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Biological markers of major psychiatric disorders

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Abstract
Psychiatric diseases are characterized by affective, behavioral, and cognitive abnormalities. Psychiatric illnesses produce some of the most challenging health problems faced by society, accounting for vast numbers of hospitalizations, disabilities resulting in billions in lost productivity, and sharply elevated risks for suicide. A substantial contribution of genetic factors to the risk of psychiatric disorders such as schizophrenia, bipolar disorder, autism has already been established. Genetic studies have provided some valuable insight into the causes and potential therapies for psychiatric disorders. There is a growing body of evidence suggesting that the understanding of the genetic etiology of psychiatric illnesses will be more successful with integrative approaches considering both genetic and epigenetic factors.

Keywords: psychiatric diseases, molecular genetics, genetic factors, epigenetic factors

Introduction
Neuropsychiatric disorders represent the second largest cause of morbidity worldwide. These disorders have complex etiology and pathophysiology. The major lacunae in the biology of the psychiatric disorders include genomics, biomarkers and drug discovery, for the early detection of the disease, and have great application in the clinical management of disease [1]. The majority of psychiatric diseases share a common feature, namely that family history of disease is a major risk factor, which is suggestive of a strong genetic component to the underlying disease risk. Epidemiological studies have estimated high heritability values of up to 80% for many common psychiatric diseases, such as schizophrenia and bipolar disorder.
In the 1960s most psychiatrists thought that the social determinants of behavior were completely independent of the biological determinants and that each acted on different aspects of mind. Psychiatric illnesses were classified into two major groups based on presumed differences in origin: (i) organic mental illnesses and (ii) functional mental illnesses. That classification, which dated to the nineteenth century, emerged from postmortem examinations of the brains of mental patients. The methods available for examining the brain at that time were too limited to detect subtle anatomical changes. As a result, only mental disorders that entailed significant loss of nerve cells and brain tissue such as Alzheimer's disease, Huntington's disease, and chronic alcoholism were classified as organic diseases, based on biology. Schizophrenia, the various forms of depression, and the anxiety states produced no readily detectable loss of nerve cells or other obvious changes in brain anatomy and therefore were classified as functional, or not based on biology.
Major advances in molecular genetics over the last 15 years have made possible to identify the genes responsible for human diseases using purely genetic approaches that do not require knowledge about disease pathophysiology. Many successes have been achieved for single gene disorders and methods are being adapted and refined for complex diseases. The main strategies include linkage and association studies to map the position of disease genes followed by investigation of potential candidate genes within these genomic regions [2].
New diagnostic approaches are based not on symptomatology but on the dysfunction of specific genes, proteins, neuronal organelles, or neuronal systems. Moreover, molecular genetics has given us insight into the mechanisms of pathogenesis of neurological disease that did not exist 20 years ago. For example, several genes including those encoding dopamine receptors 2-4 (DRD2, DRD3, and DRD4), serotonin receptor 2A (HTR2A) and

catechol-O-methyltransferase (COMT) have been implicated in the etiology of schizophrenia and related disorders. There is also growing evidence for the role of dopamine receptors 1 (DRD1), N-methyl-D-aspartate receptor genes (NMDA), brain-derived neurotrophic factor (BDNF), and dopamine transporter (SLC6A3) in both schizophrenia and bipolar disorder. Pharmacologic therapy of psychiatric disorders will likely be more effective once the molecular pathogenesis is known. Antipsychotic therapies with a partial dopamine D2 receptor agonist effect may be a plausible alternative to current therapies, and would be effective in symptom reduction in psychotic individuals. It is also possible that therapies employing dopamine D1/D2 receptor agonists or COMT inhibitors will be beneficial for patients with negative symptoms in schizophrenia and bipolar disorder [3].

Schizophrenia

Schizophrenia is a chronic, often disabling mental illness with a lifetime prevalence of ~1% worldwide, and two to three times higher mortality rates are reported in schizophrenia patients compared to the general population.

One of the most important challenges is to establish biological markers which can accurately identify at-risk individuals in preclinical stages and thus improve the effects of early intervention strategies [4]. There is a strong basis for schizophrenia as a neurodevelopmental disorder, and the illness may result from several factors: genetic inheritance, disturbance of the in utero environment, and exposure to biological and psychosocial factors in infancy and early childhood, to name a few. Early environmental risk factors for schizophrenia include urban and winter birth, fetal malnutrition and hypoxia, and prenatal viral infections; diverse risk factors such as paternal age, drug abuse, immigrant status, social adversity, and isolation also appear to be contributing factors. It is typical for a schizophrenia researcher to consider Magnetic Resonance Imaging (MRI) brain imaging or electrophysiological measures (EEG) as a biomarkers [5].

The cause of schizophrenia is unknown but a genetic component has long been established. It has been identified a candidate gene that links abnormal lipid metabolism to glial and developmental theories of schizophrenia. The gene, called Fabp7 (Fatty acid binding protein 7), encodes a protein that helps the essential fatty acid docosahexaenoic acid (DHA) assume its proper shape. It also has functional links to the glutamate receptor N-methyl-D-aspartic acid (NMDA). It has been shown that Fabp7 is responsible for differences in the animals' PPI (Prepulse inhibition test) responses and that this gene plays a vital role in brain development. Given the link between in utero malnutrition and increased risk for schizophrenia, the researchers reason that deregulation of Fabp7 and lipid metabolism during development may cause long-term changes in gene expression, explaining an excess of Fabp7 in the schizophrenic cortex. Whether Fabp7 operates alone or with other genes on chromosome 10 must be explored in future studies [6].

