The Genetics of Major Depressive Disorder

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There is consistent evidence that major depression is familial and population-based twin studies as well as hospital register-based twin studies find substantial heritability. However, there is also a large proportion of variation in liability left to be explained by nongenetic factors. Although there seems little doubt that life events play a role in precipitating depression, studies that have attempted to examine familial liability along with social adversity find that environmental measures tend to be contaminated by genetic effects. Thus, the tendency to experience (or report) life events appears to be influenced by shared family environment, and for certain types of events there is a genetic component. The molecular genetic basis of liability to depression is an under-researched area, but some candidate gene studies show potentially promising results. Systematic mapping studies aiming to cover the entire genome are currently being launched.

Introduction

Compared with the general population, the relatives of depressed probands have at least a three-fold increase in their risk of developing major depressive disorder (MDD) [1]. In a recent study using narrow ICD-10 (International Classification of Diseases of the World Health Organization, edn 10) criteria, depression was nine times as frequent in the siblings of depressed probands compared with siblings of healthy controls [2•]. Some family studies have also shown that the prevalence of MDD is greater among the relatives of those who experience their first depressive episode before the age of 20 [3], and childhood onset was recently reported as being associated with an increased familial risk [4]. However, the relationship between age of onset and family loading for depression is by no means clear. For example, in one study very early onset (before puberty) was associated with a high rate of antisocial behavior among relatives, rather than "pure" depression [5], and a twin study of depressive symptoms in childhood found that they were familial, but in children below age 11; this resulted from shared environment rather than shared genes [6].

Twin Studies

Broadly speaking, twin studies of MDD in adults suggest that genes and specific environmental factors are important, and that shared environmental factors, although important in less severe subtypes of depression, are perhaps of less significance in this patient group [7]. It is of interest to note that the heritability of unipolar depression appears to be higher than was once thought, with estimates in the region of 40% to 70%.

Recent large twin registry studies have explored the influence of genetic factors on major depression in male twins [8•,9•]. In both studies, the best fitting biometric twin model for major depression again contained only genetic and nonshared environmental factors. Lyons *et al.* [9•] in a further analysis stratified the diagnosis of major depression according to severity and found that this particular model held only for severe or psychotic depression. Dysthymia, as well as mild and moderate depression, were best explained by a nongenetic model containing only common family environment and nonshared environment. This is further evidence that perhaps more severe forms of depression differ in their etiology from milder disorders. Kendler *et al.* [8•] used an approach based on bivariate path analysis to further explore the genetic correlation in the liability to major depression in men and women, and found it to be +0.57. They concluded that although major depression is equally heritable in men and women and most genetic risk factors influence liability to major depression similarly in both sexes, genes may exist that act differently on the risk for the disorder between the two sexes.

Multivariate approaches have also been applied to the investigation of the genetic origins of comorbidity in disorders such as panic disorder, phobia, bulimia, and alcoholism, as well as major depression and generalized anxiety disorder (GAD) [10]. Two sets of shared genetic factors have been suggested by this analysis. The first contributes to major depression and GAD, and the second to

phobia, panic disorder, and bulimia. Genetic effects for alcoholism appear to be specific in nature. It is not clear, however, whether these findings can be extrapolated to clinical samples, given the somewhat more liberal interpretation of the diagnostic criteria that suggest the lifetime prevalence of major depression and GAD as 31% and 24%, respectively. There is also evidence that the covariation of anxiety and depressive symptoms in childhood (maternally rated) may be explained by a common set of genes [6]. However, this study also suggested a role for nonshared environmental factors in the comorbidity of these symptoms and the influence of specific genetic effects for depressive symptomatology.

