The role of epigenetics in mental disorders

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It is well established that the idiopathic mental disorders have a genetic basis. Yet, genetic mapping has not definitively identified any genetic mutation or polymorphism underlying these disorders. This review discusses the role of epigenetics in the pathogenesis of the idiopathic mental disorders. Epimutations and epigenetic polymorphisms are emphasized as being an interface between the genes underlying the idiopathic mental disorders and the environment. Psychosocial factors are described as important environmental factors involved in the pathogenesis of the idiopathic mental disorders, modifying the underlying genes by epigenetic mechanisms. Epigenetic strategies to identify the genes underlying the idiopathic mental disorders are described and the available molecular evidence supporting an epigenetic pathogenesis for these disorders is discussed. It also discusses the role of epigenetic factors in the pathogenesis of neuropsychiatric disorders and the relevance of the new therapeutic option, epigenetic therapy, in treating the idiopathic mental disorders and the neuropsychiatric disorders.

Key words Behaviour - epigenetics - epigenetic therapy - idiopathic mental disorders

There are two major categories of mental illness. One comprises the idiopathic mental disorders like schizophrenia, bipolar disorder and major depressive disorder (MDD) where there are no definitive structural changes in the brain. The other comprises the neuropsychiatric disorders like Alzheimer’s disease and Huntington’s disease which are characterized by definitive structural changes in the brain. The idiopathic mental disorders are common disorders, with the lifetime prevalence of MDD being about 12.5 per cent and that of schizophrenia about 1.5 per cent. The neuropsychiatric disorders are comparatively rare, except for a relatively high prevalence of Alzheimer’s disease and other dementias among the aged. Family, twin and adoption studies indicate that both these categories of disorders have a genetic basis. The idiopathic mental disorders have complex inheritance patterns involving many genes and environmental factors, while the neuropsychiatric disorders have simpler patterns of inheritance.

Genetic mapping studies of mental disorders

There has been intense interest in mapping genes underlying mental disorders for the past few decades. Two main approaches which have been used to map genes underlying these disorders are linkage and association studies.

Genetic mapping studies of neuropsychiatric disorders

Genetic mutations and polymorphisms underlying neuropsychiatric disorders like Alzheimer’s disease, Rett syndrome, Huntington’s disease and fragile X
syndrome have been mapped and characterized. The latter two diseases are associated with expansion of trinucleotide repeats resulting in disease, and are now diagnosed by molecular genetic tests.

### Genetic mapping studies of idiopathic mental disorders

An enormous amount of work has been performed in mapping genes underlying the idiopathic mental disorders using linkage and association studies. However, to date, no genetic mutation or polymorphism underlying schizophrenia, bipolar disorder, or MDD has been definitively identified by these studies.

Several reasons have been offered for the failure of genetic mapping studies in identifying genes underlying the idiopathic mental disorders: polygenic, multifactorial causation; gene-environment interactions; genetic heterogeneity; small population-wide effects of individual susceptibility genes; epistasis; differences in statistical strategies and ethnic differences across the studies; and genotyping and diagnostic errors. It has also been suggested that the assumption of these studies that the genetic basis of idiopathic mental disorders involves genetic mutations or polymorphisms may be wrong, and that instead, the genetic basis may involve defects in gene expression not involving changes in DNA sequence, i.e., epimutations and epigenetic polymorphisms.

### Mitochondrial genes and mental disorders

The role of mitochondrial genes in the pathogenesis of mental disorders has also been investigated. Although mutations of mitochondrial genes cause mental problems secondary to disorders of the brain like encephalopathy, and are involved in normal ageing and Alzheimer’s disease, no mitochondrial gene underlying an idiopathic mental disorder has been conclusively identified.

### Molecular aspects of epigenetics

Epigenetics refers to the study of heritable changes in gene expression that occur without a change in DNA sequence. Heritable defects in gene expression not involving DNA sequence changes have been referred to as epimutations. Related concepts are epialleles which refer to epigenetic variants of a genetic allele and epigenetic polymorphisms which have been described as variations of epigenetic patterns across individuals. For example, DNA methylation polymorphisms involve variations of DNA methylation across the genome.

