Chapter 14
Psychiatric Genetics-An Update

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Introduction

Over the last decade, there has been an exponential growth in understanding psychiatric illnesses with an expanded array of available treatments. The physical expression of characteristics coded by genes is known as a phenotype. The phenotype of psychiatric disorders is based on an intricate system of symptom classification which has evolved over the last several decades (American Psychiatric Association, 1994). With a better understanding of illness phenotype and comorbidities, researchers and clinicians have been able to refine treatment options.

Genetic factors play a fundamental role in the genesis of psychiatric disorders. In addition, genetic factors may also play a very important role in metabolism, distribution, and eventual response to psychotropic medications. The identification of underlying genetic variations associated with psychiatric illnesses could help us evaluate risk factors for developing phenotype targeted pharmacotherapy agents and medication doses on an individual level for an optimal outcome and relapse prevention. Most psychiatric disorders are complex in origin and are considered to have multifactorial inheritance wherein a combination of multiple susceptible genes interacts with the environment to produce a particular phenotype. In addition to genetic variance, cross-culture variations could complicate the study of prevalence and treatment of psychiatric disorders.

Culture is a broad term that includes social roles, values, and all forms of knowledge that make up a way of life. Culture may predict the way a person expresses distress, and hence symptoms of psychiatric illness expressed may be different in various cultures. Variations in interpreting illness symptoms across cultures can be challenging and may lead to imprecise or incorrect psychiatric diagnosis. Scientists have developed culture-specific screening questionnaires for emotional distress which incorporate common expressions of stress/distress

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as exhibited by that particular culture. Culture also encompasses ethnicity, race, and religion. Ethnicity and race may predispose individuals to a common genetic pool which produces phenotypic resemblance. Certain illnesses are more common in some ethnicity groups solely due to genetic makeup. Ethnicity and race confer common genes to populations and hence increase the outward expression of illnesses, inherited due to common genes.

Advances in brain research, particularly advances at the cellular and molecular level will permit us to understand cellular mechanisms responsible for psychiatric disorders. Recent attempts to understand neuronal communications in the brain have led to a rapidly expanding number of substrates that serve as neurotransmitters (compounds in the body which facilitate the transmission of nerve signals from one cell to another). Genes participate in the regulation of neurotransmitters, which play a critical role in affect modulation (how an individual feels and expresses emotion and mood) and reward systems (pleasure/pain in response to environmental stimuli). The availability of new methods for genetic analysis at the gene/ genome level (such as molecular cloning of neurotransmitters) has improved our understanding of information processing in the brain, which in turn has allowed us to improve our understanding of psychiatric disorders and mechanism of action for psychotropic medications.

Over the past two decades, research methods have been developed to determine the extent to which a specific psychiatric illness is genetically caused. All genetic illnesses have increased rate of illness among relatives of the first identified family member with the illness, known as *probands*. Psychiatric familial genetic studies have been conducted since early 20th century, although there have been some limitations to the familial studies as diagnostic criteria for psychiatric disorders have changed over time. Twin and adoption studies have demonstrated familial genetic causation in psychiatric disorders. To account for environmental factors influencing manifestation of psychiatric disorders, rates of illness amongst twins raised in the same home has been compared to twins raised apart. Advances in the field of human genetics, specifically the Human Genome Project and localization of loci for genes has improved our understanding of genes involved in psychiatric disorders.

Most psychiatric medications are administered orally. Pharmacokinetics involves ingestion, absorption, metabolism, and distribution of a drug. After oral ingestion, the drugs are absorbed by the stomach and small intestine and metabolized by the liver and then enter into systemic circulation, eventually cleared by either the liver or kidneys. Medical illnesses or other concomitant medications affecting the gastrointestinal tract, liver or kidneys can affect pharmacokinetics. Individual factors such as race, ethnicity can also affect the pharmacokinetics (absorption and breakdown of drugs in the body). Based on genetic variation between races, metabolism of psychotropic medications by hepatic P450 enzymes (those components of the liver that break down and eliminate medications from the body) can be variable depending on an individual's age, ethnicity, and use of concomitant medications. This can ultimately

affect clinical efficacy of a particular compound. This is also important as frequently a combination of medications is used for management of psychiatric illnesses. Cultural factors such as a particular food intake can also affect metabolism of psychiatric medications, for example individuals from a culture that consumes more grapefruit juice can alter activity of certain hepatic enzymes involved in metabolism of medications. This chapter will focus on the genetics of psychiatric illnesses and briefly review genetic factors that influence metabolism of psychiatric medications.

