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The genetics of bipolar disorder and its relationship with unipolar depression

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A consistent finding dating back many years is that affective disorders tend to aggregate in families. Specifically, the relatives of bipolar cases have an increased risk of both unipolar and bipolar disorder, whereas in the relatives of patients with unipolar disorder there is only an excess of unipolar cases. As in other disorders, two types of «experiments of nature», twin studies and adoption studies, have enabled researchers to decide whether the familiality of affective disorders is explicable purely in terms of shared genes, shared family environment or a combination of the two.

Twin studies have consistently shown higher concordance for mood disorders in monozygotic than dizygotic pairs. Sullivan and colleagues[1] performed a meta analysis of published twins studies of depression and concluded that the mean heritability (the proportion of variance in liability to the disorder) was 37%. However in doing so they lumped together four population-based and one hospital-based study. On its own the hospital-based twin study actually suggested a heritability of over 70%[2]. While this might suggest that more severe depression requiring specialist referral is more heritable than depression detected in community samples, there is another possible explanation. This has to do with the unreliability of the diagnosis of depression in surveys using lay interviewers, which has already been discussed in relation to epidemiological studies. The one community based twin study that took unreliability of diagnosis into account in the statistical analysis and used assessment at two time points also found a heritability of about 70%[3].

There have been been many twin studies suggesting an important role of genes in bipolar disorder (reviewed by Jones et al.[4]), however most of these have been small. The two largest studies based on hospital-based twin registers in Denmark and the UK suggest a heritability for unipolar depression of around 70% and a heritability of 80% for bipolar disorder but suggest that there is a genetic overlap between the two conditions. McGuffin et al.[5] explored this further and concluded that although such an overlap is substantial, most of the genetic liability to bipolar disorder is specific to the manic syndrome.

An adoption study in Sweden, based mainly on health insurance records[6], surprisingly found little evidence of either a genetic or family environmental component in affective illness. However, when a Danish study compared hospital records of the biological relatives of adoptees with affective illness with adopted relatives and relatives of matched control adoptees[7], an 8-fold increase in unipolar depression in the biological relatives of adoptees with affective illness was found, as well as a 15-fold increase in the rate of suicide. In another study that examined the parents of adoptees suffering from bipolar disorder, 28% of the biological parents had an affective illness compared with 12% of adopting parents[8]. A majority of the affected biological parents of bipolar probands had unipolar rather than bipolar disorder which is, however, compatible with the most recent twin analyses[5].

The data discussed so far suggest that affective disorders are polygenic. That is, they result from the combined effects of several, perhaps many genes each of which on their own have small effects. Single gene forms, if they exist at all, must be extremely rare, and the existing data are mathematically incompatible with either a single gene model or models proposing multiple single gene forms with incomplete penetrance[9]. Furthermore, a recent twin analysis challenged the conventional wisdom that bipolar disorder and schizophrenia are genetically distinct, instead suggesting that although specific genes contribute to the liability to each classic syndrome, there are also some genes that contribute to the liability to both disorders[10].

MOLECULAR GENETICS

Broadly there are the two ways that geneticists seek to find genes involved in disease. These are linkage and association studies. In linkage studies researchers now typically

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use several hundred genetic markers as evenly spaced as possible throughout the genome to try to establish the location of genes involved in susceptibility by identifying markers that are shared at a greater than chance level by multiple affected members within families, or in pairs of affected siblings. The location is then narrowed down and candidate genes within the region are examined. In association studies the most common approach is to compare variations within functional candidate genes (that is, genes that encode proteins thought to be involved in the disorder) in cases versus well controls. Very recently it has become feasible to search the entire genome using an association approach although this requires somewhere in the region of half a million markers.

To date gene finding studies have been more consistent in bipolar than unipolar disorder but interesting findings are beginning to emerge in both conditions. Badner and Gershon[11] carried out a meta-analysis of linkage studies in both schizophrenia and bipolar disorder and showed that there is significant evidence of linkage for bipolar disorder on chromosomes 13 and 22 in regions that overlap with regions implicated in schizophrenia. A subsequent search through the chromosome 13 linkage region of schizophrenia identified a novel gene, G72 (also known as D amino acid oxidase activator, DAOA) that appears to be associated with susceptibility to the disorder[12]. Other studies have now also implicated G72 in bipolar disorder[13-15]. We can conclude that molecular genetic studies are beginning to confirm the suggestion from the recent twin analysis mentioned earlier[16] that some of the genes that contribute to bipolar disorder also contribute to the liability to schizophrenia.

Studies in unipolar disorder have been reviewed by Levinson[17] who notes that two whole genome scans suggest linkage on chromosomes 12 and 15. Subsequently another whole genome scan has been conducted lending support for findings in both these regions[18]. Among the interesting candidate genes in unipolar depression is a brain derived neurotrophic factor (BDNF). BDNF shows decreased expression in hippocampus after stress or corticosteroid treatment and enhanced expression in the hippocampus and the cerebral cortex of rats treated with antidepressants. A functional variant in the gene was originally associated with bipolar disorder but a large case-control study has cast doubt on this finding[19]. However, other variants within this gene now appear to be significantly associated with unipolar depression[20]. An even more intriguing story surrounds the serotonin transporter gene which has a variant in its promoter region that results in either higher or lower activity. This appears to show an interaction with depression following stressors such as early adversity or recent life events[21] a finding that has been subsequently replicated in other (but not all) studies[22,23].

Very recently, the largest and most ambitious case-control study of bipolar disorder has uncovered some novel loci[24]. This compared 2000 well-defined bipolar cases with 3000 controls using micro array-based technology that allowed the researchers to look at approximately half a million roughly evenly spaced markers. The study revealed a new region on chromosome 16 containing, among other genes, a locus that interacts with a gene previously advocated in schizophrenia (DISC1) and implicated other loci elsewhere containing genes encoding for example a voltage gated potassium ion channel, a GABA A receptor and a metabotropic glutamate receptor. This opens up truly exciting and immediate prospects for major advances in the genetics of affective disorders.

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