The concepts of the molecular aspects of epigenetics are evolving rapidly. Three molecular mechanisms, which interact with each other, have been shown to be involved. One is methylation of DNA which usually, but not always, depending on the position of the methylation change relative to the position of the transcription start site, inhibits gene transcription. DNA gets methylated at sites where there is cytosine by the enzymatic addition of a methyl group, using S-adenosylmethionine as the methyl group source, to the carbon-5 position of cytosine. The majority of 5'-methylcytosine in mammalian DNA is present in 5'-CpG-3' dinucleotides. Non-CpG sequences may also exhibit methylation, but generally at a much lower frequency. The methylation of CpG sites within the human genome is catalyzed by four well-documented DNA methyltransferases (DNMTs) named DNMT1, DNMT2, DNMT3A and DNMT3B. DNA methylation has many functions like silencing of transposable elements, defense against viral sequences and transcriptional repression of certain genes.

Eukaryotic DNA is intimately associated with proteins to form a highly ordered and condensed DNA: protein complex called chromatin. The most abundant proteins in chromatin are a family of small basic proteins called histones. Histones can be modified by different ways like acetylation, methylation, and phosphorylation of the histone tail domains. This alters chromatin structure, leading to regulation of gene transcription. Histone modifications lead to dynamic transitions between gene activation and silencing. These “on-off” transcription states are due to differences in histone modification leading to the formation of accessible, euchromatic (on) or condensed, heterochromatic (off) states.

A third epigenetic mechanism in gene expression has been described more recently: small RNAs derived from cleavage of double-stranded RNA can silence genes at transcriptional and post-transcriptional levels. Small RNAs are 21 to 28 nucleotides long and include micro RNAs (miRNAs) and small interfering RNA (siRNAs). RNA-mediated gene silencing is important in maintaining chromosomal structure, genome defense and gene regulation.

### Environmental and stochastic factors involved in epigenetics, normal behaviour and mental disorders

Common diseases involve interactions between genes and the environment and epigenetic mechanisms are thought to be an interface between genes and the environment.
environment in these diseases. The environmental factors may impinge on epigenetic mechanisms in gene expression by many ways. Thus, dietary levels of methionine, the metabolic precursor of S-adenosylmethionine during prenatal and early postnatal life, influences susceptibility to chronic adult diseases because dietary methionine influences DNA methylation. Environmental factors also modulate proteins like enzymes associated with DNA methylation and histone modification. Other proteins like polycomb proteins (proteins that maintain many genes important for development in a repressed state) also mediate the epigenetic effects of the environment on gene expression.

Psychosocial factors have been described as important environmental factors involved in the pathogenesis of the idiopathic mental disorders and there is experimental evidence from studies on animals that psychological factors can modify behaviour by epigenetic mechanisms. For example, it has been shown in cross-fostering studies in the rat, that non-genomic transmission of maternal behaviour and stress responses occur from one generation to the next. In two strains of inbred mice it was shown that strain-related behavioral differences may result from environmental factors acting during prenatal and postnatal development, rather than from genetic differences in the offspring. In a well-conducted study on pup licking and grooming by rat mothers, increased frequency of these maternal behaviours increased the number of hippocampal glucocorticoid receptors in the pups, causing better regulation of glucocorticoid secretion. The increased glucocorticoid receptors in the pups were due to changes in DNA methylation and histone acetylation associated with the glucocorticoid receptor gene promoter. These differences emerged over the first week of life, were reversed with cross-fostering, and persisted into adulthood.

Stochastic (i.e., random) factors are thought to be involved in epigenetics and hence they may also contribute to the epigenetic defects underlying mental disorders. Recent experimental evidence suggests that genetic, epigenetic, stochastic and environmental factors can interact with each other in determining gene expression in mammals.

