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The influence of genetics on psychiatric disease

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The balance of evidence from numerous studies on psychiatric diseases and disorders suggests that for (at the least) schizophrenia, bipolar disorder, autism and unipolar depression, a significant component of these disorders can be linked to a genetic component. This article will give a broad overview of the influence of genetics on psychiatric disease, and attempt to bring in recent molecular approaches to the understanding of the effects of genetic and environmental influences on these disorders.

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▼ It is clear that environmental factors also play a major role in disease etiology. However, a reasonable argument can be made that susceptibility to environmental factors depends on an underlying genetic background. In contrast to diseases that result from gene mutations following simple Mendelian inheritance patterns (simple traits), psychiatric disorders resulting from the interaction of many genes and the environment, fall into the more challenging category of complex traits. Modern technologies such as microarray and single nucleotide polymorphism (SNP) analysis are beginning to untangle the polygenic nature of these disorders.

Understanding the genetic components of psychiatric disease

The basic process used to partition genetic and environmental contributions to psychiatric disease is to assess the relative contributions of genes and environment in family studies. This involves determining the concordance of the disorders in pairs of twins, their offspring, siblings and other relatives. These studies need to be carefully designed; studies of the relative risk in families are insufficient as relatives share not only genes but also environment.

Monozygotic (MZ) twins are genetically identical and if a phenotype is determined entirely by genetic factors, MZ twins should have a concordance for the disorder of 100%. In the same context, dizygotic (DZ) twins should have a concordance of approx 50%. However, this analysis is complicated by the following issues: (1) MZ and DZ twins share both prenatal and postnatal environments; (2) DZ twins might not be of the same sex, and therefore even stronger prenatal influences could be present; and (3) even in the case of MZ twins, the issue of whether there is prenatal placental sharing complicates the issue of the existence of identical environments. In addition, many studies have been criticized for inadequate classification of twins into MZ or DZ because of a lack of genetic typing in the study.

Sharing of prenatal and postnatal environments therefore complicates the issue of estimating the contribution of the genetic effect to a disorder. Hence, more accurate studies measure concordance rates of MZ twins raised apart. In addition, another way to control for family environmental influences is to examine the incidence of the disease in genetically-unrelated adopted siblings in families with afflicted offspring. Furthermore, the genetic contribution to complex traits, such as those described here, can be assessed by measuring the relative risk for a disorder in the immediate family, relative to the population as a whole. This is an important tool for linkage studies, which locate potential genes involved in these disorders.

For schizophrenia, Plomin and McLearn collected information from a number of linkage studies and pooled the results[1]. The results indicated a concordance rate of 48% for MZ twins and 16% for DZ twins. These demonstrate that the concordance rate is never 100% for MZ twins and, in these studies, that the concordance rate

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for DZ twins is less than half that of MZ twins. Clearly, the difference between the observed concordance rates and the expected concordance rates for MZ and DZ twins, respectively, can be attributed to environmental factors.

However, these findings based on concordance rates in twin studies, are not entirely without criticism with regard to the methodology used and the conclusions drawn. For example, data from Refs 2 and 3 suggest that many twin studies concluding the existence of a strong genetic component in schizophrenia, employed either flawed methodologies (e.g. diagnosis errors) or insufficiently accounted for the strong environmental influences present in the family situations. However, other reviews that attempt to analyze the strength of the genetic effect in schizophrenia whilst acknowledging the environmental effects, recognize that an interaction between a polygenic model and a series of environmental influences must be used to explain the data[4,5]. The balance of evidence from more recent and carefully controlled studies, as well as meta-analysis approaches (based on a combination of twin and familial studies), still leads to the conclusion that these disorders are multigenetic in nature[6].

Another significant obstacle to unraveling the multigenic nature of these disorders is the lack of relevant animal models. Although some animal models have been used in the development of pharmacological treatments for schizophrenia (e.g. the rat pre-pulse inhibition model), whether such models effectively mimic the human analog of the disorder remains unclear. Perhaps with a better understanding of the human disease achieved through modern gene-expression technology, we will be able to validate existing animal models of schizophrenia and depression. This could then enable more effective molecular biology and genomic tools to be used to dissect the mechanisms that generate these disorders in rodents and hence, by analogy, in humans.

This review will discuss, in some detail, evidence for the involvement of genetic factors in each of the four major psychiatric disorders: schizophrenia, mood and bipolar disorder, and autism. The most detailed evidence available is for a model in which schizophrenia can best be described as resulting from the interaction of many genes. Although there is substantial evidence that suggests the other disorders have a significant genetic component, the evidence is less well-developed.

Schizophrenia

Tsuang has reviewed studies that attempt to dissect the environmental and genetic components of schizophrenia[7]. He concluded that, despite the argument that many previous twin concordance have been flawed, recent studies and the balance of evidence from earlier studies, have demonstrated a familial genetic propensity. In addition, he suggests that a working model of schizophrenia is one in which a neuro-developmental disease, which has a strong genetic component and environmental modification as the embryo develops, is coupled to later brain maturation events. These reflect both the initial embryonic developments and later environmental modification of brain maturation. This theme is further explored with the idea that schizophrenia gradually develops in the three decades after birth, with increasing progressive neurodegeneration in the neurotransmitter systems of the brain, which ultimately lead to structural brain abnormalities[8].