Genetics of Schizophrenia

Schizophrenia affects 1% of the world's population (Robins & Regier, 1991). Clinical symptoms include hallucinations, delusions, disorganized thoughts and speech, and social withdrawal. Bipolar disorder, characterized by psychosis and cognitive changes, has been shown in familial studies to have phenotypic overlap with schizophrenia (Craddock, O'Donovan, & Owen 2005). The heritability of schizophrenia has been estimated to be approximately 80% (Cardno & Gottesman, 2000) with schizophrenia occurring worldwide and across ethnic subgroups.

A familial form of schizophrenia may be predicted by factors such as structural brain abnormalities, age at onset versus probands who suffered infections or obstetrical complications at birth may be at lower familial risk. (Bersani, Taddei, Venturi, Osborn, & Pancheri, 1995). Elevated risk of schizophrenia in the first-degree relative of schizophrenia probands has been demonstrated by familial studies. The highest risk is seen in children (12.8%), followed by siblings (10.1%) and parents (5.6%) compared to the general population (0.9%) (Gottesman & Shields, 1982). Twin and adoption studies can be used to separate the contribution of genetic and environmental causes. Monozygotic twins are genetically identical and dizygotic twins on an average share 50% of the alleles (gene materials). Genetic inheritability of schizophrenia is further strengthened by studies conducted in monozygotic and dizygotic twins. Monozygotic co-twins have three times elevated risk of developing schizophrenia (59.2%) compared to dizygotic co-twins (15.2%) (Kendler, 1986). Males and females with early onset may be at elevated familial risk (Pulver et al., 1990; Sham et al., 1994); however, this finding has not been replicated in all studies. Probands who develop schizophrenia and had suffered obstetrical complications at birth are at a lower familial risk compared to those without obstetrical complications (Bersani, Taddei, Venturi, Osborn, & Pancheri, 1994). Ventricular enlargement, a type of structural brain abnormality seen in schizophrenia, predicts lower familial risk in male probands compared to female probands (Goldstein, Tsuang, & Faraone, 1989). Various adoption studies have documented genetic heritability of schizophrenia by studying the prevalence of schizophrenia in offsprings of schizophrenic mothers separated at birth

(Tienari, 1991). The risk of developing bipolar disorder is also elevated in relatives of schizophrenic probands, indicating possible overlap in the phenotypic spectrum (Pope & Yurgelun-Todd, 1990, Craddock, O'Donovan, & Owen 2005). Relatives of patients with schizophrenia may be at an elevated risk for developing psychotic affective illnesses.

The chromosomal location of a DNA sequence is referred to as genetic locus. Genetic linkage studies have identified a large number of presumptive loci for schizophrenia including 1q21, 1q42, 5q, 6p, 6q, 8p, 10p, 10q, 13q, 17p, and 22q (Owen, Craddock, & O'Donovan, 2005). Some of the common loci are also identified in other severe psychiatric illnesses such as bipolar disorders. Many chromosomal aberrations are also being investigated in patients with schizophrenia, some with crucial role in dopaminergic pathways. An excess of the neurotransmitter dopamine and its blockage by antipsychotic medications is presumed to be the mechanism of action for medication treatment of hallucinations and delusions seen in schizophrenia.