Major Depressive Disorder

Major depressive disorder (MDD) is an affective disorder and the symptoms include feelings of profound sadness, worthlessness, despair and loss of interest in all pleasures. The individuals having depression also experience mental slowing, a loss of energy and an inability to make decisions or concentrate. The symptoms can range from mild to severe, and are often associated with anxiety and agitation. Worldwide, its prevalence is 21% in women and 13% in men. Its occurrence is two to three times more common in first-degree relatives of depressed persons, suggesting a genetic predisposition [7, 8]. According to projections, MDD will become the second leading cause of disability worldwide by the year 2020 (7, 8). Major depressive disorder results from multiple genes interacting with environmental factors such as early stressful life events [9]. Biological markers for depression are of great interest to aid in elucidating the causes of major depression. The most robust biological markers of major depression includes decreased platelet imipramine binding, decreased 5-HT1A receptor expression, increase of soluble interleukin-2 receptor and interleukin-6 in serum, decreased brain-derived neurotrophic factor in serum, hypocholesterolemia, low blood folate levels, and impaired suppression of the dexamethasone suppression test [10].

The list of molecular players involved in depression's phenotypes has now expanded to include genes from diverse aspects of cellular physiology such as numerous neurotransmitter and neuropeptide systems, steroid hormones, neurotrophic and cytokine signaling cascades, ion channels, circadian genes [11, 12], transcription factors (e.g., CREB NFκB, and ΔFosB) [13, 14].

Bipolar Disorder

Bipolar disorder (BD) is a chronic mental illness, which begins, in adolescence or early adulthood. Bipolar Disorder includes (i) Major Depressive Episodes and (ii) Hypomanic episodes. The classification was divided into Bipolar I and Bipolar II. However, Bipolar II is often a first step to Bipolar I. It is seen that over five years, between 5 and 15% of those with Bipolar II change diagnosis to Bipolar I. Approximately 0.5% of people develop Bipolar II in their lifetimes. The psychobiology of therapeutic approach to bipolar disorders is still complex [15]. Several hypotheses have been postulated, including alteration in genetic factors, protein expression, calcium signaling, neuropathological alteration, mitochondrial dysfunction and oxidative stress in BD. The data suggested that BD might be associated with neuronal and glial cellular impairment in specific brain areas, including the prefrontal cortex. Molecular genetic positional and candidate gene approaches are being used for the genetic dissection of bipolar disorder.. Regions of interest include chromosomes 4p16, 12q23—q24, 16p13, 21q22, and Xq24—q26 [16].

Autism

The increasing autism incidence estimates are generating strong interest in identifying its salient risk factors. Recognition of the importance of genes in this and other disorders has promulgated the development of valuable research tools [17]. It has been reported that mutations in two neuroligin genes contribute autism phenotype. These results indicate that mutations in neuroligin 3 (NLGN3) and aa neuroligin 4 (NLGN4) genes are responsible for at most a small fraction of autism cases and additional screenings in other autistic populations are needed to better determine the frequency with which mutations in NLGN3 and NLGN4 occur in autism [18].

Attention Deficit Hyperactivity Disorder

Attention-Deficit Hyperactivity Disorder (ADHD) is a common, long-lasting, treatable childhood psychiatric disorder, characterized by a pattern of developmentally inappropriate inattention, motor restlessness, and impulsivity that affects approximately 3-7% of school-aged children [19]. Genetic factors are implicated in ADHD, but the mechanism of action is not completely understood. Twin, family and adoption studies of ADHD have supported a strong genetic contribution to the disorder, with heritability ranging from 60-90% [20]. Genes regulating neurotransmitter systems have been implicated in ADHD. Candidate gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder, with meta-analyses supportive of a role of the genes coding for: dopamine receptor (DRD4, DRD5), solute carrier family 6 (SLC6A3), synaptosomal-associated protein 25 (SNAP-25), and 5-hydroxytryptamine receptor 1B (HTR1B) [21]. Genome scan studies on potential alleles for ADHD have demonstrated linkage on chromosomes 5p13, 6q12, 16p13, 17p11 and 11q22-25 [22]. Sometimes ADHD-like symptoms are exhibited by patients with established neurogenetic disorders such as Tuberous Sclerosis Complex, Neurofibromatosis I, Turner Syndrome, Williams Syndrome, Velocardiofacial syndrome, Prader-Willy syndrome, and Fragile X Syndrome. Although each syndrome may arise from different genetic abnormalities with multiple molecular functions, the effects of these abnormalities may give rise to common effects downstream in the biological pathways or neural circuits, resulting in the presentation of ADHD symptoms [23].

Conclusion

A robust body of genetic data indicates the existence of susceptibility genes in bipolar disorder. Molecular genetics provides powerful tools for investigating neuropsychiatric disorders. Identification of susceptibility genes will contribute to improved treatment and patient care. Improved understanding of disease pathogenesis has the potential to revolutionize the practice of clinical psychiatry.

Conflict Of Interest Statement

This paper does not contain any conflict of interest.

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