501	3.526	1.197
2017	0.258	0.557	0.158	3.302	0.527	3.530	1.127

*****disorders not described in details in the current study

Depression is a common mental disorder and one of the main causes of disability worldwide. Globally, an estimated 264 million people are affected by depression. More women are affected than men. A deeper understanding of the aetiology of depression including both its genetic and environmental determinants as well as their interplay (e.g. gene-environment interaction; G x E) will have implications for preventing depression and informing its clinical treatment. Major depressive disorder and the neuroticism personality trait have overlapping genetic susceptibilities[6]. The pattern of depression in biological and adoptive relatives of adult adoptees supports the findings of twin studies also indicating that genes play a key role in the aetiology of depression, but non-shared environmental influences are also important[16].

Several theories have been suggested to explain the onset of depression and have been confirmed by biochemical, immunological and physiological studies. Parallel to the well-known "monoamine," "cytokine," and "stress-induced" (hypothalamus–pituitary–adrenal (HPA) axis and stress theories) depression models, the phenomena of altered brain neural plasticity and neurogenesis and circadian rhythm desynchronosis (the chronobiological model) have been proposed to explain the onset of depression[10].

The bipolar disorder affects about 45 million people worldwide. The prevalence of bipolar disorder across the world varies from 0.3 to 1.2 percent by country. Globally, an estimated 46 million people had bipolar disorder in 2017 with 52 and 48 percent being female and male respectively. According to WHO[17], some research suggests that people with certain genes are more likely to develop bipolar disorder than others. But genes are not the only risk factor for bipolar disorder. Studies of identical twins have shown that even if one twin develops bipolar disorder, the other twin does not always develop the disorder, despite the fact that identical twins share all of the same genes [19, 20].

Schizophrenia on the other hand, is a severe mental disorder, affecting 20 million people worldwide. The prevalence of schizophrenia typically ranges from 0.2 to 0.4 percent across countries. It is estimated that 20 million people in the world had schizophrenia in 2017; the number of men and women with schizophrenia was approximately the same (around 10 million each). According to WHO [17], scientists have long known that schizophrenia sometimes runs in families. However, there are many people who have Schizophrenia who do not have a family member with the disorder and conversely, many people suffer with one or more family members with the disorder who do not develop it themselves[19,20].

The prevalence of anxiety disorders across the world varies from 2.5 to 7 percent by country. Globally an estimated 284 million people experienced an anxiety disorder in 2017, making it the most prevalent mental health or neurodevelopmental disorder. Around 63 percent (179 million) were female relative to 105 million males. According to WHO[17], researchers are finding that both genetic and environmental factors contribute to the risk of developing an anxiety disorder.

Although the risk factors for each type of anxiety disorder can vary, some general risk factors for all types of anxiety disorders include: temperamental traits of shyness or behavioural inhibition in childhood, exposure to stressful and negative life or environmental events in early childhood or adulthood and a history of anxiety or other mental illnesses in biological relatives, Some physical health conditions such as thyroid problems or heart arrhythmias, or caffeine or other substances/medications, can produce or aggravate anxiety symptoms; a physical health examination is helpful in the evaluation of a possible anxiety disorder[19,20].

Genetic and epigenetic factors

Factors responsible for Psychological Disorders: Psychological or mental functioning like any other metabolic processes shows biological control. Twin research, multi-generational family study and population-based cohorts provided ample empirical evidence of a genetic predisposition for negative emotional states. The biological basis of psychological disorders exhibit two parts: the genetic and heritable part as well as environmental influences[12]. The genetic liability of mental disorders involves the candidate gene approach or association of multiple genes.

Human cells are exposed to different exogenous and endogenous insults in its lifetime. The unwanted metabolic products created by these events cause substantially high levels of DNA damage in the brain accompanied with morphological and functional alterations. Environmental factors may involve: Exposure to viruses, Malnutrition before birth, Problems during birth, Psychosocial factors. DNA damage as well as unrepaired DNA lesions have been associated with many neurological disorders[13].

Identified Candidate Gene for Different Psychological Disorders

Depression: Genome wide linkage studies indicated that human chromosome 15q, 17p and 8p are related to depression. Candidate gene association studies focused on functional polymorphism in previously identified loci as well as new loci encoding for potentially relevant genes. Multiple genes with small additive effects make this diagnosis more challenging. Apolipoprotein E (APOE), guanine nucleotide binding protein (GNB3), methylene tetra-hydrofolate reductase (MTHFR), dopamine transporter (SLC6A3) and seratonin transporter (SLC6A4) genes were significantly associated with major depressive disorders[12]. Genomic studies with 430,000 SNPs in 1738 cases of major depression suggested the involvement of pre-synaptic protein (PCLO) on chromosome 7. One particular SNP rs2522833 in PCLO shows convincing evidence for a causal association with major depressive disorder[14].