Genetic factors that differ across ethnic subgroups may also be involved in development of side effects to schizophrenia medication treatments such as decrease in white blood cell count, also known as agranulocytosis. Previous studies have found genetic factors important in the development of agranulocytosis (cessation in the body's ability to produce infection-fighting white blood cells) to the novel antipsychotic medication, clozapine, in Ashkenazi Jewish patients suffering with schizophrenia (Lieberman et al., 1990). Other social factors across various ethnic groups can affect tolerability and response to the medications such as use of tobacco and caffeine. Cigarette smoking can cause alteration in blood levels of antipsychotics medications such as clozapine (Derenne & Baldessarini, 2005). Tobacco use via cigarette smoking can cause induction of cytochrome enzymes in liver (1A2) which can lower serum levels of clozapine and olanzapine (Zullino, Delessert, Eap, Preisig, & Baumann, 2002). Tobacco use is also influenced by cultural factors and is more prevalent in minorities such as African American and Hispanics. Tobacco use could potentially result in lower levels of antipsychotics as above and lack of clinical improvement. Tobacco smoking should always be taken into consideration especially when most of the hospitals do not allow smoking, and patients who had quit smoking during hospitalization are likely to resume upon discharge from the hospital.

Genetics of Mood Disorders

Mood disorder is a broad term that includes bipolar disorder and unipolar depression. Core features of bipolar disorder include mood elevation above the baseline (mania and hypomania) associated with depressive episodes. It affects 3–7% of the population (Calabrese et al., 2003). Core feature of Major Depressive Disorder (MDD) are depressed mood or loss in interest or pleasure with

five other neurovegetative symptoms per DSM-IV to be present for at least 2 weeks. As with schizophrenia, bipolar disorder appears worldwide across ethnic subgroups.

Family studies of bipolar disorder predict a higher prevalence of psychiatric disorders among the first-degree relatives of bipolar disorder probands. These disorders include Bipolar I disorder, bipolar II disorder, schizoaffective disorder, and recurrent unipolar depression (Gershon et al., 1982; Weissman et al., 1984a; Winokur, Coryell, Keller, Endicott, & Leon, 1995).Early age at onset has been shown in multiple studies with depressed and bipolar probands to be associated with an increased rate of illness 2- to 3-fold among adult relatives (Weissman et al., 1984b). The magnitude of association of family history of depression varies by age of onset, with highest risk estimated for MDD prior to age 20, whereas family history is not associated with MDD for onset after age 50 (Tozzi et al., 2008) . Relatives of bipolar disorder probands associated with psychotic symptoms have a significantly higher risk of psychotic mood disorder compared with risk of relatives with nonpsychotic bipolar disorder probands. This reflects the partial overlap in risk for bipolar disorder and schizophrenia categories, associated with psychotic symptoms (Potash et al., 2003). Psychotic features may be mood-congruent such as delusions of deserved punishment during depression or mood incongruent such as feeling delusions of thought insertion during depressive episodes. A proband with mood incongruent psychotic features with bipolar disorder predicted mood-incongruence in relatives with bipolar I disorder. Mood-incongruent psychotic features show evidence of familial aggregation and suggest linkage to two chromosomal regions previously implicated in major mental illness susceptibility (Goes et al., 2007).

Familial studies also suggest that there may be a genetic basis for the trait of postpartum mood symptoms generally and postpartum depressive symptoms in some women with bipolar disorder (Payne et al., 2008).Twin studies of bipolar disorder have indicated an estimated heritability of 80% and some shared liability with recurrent unipolar depression (McGuffin et al., 2003). Common susceptible genes have also been identified between bipolar disorder and schizophrenia. The evidence is suggestive of five genomic regions which may represent shared genetic susceptibility for bipolar disorder and schizophrenia (Berrettini, 2003). Adoption studies have also provided clues to increased prevalence of bipolar disorder and unipolar depression in relatives of bipolar disorder probands.

The cytochrome P450 enzyme, located in the liver, is involved in metabolism and breakdown of ingested medications and toxins for elimination from the body. Genetic differences in the presence and/or activity of certain P450 enzymes can account for interindividual variability and effectiveness of psychiatric medications. Low metabolizers are individuals with low-to-no activity of an enzyme which could result in accumulation of high concentration of a drug leading to increase in side effects and toxicity of the drug. Recently the Food and Drug Administration has issued a warning that Asian patients with a specific human leukocyte antigen (HLA-B 1502) may be at increased risk of developing a severe, potentially life-threatening type of skin rash called Stevens

Johnson syndrome. About 10% of Asian people have this allele. Some anticonvulsant medications often used to treat bipolar illness (for example carbamazepine and lamotrigine) are associated with skin rash or Stevens Johnson Syndrome in some individuals, and should thus be used carefully, after weighing benefits exceeding risks in HLA-B 1502 positive Asian population (Food and Drug Administration, 2008).

