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Current Methodological Issues in Candidate Gene Association Studies in Psychiatric Disorders

Leo Sher, M.D.

Abstract

One of the most rapidly emerging areas of neuroscience research is the study of genetic approaches to complex psychiatric disorders. The author discusses potential benefits and pitfalls of candidate gene association studies. Association studies search for correlations in the population between a DNA marker and a disorder. The so-called candidate gene approach is frequently used in association studies. Candidate gene studies are usually based on hypotheses about relationships between specific known loci and particular phenotypes. The aim of molecular genetic studies of behavioral disorders includes the development of predictive and diagnostic testing for psychiatric disorders that can help to establish the accurate diagnosis and the identification of target for therapeutic drugs. To date, case-control association studies investigating polymorphisms of candidate genes in psychiatric disorders have produced a lot of positive and negative findings with few consistent replications. The false positive and false negative findings in candidate gene association studies are due to population stratification, heterogeneity of psychiatric disorders, multiple tests, low prior odds of association, and small sample size. A researcher planning a genetic association study for a psychiatric disorder needs to have the following: 1) suitable phenotypes; 2) a good rationale for studying not only the gene in question, but the specific polymorphism; 3) enough subjects and control for meaningful analyses; and 4) use of ethnically homogenous case-control data sets or family based association designs.

INTRODUCTION

A long time ago people have recognized that behavioral disorders run in families (1,2). Theories about the inheritance of behavior date to ancient Greece. It has been suggested that Hippocrates (460–377 B.C.) was the first to stress heredity and predisposition in relation to psychiatric diseases (3). The relationship between heredity and psychiatric disease was also noted by another ancient scholar—

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Euripides (484–406 B.C.) (4). Felix Plater (1536–1614) is regarded as one of the earliest classifiers of psychiatric disorders (3). In his effort to study psychiatric illness, he classified mental disorders into acquired, congenital, and hereditary afflictions. Robert Burton (1577–1640) wrote in his book *The Anatomy of Melancholy* that the “inbred cause of melancholy is our temperature, in whole or part, which we receive from our parents” and “such as the temperature of the father is, such is the son’s, and look what disease the father had when he begot him, his son will have after him” (5). Burton continued, “I need not therefore to make any doubt of melancholy, but that it is an hereditary disease.”

The study of genetics is changing our understanding of the world. Just as we cannot step in the same river twice, we will never be able to see the world in the same way as we did before the recent discoveries in behavioral genetics. The promise of genetic research is very considerable, and the resources put into genetic research reflects this. One of the most rapidly emerging areas of neuroscience research is the study of genetic approaches to complex psychiatric disorders. Family, twin, and adoption studies have produced data that firmly support the genetic basis for the inheritance of psychiatric disorders.

Genetic factors can interact with environmental factors to influence the vulnerability to psychiatric disorders in different ways (6-12). For example, Kendler (6) explored two such mechanisms: “genetic control of sensitivity to environment,” and “genetic control of exposure to the environment.” “Genetic control of sensitivity to the environment” suggests that genes, in part, render individuals relatively vulnerable or relatively invulnerable to the pathogenic effects of environmental stress. The depressogenic effect of stressful life events is substantially greater in those at high versus low genetic risk to the mood disorders. “Genetic control of exposure to the environment” suggests that genetic factors influence the probability that individuals will select themselves into high vs. low risk environments. The genetic risk factors for major depression in part express themselves by influencing the probability that individuals will experience stressful life events, particularly of an interpersonal nature.

ASSOCIATION STUDIES

Molecular genetic studies attempt to identify the specific allele that may be responsible for the familiarity and heritability of phenotype (7–9,13). In the last ten years, there has been a considerable interest in candidate gene association studies of psychiatric disorders (7-9,13-17).

All humans have considerable genetic variation, or polymorphism (8,9,13). A gene is called polymorphic if no single form of the gene has an abundance of more than 99% in a population. Gene variants, including polymorphisms, are related to the development of diseases that are genetically influenced. Association studies search for correlations in the population between a DNA marker and a disorder. In other words, association studies compare distributions of marker alleles in cases and controls. If persons with a disorder have an increased frequency of a specific allele,

or genotype, it may mean that the gene contributes to vulnerability to the disease. The so-called candidate gene approach is frequently used in association studies (7-9,13-17). Candidate gene studies are usually based on hypotheses about relationships between specific known loci and particular phenotypes. When biological investigations have provided some clue as to the possible involvement of known genes, these genes may become candidates for studies. Although candidate gene studies in psychiatry have been criticized because of our limited knowledge of the underlying pathophysiology of illness, there is also much we do know. For example, we do know that the serotonergic system is involved in the pathophysiology of mood disorders (11,18).