Scope for epigenetics in mental disorders

Several lines of evidence suggest that epigenetic mechanisms in gene expression are involved in mental disorders: the genetic information available in the human genome is insufficient to specify all the neuronal interconnections in the human brain and hence human brain development requires further information in the form of epigenetics in which specific genes within brain cells are activated and modulated during development. Among all organs, epigenetics play the greatest role in the development of the brain; and epigenetics is thought to have played a major role in the evolution of human mental functions and abilities.

Since epigenetic mechanisms in gene expression do not involve changes in DNA sequence, and involve environmental inputs, epigenetics may explain many clinical aspects of the idiopathic mental disorders like a high degree of discordance of monozygotic twins for these disorders; the relatively late age of their onset; differences between the sexes in the rate and course of illness; fluctuations in the course of illness; and parent-of-origin effects, i.e., the phenomenon that in some idiopathic mental disorders risk to offspring depends on the sex of the affected parent. For example, some clinical and molecular studies have shown that chromosome 18 is associated with parent-of-origin effects in bipolar disorder. A common mechanism involved in parent-of-origin effects is genomic imprinting, the essence of which is differential epigenetic modification of genes depending on their parental origin.

Epigenetic strategies to identify genes underlying the idiopathic mental disorders

The epigenetic strategies that may help identify the genes underlying the idiopathic mental disorders have been outlined. One strategy involves detection of abnormalities in DNA methylation and modifications of histones in chromatin in leucocytes or postmortem brain tissue in patients with these disorders. There are many technical problems associated with these methods as for these studies the tissue where the disease process originates is essential and hence brain tissues need to be studied; long postmortem brain storage changes chromatin causing difficulties in studies on histone modifications; the studies are labour-intensive and pose major problems in data analysis. With recent developments in technology like high-throughput microarray-based DNA methylation profiling, there are better prospects for these studies.

Another epigenetic strategy to identify genes underlying the idiopathic mental disorders involves detecting abnormal gene expression patterns in postmortem brain tissue of patients with these disorders.
These studies face many difficulties in choosing the precise cell population to be studied, distinguishing changes in gene expression caused by disease from experimental noise, and lack of correlation between changes in gene expression and protein changes within individual neurons. These patterns may reveal the influence of epigenetic mechanisms on expression of the underlying genes.

**Molecular evidence for epigenetic mechanisms underlying mental disorders**

Molecular studies on epigenetic mechanisms in patients with idiopathic mental disorders are still in infancy. Petronis et al. investigated the methylation patterns of DNA obtained from lymphocytes at the 5’ regulatory region of the dopamine D2 receptor gene in two pairs of monozygotic twins, one concordant and the other discordant for schizophrenia. Many DNA methylation differences were found in the analysed region both within and between the monozygotic twin pairs. The affected twin from the pair discordant for schizophrenia was epigenetically more similar to the affected concordant twins than to his unaffected monozygotic co-twin. In another study, methylation of the promoter of the RELN gene, the gene that encodes the protein reelin in frontal lobe brain samples from 10 patients with schizophrenia was investigated. It was found that there was hypermethylation of this gene causing decreased expression. These results were corroborated by another study which investigated methylation within the CpG island of the RELN promoter in genomic DNA obtained from the cerebral cortex of 15 patients with schizophrenia and 15 nonpsychiatric subjects. It was found that methylation of this promoter region caused reduced expression of reelin in patients with schizophrenia. DNA methylation of SOX10, an oligodendrocyte-related gene, was found to be increased by Iwamoto et al. in postmortem brain in patients with schizophrenia, resulting in reduced expression of the gene. In another study, in a subgroup of 8 of 41 patients with schizophrenia there were high levels of H3-(methyl) arginine 17 in the prefrontal cortex, causing decreased expression of 4 metabolic transcripts. However, as a group, the 41 patients showed no significant alterations in histone profiles or gene expression compared to matched controls.