Antidepressants are also metabolized by hepatic cytochrome enzymes. Genetic differences in the presence or activity of certain cytochrome enzymes can account for substantial interindividual variability in blood levels of certain psychotropic medications and can significantly affect tolerability and effectiveness of any particular medication. The enzymes 2D6, 3A4, 1A2, and 2C are involved in pharmacokinetics of antidepressant drugs and can contribute to wide interpatient and interethnic variability. Cytochrome enzyme 2D6 has low activity in 3–10% of Caucasians and 2% of African Americans and Asian population (Richelson, 1997). It is inhibited by the antidepressants fluoxetine, paroxetine, and sertaline and induced by mood stabilizers such as carbamazepine. A small percentage of African Americans, Asians, and Caucasians are slow metabolizers with respect to cytochrome enzyme 1A2 which is involved in the metabolism of antipsychotic medications such as haloperidol, clozapine, and olanzapine. A study that involved genotyping patients with respect to CYP2C9, CYP2C19, and CYP2D6 alleles indicated significant influence of CYP2D6 genotype and minor influence of CYP2C19 on plasma concentration of patients taking antidepressants (Grasmäder, Verwohlt, & Rietschel, 2004).

Other Psychiatric Disorders

Family studies have demonstrated an increased prevalence of anxiety disorders among first-degree relatives of probands with anxiety disorder. Twin studies of individuals with generalized anxiety disorder have concluded that this order has increased prevalence in monozygotic twins (Kendler, Neale, Kessler, Heath, & Eaves, 1992). The relative risk of inheriting panic disorder among first-degree relative of panic disorder probands ranges from 2.6- to 20-fold, with a median value of 7.8-fold (Knowles & Weissman, 1995). Posttraumatic stress disorder (PTSD) which is caused by environmental factors has not been found to have increased familial prevalence in family studies (Davidson, Smith, & Kudler, 1989).

Family, twin, and adoption studies have demonstrated that genetics may influence the risk of substance use. The types of drugs available dictate which drugs are used when experimentation with drugs begins. Rates of substance abuse vary based on ethnicity, religion, and physical availability of drugs, as well as peer group pressure. Risk of alcoholism is increased 7-fold in first-degree relatives of alcoholic probands (Merinkagas, 1989), hence demonstrating high familial prevalence of alcoholism in family studies. Adoption studies have also provided strong evidence of genetic factors involved in alcoholism, especially

alcoholism in biological parents which predicts higher rates of alcoholism in male children. The evidence does not support heritability as strongly in female children of alcoholic parents raised by adoptive parents (Cadoret, Cain, & Grove, 1980). Sons of alcoholic parents, compared to sons of nonalcoholic parents, show that they have decreased intensity of subjective feeling of intoxication, reduced objective signs of intoxication, and earlier and more severe alcohol-related problems with poorer treatment outcomes (Schuckit & Gold, 1988).

Conclusion

The field of psychiatric genetics has witnessed unprecedented efforts over the last two decades to identify the underlying genetic basis of psychiatric disorders. Psychiatric disorders are frequently complex, and patients suffer with comorbidities which limits the clinical classification system, although familial, twin, and adoption studies have strongly favored the genetic basis of psychiatric illnesses. So far, a number of risk genes have been identified, but no single gene has been identified that explains the inheritability of respective psychiatric disorders. It is possible that single genes resulting in major phenotypic manifestations of psychiatric disorders might not exist. However, increased risk for psychiatric disorders could result from additive effects of a large number of small genes and their interaction with environmental effects stressors.

The medication armamentarium for treatment of psychiatric disorders is expanding at an exponential pace. The availability of new genetic information, especially development in the field of pharmacogenetics, will empower health care providers and their patients to make appropriate medication selections, adjust pharmacotherapy on an individual level to maximize tolerability, and ultimately improve health outcomes.

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