In the search for candidate genes, those physiological and biochemical systems that have been theorized to be important in the pathogenesis of behavioral disorders are logical ones on which to focus (8,9,13). One starting point for understanding vulnerability to behavioral disorders is to look for variants in genes involved in neurotransmitter metabolism. Genes for receptors, transporters, and metabolizing enzymes are good candidates. Because of the complexity of causation of psychiatric disorders, any genetic determinants of vulnerability to psychiatric disorders are likely to be subtle. A gene variant found to be associated with a disorder may be neither necessary nor sufficient to cause the illness; rather, it is an indicator of the relative risk or susceptibility.

BENEFITS

The aim of molecular genetic studies of behavioral disorders includes the development of predictive and diagnostic testing for psychiatric disorders that can help to establish the accurate diagnosis and the identification of target for therapeutic drugs (8,9,19). Successful pharmacological treatment of patients with psychiatric disorders suggests the existence of biologic pathways in which genetic variation is likely to affect liability to behavioral disorders and treatment response. Drug therapy in the future may be personalized: the choice of drug may be determined by the genes a patient carries.

Studies of the genetics of psychiatric diseases can also help us to understand better the role of environmental factors in the development of these disorders (6,8,9,20-22). The triggering of psychiatric disorders may be influenced by complex interactions of genetic factors with multiple environmental components. Molecular genetic research may help to elucidate causal processes as they apply to both brain systems and nature-nurture interplay.

INCONSISTENT RESULTS OF CANDIDATE GENE ASSOCIATION STUDIES IN PSYCHIATRIC DISORDERS

By the present time, case-control association studies investigating polymorphisms of candidate genes in psychiatric disorders have produced a lot of positive and negative findings with few consistent replications.

Collier et al. (23) found that a short variant of the serotonin transporter-linked polymorphic region (5-HTTLPR) is associated with bipolar disorder and unipolar depression. However, Mendes de Oliveira et al. (24), Gutierrez et al. (25), and Kunugi et al. (26) reported no association between the 5-HTTLPR polymorphism and bipolar disorder. Rees et al. (27) found that the 5-HTTLPR polymorphism is not associated with bipolar disorder and unipolar depression.

Schmidt et al. (28), Sander et al. (29,30) and Hallikainen et al. (31) found that the frequency of the short allele of the 5-HTTLPR is significantly increased in alcoholic patients with severe dependence as compared with nonalcoholic control subjects. Similar results were reported by Hammoumi et al. (32) and Lichtermann et al. (33). Thompson et al. (34) reported a trend toward increased frequency of the short allele in alcohol-dependent subjects. Turker et al. (35) found the existence of a significant association between the short allele of the serotonin transporter gene promoter and high ethanol tolerance in young adults. In contrast, Edenberg et al. (36), Jorm et al. (37) and Gorwood et al. (38) did not find an association between the 5-HTTLPR and alcohol misuse or dependence.

Ogilvie et al. (39) reported an association between unipolar depression and a nine-repeat allelic variant of a variable tandem repeat (VNTR) marker in the second intron of the serotonin transporter gene. Three subsequent studies did not find this association (40-42).

Collier et al. (43) and Rees et al. (27) found that a nine-repeat allelic variant of a VNTR marker in the second intron of the serotonin transporter gene is associated with bipolar disorder. Hoehe et al. (42) reported that the polymorphism of the VNTR is not associated with susceptibility to bipolar disorder.

A 5-HT_{2A} receptor promoter polymorphism, -1438G/A, was reported to be associated with susceptibility to anorexia nervosa (44-46). However, Campbell et al. (47) and Ando et al. (48) found lack of association between the 5-HT_{2A} gene promoter polymorphism and anorexia nervosa.

Two studies showed that the personality trait of Novelty Seeking is associated with a polymorphic exon III repeat sequence at the dopamine D₄ receptor gene locus (49,50). Several subsequent studies did not confirm these findings (51-54).

There are many more inconsistent and conflicting results of association studies in behavioral genetics (16,17,55-58). A few examples exist of success using association to find genes for complex diseases (59-61). An association between the apolipoprotein E (APOE) gene and sporadic Alzheimer's disease was a primary chance finding with limited biological guidance (60), and in insulin-dependent diabetes mellitus (IDDM) the insulin gene was the logical candidate for IDDM (61). There is a handful of replicated findings in complex traits. However, hundreds of initially positive results are not subsequently replicated. It is clear that there are difficulties and limitations related to case-control association studies.