There is also evidence for abnormal epigenetic mechanisms in gene expression in idiopathic mental disorders. In studies of postmortem temporal cortex of patients with schizophrenia significantly altered expression of several genes including that encoding histone deacetylase 3 were found. Studies of the gene encoding 67-kDa glutamic acid (GAD67), and the RELN gene in GABAergic interneurons in postmortem prefrontal cortex of patients with schizophrenia have shown downregulation at transcriptional and translational levels. These changes were also found in psychotic patients with bipolar disorder but not in nonpsychotic depressed patients. There is evidence suggesting that these changes are due to over-expression of DNA methyltransferase-1 (DNMT1) in these neurons. Corroborating these data in humans, in the brain of mice protracted treated with methionine (6.6 mmol/kg twice a day for 15 days), there was hypermethylation of the promoter regions of the genes encoding reelin and GAD67, decreasing their transcription.

As mentioned above, genetic mutations and polymorphisms have been identified in neuropsychiatric disorders. These genetic mutations and polymorphisms may also be epigenetically modified. Thus, many cases of Rett syndrome are due to mutations in the MeCP2 gene, the gene that encodes the protein MeCP2. MeCP2 belongs to a family of proteins called methyl-CpG-binding proteins that share a methyl-CpG-binding domain comprising about 70 amino acid residues. These proteins are thought to regulate gene transcription by epigenetic mechanisms. In most cases of fragile X syndrome, a CGG repeat in the 5’ untranslated region of the fibrillarin (FMR1) gene on the X chromosome expands to greater than 200 repeats becoming hypermethylated, transcriptionally silencing the gene. Histone modification has also been reported in patients with fragile X syndrome. In Alzheimer’s disease at present there is inconclusive evidence for the involvement of epigenetic mechanisms in disease pathogenesis, but there is presumptive evidence for their involvement. Thus, studying the methylation status in a CpG region of the amyloid precursor protein (APP) gene by bisulphite sequencing in human postmortem cerebral cortices showed a negative relationship between age and methylation. Hypomethylation of the APP gene in brain genomic DNA obtained from an Alzheimer’s disease patient has also been reported. This suggests that epigenetic modifications may contribute to the pathogenesis of Alzheimer’s disease.

**Clinical implications of epigenetics of mental disorders**

The knowledge of the role of epigenetics in the pathogenesis of the idiopathic mental disorders at present is scarce. However, it has been predicted that in
future epigenetics will impact the management of these disorders, providing new opportunities for their diagnosis and treatment. An important goal in future will be to improve our understanding of the interplay between epigenetic mechanisms, gene expression and the environment in the pathogenesis of these disorders.

A new therapeutic option, epigenetic therapy, may be applicable to patients with the idiopathic mental disorders. In epigenetic therapy, drugs like inhibitors of histone deacetylation and DNA methylation modify histones and DNA methylation patterns. Many such drugs are undergoing preclinical and clinical trials for the treatment of non-psychiatric conditions. Valproic acid and its salt, sodium valproate, which have been used to treat bipolar disorder by unclear mechanisms for the past few decades, may at least partially act in this disorder by epigenetic mechanisms. Since epigenetic factors have been shown to be involved in neuropsychiatric disorders, epigenetic therapy may prove to be useful in these disorders also. Potential problems of epigenetic therapy include nonspecific activation of genes in cells and carcinogenicity.

Conclusions

Several lines of evidence suggest that epigenetic factors play an important role in the pathogenesis of the idiopathic mental disorders. At present, the genes encoding reelin and GAD67 have been implicated as epigenetically modified genes associated with the pathogenesis of schizophrenia and bipolar disorder. More epigenetically modified genes underlying the idiopathic mental disorders are likely to be identified. Identification of the epigenetic defects underlying these disorders may help patients with these disorders benefit from epigenetic therapy. Since genes underlying the neuropsychiatric disorders show epigenetic changes in addition to changes in DNA sequence, patients with these disorders may also benefit from epigenetic therapy.

References


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