Anxiety and Panic disorder: Tmem132D is a single pass transmembrane protein with a molecular weight of 132 kDa and regarded as a cell surface marker for oligodendrocyte differentiation. According to Beiko and Strange,[2] alpha-1 antitrypsin deficiency is related to onset of anxiety and depression in certain environmental conditions. Early onset of pulmonary disease leads to AATD-COPD with worse clinical and psychological outcome. Tmem is more expressed in the cortical region of the human brain causing anxiety and panic disorder with two SNP variants rs11060369, rs7309727 respectively. Higher anxiety with a higher amygdala volume is associated with variant rs11060369, suggesting a more generic role of the candidate gene.

The differential expression of Tmem132D mRNA revealed two SNP polymorphisms in the putative 1000 bp promoter region. Substitution of G nucleotide at -519 and -310 with A causes significant reduction in promoter activity. Similarly, deletion of G nucleotide causes the same anomaly. SNP in the 3rd Exon (rs36596918) of Tmem132D causes substitution of an arginine amino-acid with a lysine, another SNP in the 9th Exon (rs13478518) co-segregates with anxiety related behaviour. A modulating role of Tmem132D and DNA methylation is detected in panic disorder syndromes [8].

Bipolar Disorder and Schizophrenia: Bipolar disorder and Schizophrenia are highly heritable diseases. Modification in a calcium channel gene (CACNA1C, Gene Bank Accession No. MH645925-MH645951) is strongly linked with both the diseases. Genome wide association studies detected a human specific tandem repeat in the 100 kb interval region in the third intron of the CACNA1C gene [11]. A larger tandem repeat of 30 bp units is often repeated 100 times. Human population shows polymorphism in both size and sequence for this 30-mer repeat region. Humans differ from their non-human counterparts by the presence of the 30 mer sequence 10 times though only one copy is present in primates.

4 SNPs are detected in the 30 mer region forming protective and risk haplotypes. The repeat arrays characteristic of the protective haplotypes drove significantly higher luciferase activity than the risk types. The transcriptional enhancer is located on the topologically associating domain (TAD) with seven other downstream genes. The base-pair changes alter the predicted binding sites for a number of potential trans-regulatory factors. Both loss and gain of function alteration in the CACNA1C gene can lead to behavioural changes in humans. The tandem repeats are transcribed and translated even in the absence of ATG start codon.

The tandem repeat contains canonical splice site consensus sequence, with donor, acceptor and branch sites and a polypyrimidine tract. Head to tail organization of this 30-mer repeat shows a CpG site as the tandem motif ends with C and the next one starts with a G nucleotide. This tandem repeat is the causal basis for species specific evolution as well as individual to individual variation in complex phenotypes such as neurological function in humans. This finding can assist in the precise drug mediated control of bipolar disorder and Schizophrenia by targeting the calcium channel gene.

miRNA and Post transcriptional modifications: Scientists believe that many different genes may increase the risk of Schizophrenia, but that no single gene causes the disorder by itself. It is not yet possible to use genetic information to predict who will develop Schizophrenia. Scientists also think that interactions between genes and aspects of the individual's environment are necessary for Schizophrenia to develop. This disorder is the most common psychiatric disorder leading to long term disability. Aberrant expression of some mRNA and protein lead to the development of this disorder. Some endogenous, small, abundant and non-coding miRNAs were associated with this disease. This single stranded RNA of 17-25 nucleotide length can bind to the 3' untranslated region of targeted mRNA and control the post-transcriptional modification leading to different patho-physiological expressions.

Two single nucleotide polymorphisms (SNPs) were identified as markers for Schizophrenic patients. Rs 1625579 of MiR-137 and Rs 107822 of MiR-219 were regarded as strong SNPs for schizophrenia but it shows geographical and racial differences in expression. Though a positive association exists between the Rs 1625579 of MiR-137 locus and disease occurs in European-Caucasian ancestry, yet the role of this MiR is negative in some Chinese populations. Rs 107822 of MiR-219 shows strong involvement in pathogenesis of schizophrenia along with some specific allelic combinations in Chinese populations[15]. The positive side of this study is the identification of some heritable markers for early detection of this disease.