Gene-Environment Interplay

Although older terminology suggested that some forms of depression were *reactive* and others *endogenous*, there is little genetic evidence to support such a separation. A recent twin-family analysis showed that it is unlikely that there are two broad subtypes of depression, one mainly genetic and the other mainly nongenetic [11]. Rather, it seems probable that depression generally results from a combination of genetic liability and environmental adversity. However, the relationship between these factors is complicated. One of the first studies to explore gene–environment interplay found an increased rate not only of depression among relatives of depressive probands [12], but also an increase in reported life events. The authors suggested that part of the association between life events and depression may be due to this familial aggregation. Such findings suggest the possibility that familial factors may be influencing the liability to major depression indirectly, by predisposing an individual to a more aversive environment [13••]. Several studies have supported the surprising proposition that life events may be partly genetically influenced [13••,14]. Kendler [13] categorized life events, according to their likely range of impact, into *personal events*, which focused primarily on the proband, and *network events* where the impact extended to other individuals in the proband's social circle. For network events twin resemblance appeared to result purely from common environmental effects, whereas for personal events twin resemblance appeared to be due to genetic influence only. In a third category, *interpersonal difficulties*, both genetic and common environmental factors appeared to operate. The distinct familial origins of different categories of events are underlined by a recent sib pair study [2•]. This study showed positive correlations between siblings for events classified as *independent* (that is, not likely to result from the subject's deliberate actions), but this was almost entirely explained by *shared* events such as death or illness of a parent. Nevertheless, it remains that some life events (or how they are reported) are influenced by genetic factors, and there is evidence that the genetic factors operating in depression and in the predisposition to life events are positively correlated, thereby implying an association via a common set of genes [15,16•,17•]. To what degree, therefore, is the relationship between stressful life events and depression due to a causal relationship, with life events contributing directly to the onset of major depression? Kendler *et al.* [18] explored this question in their population-based sample of female twins and found strong evidence that the observed association was, at least in part, causal.

Molecular Genetics

Having demonstrated a genetic contribution to anxiety and depressive disorders, the next stage of the investigation draws on molecular genetic methods in an attempt to locate and identify the genes involved. Depression does not follow mendelian segregation patterns, thereby indicating a complex mode of inheritance. It is likely that the genetic influences on these disorders are multigenic in nature, acting in concert with environmental factors. Segregation analyses have been unable to confirm specific modes of inheritance. Given that the genome contains 3 billion base pairs and over 100,000 genes, the task of locating a susceptibility gene for a particular disease is formidable. Linkage analysis, by detecting the co-inheritance of chromosomal regions and disorder within families, offers a possibility of achieving this.

Linkage Studies

Linkage studies of affective disorder have primarily focused on the bipolar phenotype and there have been few recent linkage studies of major depression. Older studies, predating the availability of DNA markers, made use of classical genetic markers such as blood group antigens and protein polymorphisms with inconclusive results. More recently analyses using DNA polymorphisms have concentrated on excluding linkage to chromosomal regions known to contain possible candidate genes, such as those involved in neuroendocrine or neurotransmitter systems [19,20], or those implicated in bipolar disorder [21]. These have employed parametric linkage methods. Such conventional lod score linkage analysis requires precise knowledge of the disease mode of transmission and assumes a gene of major effect is operating [22]. As stated previously, the mode of inheritance is unknown for depressive disorders, and parametric linkage analysis requires reasonably accurate specification of parameters such as gene frequency and penetrance. Mis-specification of the parameters of such a model introduces the possibility of error. An alternative linkage strategy requiring no information about the mode of inheritance, and useful in disease involving several (oligogenic) or many genes (polygenic), is the affected sib pair method. This nonparametric linkage method is associated with some loss of statistical power. Although such analysis has been used in linkage studies of depression [23] only a small number of pedigrees were involved, whereas very large samples sizes (many hundreds of families) are likely to be required to detect genes of small effect [24]. Genome-

wide screens of several hundred roughly evenly spaced DNA markers are commencing in a number of centers. These should be successful if there are relatively common genes that contribute at least a moderate relative risk of around 2 or more, but if depression turns out to be highly polygenic other methods will be required [24].

