Candidate gene studies in psychiatric disorders: promises and limitations

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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 we did before the recent discoveries in behavioural genetics. The frequent reports in the mass media about the recent advances in genetic research suggest that the general public endorses genetic research. 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.

Molecular genetic studies attempt to identify the specific allele that may be responsible for the familiality and heritability of phenotype. Association studies search for correlations in the population between a DNA marker and a disorder.1,2 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. When biological investigations have provided some clue about the possible involvement of known genes, these genes may become candidates for studies.

In the search for candidate genes, those physiological and biochemical systems that have been theorized to be important in the pathogenesis of behavioural disorders are logical ones on which to focus. One starting point for understanding vulnerability to behavioural disorders is to look for variants in genes that are involved in neurotransmitter metabolism. Genes for receptors, transporters and metabolizing enzymes are good candidates. However, because of the complexity of causation of psychiatric disorders, any genetic determinants of vulnerability to psychiatric disorders are likely to be subtle.

Potential benefits

At the present time, the detection of psychiatric disorders depends largely on symptom collation; useful physiological identifiers are lacking. It is conceivable that psychiatric diseases might be better identified if accessible biological methods for identifying behavioural disorders could be discovered. The purpose of molecular genetic studies of psychiatric disorders includes the development of predictive and diagnostic tests for psychiatric disorders and the identification of targets for therapeutic drugs.1,3 Successful pharmacological treatment of patients with psychiatric diseases suggests the existence of biologic pathways in which genetic variation is likely to affect both liability to behavioural disorders and treatment response. Some of
these molecular targets for therapy may be common to different treatment modalities. Drug therapy in the future may be personalized so that the choice of drug may be determined by the genes a patient carries.

Because the triggering of behavioural disorders is most likely influenced by complex interactions of genetic factors and multiple environmental components, studies of the genetics of psychiatric disorders can also help us to understand better the role of environmental factors in the development of these conditions. Molecular genetics may thus help to elucidate causal processes as they apply to both brain systems and nature–nurture interplay.

Major limitations

To date, case–control association studies investigating polymorphisms of candidate genes in psychiatric disorders have produced many positive and negative findings, with few consistent replications. It is clear that there are both difficulties and limitations related to case–control association studies.

A major problem of association studies in psychiatric genetics is that psychiatric diagnoses are not biologically real disease entities. Syndromal psychiatric diagnostic categories, such as depression or schizophrenia, include etiologically, pathologically and prognostically heterogenous disorders. The broad categorical classification of behavioural disorders used in psychiatry at the present time is not suitable for genetic association studies — psychiatric phenotypes are so broad that researchers cannot establish the defining relationship between the behaviour 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 difficult issue is how to get more homogenous and more narrowly defined phenotypes. The identification of a credible biological marker would probably be the optimal measure for refining the disease phenotype. Various ideas related to this matter have been suggested. Tsuang and Faraone developed the concept of target features: clinical or neurobiological characteristics that are expressions of the underlying predisposition to a disease. These features may be more closely linked to brain function than clinical psychiatric phenotypes and, therefore, may be good biological markers in genetic studies. Also, to reduce the heterogeneity of schizophrenia, Carpenter et al proposed a differentiation between deficit and non-deficit schizophrenia (i.e., genetic vulnerability for deficit and nondeficit schizophrenia may be different). Success in genetic research will depend on better definition of the phenotypes and studies of more homogenous and more narrowly defined phenotypes.

Another major problem with case–control association studies is that relationships that appear to be significant may actually be 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. It has been proposed that family-based studies that compare cases with relatives can eliminate such artifacts. However, intrafamilial 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). Even when an intrafamilial design is used, samples should be drawn from a population that is as ethnically homogeneous as possible.

The false-positive and false-negative findings in candidate gene association studies are not only due to heterogeneity of psychiatric disorders or population stratification, but probably often to multiple tests, low prior odds of association and small sample size. If a great number of patient–control comparisons are made, 1 or several “significant” allelic associations will be found, even if no true association exists. It is rarely possible to define highly plausible candidates, and the prior odds against true association are considerable. As well, many negative studies have very little power to detect moderate or small effect sizes.

Conclusion

The behavioural genetic research road is a long and difficult one with many problems to be overcome. Future association studies will require the selection of suitable phenotypes, the careful choice of candidate genes and of the candidate variant within each gene, the use of ethnically homogenous case–control data sets or family-based association designs, the minimization of arbitrary grouping of genotypes and appropriate correction for multiple testing. The practical
implications of identifying numerous genes with minor effects remain debatable, but it is to be hoped that efforts of psychiatric geneticists will be rewarding. Future genetic studies may not only advance our understanding of the role of genetic factors in the etiology of psychiatric disorders, but also be useful in refining conceptions of psychiatric disorders themselves and possible approaches to the treatment of these conditions.

References