LIMITATIONS

A major problem of case-control association studies is that significant-appearing relationships may be found as an artifact of genetic differences

between the cases and controls because population stratification (or admixture) due to ethnic variation or other confounding factors can generate considerable population differences in marker allele frequencies (8,9,13-17,57,59). It has been proposed that family-based studies that compare cases with relatives can eliminate such artifacts (62,63). However, intra-familial association studies do not overcome the problem of ethnic differences in disease etiology (there may be differences in the contribution of a given allele in different ethnic groups) or allelic association due to tight linkage (a disease locus and the associated marker locus may be tightly linked, that is, physically close to each other) (16,57). Even when intra-familial design is used, samples should be drawn from as ethnically a homogeneous population as possible.

Another major problem of studies in psychiatric genetics is that psychiatric diagnoses are not known to be biologically homogenous entities: syndromal psychiatric diagnostic categories such as depression or anxiety disorders potentially include etiologically, pathologically, and prognostically heterogeneous disorders (64-68). The broad categorical classification of behavioral disorders that is used in psychiatry at the present time is not suitable for genetic association studies. At the present time psychiatric phenotypes are so broad that researchers cannot establish the defining relationship between the behavior and the genes. In other words, failure to obtain convincing results in psychiatric genetics can partly be attributed to the fact that progress in molecular biology has not been followed by an equivalent development in phenotypic description. The important and complex problem is how to get more homogenous and more narrowly defined phenotypes. Identification of a plausible biological marker would probably be the optimal measure for refining the disease phenotype. Numerous ideas related to this matter have been suggested. Tsuang and Faraone (69) proposed the concept of target features. Target features are clinical or neurobiological characteristics that are expressions of the underlying vulnerability to a disease. Target features may be more closely linked to brain function than clinical psychiatric phenotypes and, therefore, may be credible biological markers in genetic studies. To reduce the heterogeneity of schizophrenia Carpenter et al. (70) proposed to differentiate between deficit and non-deficit schizophrenia (genetic vulnerability for deficit and non-deficit schizophrenia may be different). Better definition of the phenotype can enhance the chance of detecting significant associations. Success in genetic research will depend on examining more homogenous and more narrowly defined phenotypes.

The false positive and false negative findings in candidate gene association studies are not only due to population stratification or heterogeneity of psychiatric disorders, but probably often to multiple tests, low prior odds of association, and small sample size (13,16,57). If a great number of patient-control comparisons are made one or several 'significant' allelic associations will be found even if no true association exists. It is rarely possible to define highly credible candidates and the prior odds against true association are very considerable. Many negative studies have very little power to detect moderate or small effect sizes.

CONCLUSION

Mental disorders are very challenging to genetic researchers because they do not stem from errors in single genes. Besides, both genes and environment appear to be complexly and interactively involved in the development of mental disorders, perhaps with multiple components of each. Furthermore, a mental disorder such as schizophrenia may be at the most severe end of a continuum of schizophrenias that include schizoaffective disorder, schizophreniform disorder, schizotypal personality disorder, and possibly other variants. Growing scientific evidence suggests that other major psychiatric disorders may follow the same pattern.

The behavioral genetic research road is long and difficult one with many problems to be overcome. A researcher planning a genetic association study for a psychiatric disorder needs to have the following (8,9,14,16,57,71): 1) suitable phenotypes; 2) a good rationale for studying not only the gene in question, but the specific polymorphism; 3) enough subjects and control for meaningful analyses; and 4) use of ethnically homogenous case-control data sets or family based association designs.

The practical implications of identifying numerous genes with minor effects remain debatable. Detecting candidate genes with even a small effect is important if the genes are tied to a functional change involved in the pathogenesis of a complex disease that likely reflect the action of many genes.

It is to be hoped that efforts of psychiatric geneticists will be rewarding. Future research may clarify the role of different genes in the development of psychiatric disorders. Genetic studies may advance our understanding not only of the role of genetic factors in the etiology of psychiatric disorders but may also be useful in refining conceptions of psychiatric disorders themselves, and possible approaches to the treatment of these conditions. There is a hope that the progress of science in the 20th century will be dwarfed by the immense progress of the 21st, and that behavioral genetics will be part of it.

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