Association Studies

This method allows the detection of much smaller effects (relative risks of less than 2) but is limited by the fact that allelic association results either from very tight linkage between a marker and a disease susceptibility locus (resulting in linkage disequilibrium) or from the marker locus itself conferring susceptibility. This means that until recently it has not been feasible to consider a whole genome scan for association (although methods are now emerging to accomplish this [24]. Therefore, research has focused on candidate genes. Candidate genes for major depression and anxiety disorders have primarily been suggested by the molecular mechanisms implicated in the action of therapeutic drugs and the putative pathophysiology for these disorders. Of particular interest are genes associated with neurotransmitter systems. Many of the association studies associated with these phenotypes have focused on the serotonergic system and in particular the serotonin transporter gene located on chromosome 17 (17q11.1-17q12). Many antidepressant and anxiolytic drugs such as tricyclic antidepressants and the newer serotonin selective reuptake inhibitors influence the transporter facilitated uptake of serotonin. Several polymorphisms of the serotonin transporter (*SERT*) gene have been described.

A 44 bp insertion/deletion polymorphism in the transcriptional control region of the gene has been described by Heils *et al*. [25]. The short version of this promoter polymorphism was shown to be associated with decreased transcriptional efficiency resulting in reduced serotonin transporter expression. Since an original report of association between this genetic variant and personality traits that are likely to be relevant to vulnerability to depression [26], various studies have explored this further. Katsuragi *et al*. [27] replicated the finding in a Japanese sample but several other studies have failed to do so [28–30]. Ohara *et al*. [31] described a tendency for the shorter variant of this polymorphism to be more frequent in patients diagnosed with an anxiety disorder using DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, edn 4) criteria. Associations of this polymorphism with affective disorders have also been described [32]. Similar associations have been shown for both unipolar and bipolar subtypes separately [33], although this too has not been replicated [34].

A further variable number tandem repeat polymorphism, in the second intron of the serotonin transporter gene, has also been described [35]. Several variants of this polymorphism were found to be associated with affective disorder [36,37]. In particular an association of the nine copy variant with unipolar depression has been reported [38,39]. However, this has not been replicated in independent studies [40]. Gelernter *et al*. [41•] investigated the range of allele frequency variation for both the promoter and second intron polymorphisms of the serotonin transporter gene in seven different populations and found significant global variation. Linkage disequilibrium varied among the populations suggesting a large potential for population stratification in association studies employing population controls; as the majority of studies exploring depressive and anxiety related phenotypes have done. Taken as a whole, therefore, the various association findings suggest that polymorphic variation at this gene results in some phenotypic effect but it is unclear at present what phenotypic construct best captures this [30].

Other candidate gene association studies in depression and anxiety have investigated the dopamine receptor genes [42], the tryosine hydroxylase gene [43], genes related to the gamma-aminobutyric acid system [44], and the catechol-O-methyltransferase gene [45,46]. Candidate gene approaches are limited in that they are only as good as the current understanding of the disease pathophysiology [47]. However, the possibility of a genome-wide search for association, similar to that for linkage studies, is increasingly feasible with the development of high throughput genotyping techniques such as DNA pooling [48]. In order to scan systematically for allelic association, however, a much denser map of polymorphic markers would be required and biallelic single nucleotide polymorphisms are likely to provide this in the near future [24].

Conclusions

The genetics of unipolar depression is a neglected area in comparison with bipolar disorder or schizophrenia despite being a much more common disorder. This may be because the role of psychosocial adversity has seemed so obviously important and depression appears as an understandable reaction to stress. However familial aggregation is a consistent finding and recent twin studies suggest that heritability is substantial. Studies trying to incorporate environmental measures within a genetic design have only really taken place in the past 10 to 15 years and suggest a complicated picture where measures of stress are actually confounded by familial or genetic effects. The future is likely to see an increasing emphasis on trying to elucidate gene–environment interplay. Molecular genetic studies of unipolar disorder have scarcely begun and have so far been mainly restricted to candidate genes but is likely that more systematic approaches using linkage and linkage disequilibrium mapping will identify susceptibility loci within the foreseeable future.

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