Multiple Allelism: Obsessive Compulsive Disorder (OCD) is associated with a triallelic gene HTTLPR that forms a seratonin transporter. The serotonin transporter gene shows a functional polymorphism in the 5' flanking region of the gene, a widely studied locus. HTTLPR consists of a varying number of copies of 20-23 bp imperfect repeat sequences. The frequency of L allele is 16 repeat (0.60) and S allele is 14 repeat (0.40). Substantial inter population variation exists for this particular trait, rare alleles contain up to 20 copies of the repeat[4]. Apart from the tandem repeat, a SNP polymorphism from A to G conversion was detected in HTTLPR variant alleles. OCD affects patients throughout their lives leading to diminished quality of life of patients, families, reduced productivity and high healthcare costs. OCD is moderately heritable; replicated genes for OCD are unknown, with the possible exception of uncommon 425Val allele in HTT[4].

Integration and effect of pathogens: A number of Central Nervous System (CNS) disorders are caused by viral agents. The potential latency and neurotropism aid in viral

pathogenesis. Human herpes virus 6 (HHV-6) is a T-cell tropic virus and plays a pathogenic role in the development of neurologic disorders including epilepsy and multiple sclerosis as well as skin diseases. The association between schizophrenia and bipolar disorder with human herpes virus 6 (HHV-6) was mentioned by scientists for a long time. Real time PCR analysis of peripheral blood mononuclear cells (PBMC) of Schizophrenia and bipolar disorder patients including healthy control manifested a low and insignificant correlation between HHV-6 and Schizophrenia and Bipolar Disorder[18].

Epigenetic Control and DNA methylation: According to Cappi et al,[3] epigenetic factors play a significant role in the development of Obsessive Compulsive Disorder. Oxytocin has been linked to the pathophysiology of OCD. The most widely studied epigenetic alteration in humans is the DNA methylation (DNAm). The epigenetic mechanism controls gene expression. In mammalian cells a guanine preceded cytosine (cytosine-phosphate-guanine) locus is hotspot for DNA methylation. Autism, psychopathy, acute psychosocial stress in the population along with anorexia remain associated with methylation of oxytocin receptor gene (OXTR). Two target sequences present in the exonIII of OXTR were directly rich in CpG Methylation Island and related to epigenetic reprogramming and alteration in gene expression.

Functional assay and bio-informatics studies indicate differential methylation in enhancer in IGF2 locus regulating tyrosine hydroxylase gene (TH). TH is the rate limiting enzyme for dopamine synthesis. Epigenetic misregulation of the enhancer drives psychotic symptoms by dopaminergic abnormalities. The hypomethylated HGF2 locus in major psychosis overlapped an enhancer in the adult frontal cortex[9].

Microdeletions and microduplications underlie greater than 15% of the mental diseases changing the submicroscopic copy number of specific DNA fragments in the population[7]. 17q21.31 as well as 15q24 microdeletions remain associated with several mental disorders. Another rare but authentic deletion involves 16p11.2-p12.2. Deletion/deficiency in large hotspot regions 10q22-q23 are rare but recurrent and leads to cognitive impairment and behavioral abnormalities. Segmental duplications in genomic regions are responsible for mental diseases. Duplicated sequences promote recurrent rearrangement and proved pathogenicity with fewer patients and control. A wide range of neurocognitive diseases such as autism, mental retardation, epilepsy, schizophrenia arise from variant phenotypes associated with rearrangement of 16p11.2, 1q21.1 and 15q13.3.

Conclusion

Present genetic understanding of the psychological disorder leads to a paradigm shift from phenotype-first approach to a genotype-first approach. Twin and family study along with segregates, variants and linkage analysis lead to understanding of the genetic and environmental basis of a psychological disorder leading to compartmenting of heritable and non-heritable risk factors. An understanding of the role of micro deletions and duplications could assist a psychologist in the early detection of diseases. Large numbers of cohort studies can precisely assess the type of disorder and judiciously exclude the examination of a related one. Genome wide association study with oligonucleotide microarray technologies could identify short read copy number variants generating intra as well as infra species markers.

In recent years, the study model also includes the integration of DNA based repair mechanisms. In some disorders the comparison between normal and affected humans showed structural variation in different parts of the brain leading to epigenetic understanding of the up regulation of disease occurrence and control.

This review recommends that a multi-omic study approach with large cohort based studies of genetic and epigenetic factors could play a significant role in early detection and efficient management of psychological disorders. The total understanding of epigenomic tools can form an ultimate causal link between underlying genome and regulatory epigenome in the initiation and development of psychological disorders.

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