The search for genes through linkage studies continues with the idea of identification of specific vulnerability genes[9]. At least five chromosomes have been implicated through linkage studies, with the strongest evidence being for sites on chromosomes 6p, 8p and 22q (Ref. 6), although this review indicated that there was almost as much evidence showing no linkage at these sites. Evidence for linkage on chromosome 22q is also ambivalent, even when generated by the same group[10,11]. It is therefore clear that significant additional work needs to be done to generate robust datasets that can withstand critical analysis and replication.

More recent molecular studies have been directed towards dissecting the genetic components of schizophrenia using microarrays[12,13] (Vawter M.P. *et al.*, Examining functional genomic expression in schizophrenia with cDNA microarrays. *Society for Neuroscience Meeting*, 4–10 November 2000, New Orleans, LA, USA). These studies indicate that there are gene expression differences between schizophrenic and normal patients. However, careful analysis of age distribution in the sample population used for the studies, suggests that further work needs to be done to ensure that the results are representative of the disorder. It is clear that these limited numbers of studies are only the beginning of this approach to understand the genetic components of schizophrenia and other psychiatric diseases. Furthermore, the same case-controlled and critical approaches need to be taken with this molecular approach as with other association and twin concordance studies. One recent review is an excellent summary of the current state of knowledge about pharmacogenomics and schizophrenia and discusses the inter-relationships between genetic variants of drug metabolism, drug targets and background genetic analysis of the disease[14].

Attempts have also been made to identify the environmental factors that might contribute to schizophrenia. One suggestion has been that retroviruses might be involved in the pathogenesis of the disease[15]. A recent paper indicated that retroviral RNA could be identified in the cerebrospinal fluid and brains of individuals with schizophrenia, but not in control individuals[16]. However, expression of retroviral sequences has not, until now, been confirmed by past studies, and these results

should be viewed with caution until they can be replicated. Other viruses that have been suggested as environmental contributors to schizophrenia include influenza viruses[17], primate viruses[18] and Borna virus[19]. However, the evidence for these viruses contributing to the development of schizophrenia is inconclusive.

Autism

Evidence for concordance between twins from the largest study[20] supported two previous epidemiological studies of autistic twins[21–24]. The study conducted in 1995 indicated that 60% of MZ twins were concordant for autism versus 0% DZ twins[20]. Moreover, if a broader spectrum of related cognitive or social abnormalities were considered, then 92% of MZ twins were concordant versus 10% of DZ twins. These results parallel those found by Folstein and colleagues[21] and have led to the definition of a broader autism phenotype[25], which might indicate that autism has an oligogenic etiology. They have also guided attempts to identify susceptibility loci for autism using linkage analysis. Monaco and colleagues at the Wellcome Trust Center for Human Genetics (University of Oxford, UK) undertook a total genome scan approach. These results indicated a locus on chromosome 7, together with more weakly positive findings on five other chromosomes[26].

An alternative approach to total genome scans is the use of association studies, which have indicated the possibility of a locus on chromosome 15 (Ref. 27). There is some evidence from the studies by other groups that these loci could indeed have a role in autism etiology[28,29]. These approaches have been effectively summarized[27,28,30–32]. This latter paper (Ref. 32) also summarized the results of other groups[23,33], indicating that the analysis of autism is consistent with data that fits a model in which several genes (two to five) act in a multiplicative manner, thereby leading to an autistic disorder.

Although these studies concentrate on the molecular approaches to understanding autism, there are clear indications from both imaging studies and neuropathology that significant differences are observed between brains of autistic patients and control patients. These studies are well summarized[34] and lead to the conclusion that the underlying genetic component of autism leads to a neuro-development effect.

Mood disorders

Disorders of mood have been sub-classified according to the type of mood disturbance. In this context, unipolar depressive disorder is diagnosed when the patient experiences only depressive episodes, and bipolar disorder is diagnosed when the patient experiences both manic and depressive episodes. In their review of the inheritance of mood disorders, Tsuang *et al.* summarized the population-based epidemiologic data for mood disorders, and, coupled with data from studies over the past three decades, concluded that both unipolar and bipolar disorders have a familial relationship[35].

An analysis of twins exhibiting bipolar disorder showed a 67% concordance rate in MZ twins and a 20% concordance rate in DZ twins[36]. A review of 12 studies of twins, including both bipolar and other mood disorder patients, showed a 55% concordance rate among MZ twins and only 5% for DZ twins for bipolar disorder[37].

Recently, a review and meta-analysis of the genetic epidemiology of major depression was conducted[38]. The authors were very careful in this meta-analysis to include only those studies that were both large and carefully conducted. From the results of their study, they concluded that genetic influences are the most important contributor to familial aggregation (two of the three adoption studies, and all of the twin studies). They concluded that, unlike the heritability of schizophrenia and bipolar disorder, which are of the order of 70% (Ref. 39), the heritability of major depression is probably in the range of 31–42%. They also concluded that the data were consistent with the conceptualization of major depression as a complex disorder that arises from both genetic and environmental factors. In addition, they found that the conclusions they derived were consistent across the different methodologies used (five family studies, two of three adoption studies, and all twin studies) and that the estimates of heritability were relatively similar. Twin studies have recently been reviewed and similar conclusions have been drawn[40].

Molecular biology and molecular pharmacology have led to a better understanding of the biology of neurotransmitter systems in the brain and could therefore contribute to a molecular understanding of depression. It is no surprise that the components of the serotonin neurotransmitter system have been of special focus as a risk factor for schizophrenia, autism, depression, aggression, obsessive-compulsive disorder and alcoholism. This system has been recently reviewed in this context[41]. Much of this research is based on the observation that many of the drugs typically used in psychiatry have serotonergic neurons as their site of action.

These studies have begun to address some of the issues involved in the differential efficacy of medications currently used in patients. It seems logical to believe that variations in the genetic background of individuals, both with respect to drug pharmacokinetics and pharmacodynamics, would have a profound impact on the efficacy of drugs, over and above any variation that might be caused by polymorphisms in the drug target. There is an opportunity here to take advantage of molecular knowledge of these disorders and initiate novel approaches to drug discovery based on the understanding of the polygenic nature of the disorders.

Molecular genetics and SNPs

Recent studies have attempted to use molecular genetic approaches in the identification of genes involved in schizophrenia. These include a study of the potential involvement of trinucleotide repeats in schizophrenia[42]. This study looked for evidence of CAG or GAA repeats in families with schizophrenia and MZ twins with schizophrenia. However, no evidence was found to support the involvement of such repeats in the disorder (the study did not rule out other trinucleotide repeats or repeats that were below the level of detectability). This finding is contrary to the study of Huntington's disease in which the involvement of such repeats is well established.

The significance of SNPs that affect genes in the serotonin system was also described[41], although the main conclusion from an analysis of available evidence was that the data are not sufficient to clearly associate the known polymorphisms in the serotonin neurotransmitter system with any of the major psychiatric disorders. However, recent evidence suggests that polymorphisms or deletions in the α-2-adrenergic receptor could be associated with schizophrenia[43].

Gene expression studies

The improved cost-effectiveness of microarrays over the past few years has led to an explosion in the literature of gene expression in experimental systems and for various disease states. These studies range from cancer, neurological disorders (Olsen, M.K. *et al.*, Disease processes in amyotrophic lateral sclerosis revealed by gene expression analysis. *Society for Neuroscience Meeting*, 4–10 November 2000, New Orleans, LA, USA; Buxbaum, J.D. *et al.*, RNA profiling in neuropsychiatric disorders. *Society for Neuroscience Meeting*, 4–10 November 2000, New Orleans, LA, USA), studies of animal-model systems for drug abuse (Peris, J. *et al.*, Cocaine sensitization alters gene expression in the rat striatum. *Society for Neuroscience Meeting*, 4–10 November 2000, New Orleans, LA, USA), and *in vitro* cell-based morphological changes (Leblanc, G.G. *et al.*, Functional genomics in the nervous system. *Society for Neuroscience Meeting*, 4–10 November 2000, New Orleans, LA, USA). However, these studies must be considered very critically, as quality control and statistical reproducibility issues often cloud useful interpretation of the data. Even though the cost of microarrays has dropped, they remain expensive enough that results are often from single experiments using single arrays. Also, in many cases (especially those involving human postmortem tissue from difficult to access locations such as brain), experimental sample quantities often only enable single experiments to be completed. Thus, much of the data from the literature still needs critical evaluation and confirmation by other independent technologies such as reverse transcription-PCR (Wen, X. *et al.*, Extending gene expression microarray surveys by quantitative PCR. *Society for Neuroscience Meeting*, 4–10 November 2000, New Orleans, LA, USA). A recent review also discusses the use of microarrays for the identification of drug targets, and showed how intracellular signaling pathways could be investigated following mitogenic activation of fibroblasts[44,45].

As mentioned above, three reports of gene expression using microarrays have been reported for schizophrenia. These studies, which used a limited number of diseased and normal brain samples, suggest that different gene expression patterns could be found[11,12] (Vawter, M.P. *et al.*, Examining functional genomic expression in schizophrenia with cDNA microarrays. *Society for Neuroscience Meeting*, 4–10 November 2000, New Orleans, LA, USA). It is clear that further studies of this type will help to resolve the genetics of this and other psychiatric disorders.

Conclusion

From the balance of evidence we can conclude that schizophrenia, autism, mood disorders and bipolar disorder have significant multigenic components. This is strongly supported by the high concordance rates in studies of twins, which indicate that MZ twins have a significantly higher concordance rate as compared with DZ twins, in all of these disorders. This is true despite recent criticism of the methodologies employed in these types of study. More recent studies of twins have been better controlled and still give similar results to the older groups of studies.

Recent applications of molecular biology in gene linkage and association studies, in addition to the use of microarray technologies and SNP analysis, have provided some hints towards identification of the genes involved in these psychiatric disorders. However, these technologies are still in the early stages of effective application to the identification of both the genes involved in the disorders and their interaction.

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