Current strategies for investigating the genetic and environmental risk factors for affective disorders*

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It is probable that the genetic components of affective disorders (bipolar affective disorder, major depressive disorder and anxiety states) result from multiple genes that confer a susceptibility or liability to develop the disorder when other (environmental) risk factors are also present. In general, bipolar affective disorder has been found to have the highest heritability (i.e. the proportion of variance explained by additive genetic factors) of around 80% (McGuffin *et al*, 2003), followed by major depression (between 40% and 70%, depending on the stringency of the definition; Kendler *et al*, 1993; McGuffin *et al*, 1996) and then by anxiety disorders, with heritabilities of around 40–50% (Eley *et al*, 2002).

For affective disorders in adult life, the role as precipitants of certain proximal factors such as severe and threatening life events has been well replicated (Brown & Harris, 1978). There is also much evidence of distal factors such as childhood adversity contributing to vulnerability (Gilman *et al*, 2003). Important developmental aspects include the continuities between childhood depressive symptoms and adult depression and the changing contributions of genes and environment throughout the life span. For example, recent findings support and extend earlier work that has shown increasing genetic influence on depressive symptoms as children grow into adolescence (Scourfield *et al*, 2003).

AFFECTIVE DISORDERS: ONE OR MORE SET OF GENES?

The classification of affective disorders has often been the subject of debate, generating considerable controversy as to whether schemes of subtyping are of any use (Kendell, 1976; Farmer & McGuffin, 1989). One typology that has stood the test of time and seems clinically useful is the unipolar/bipolar subdivision. Until recently, a common view (Gershon *et al*, 1982) was that bipolar affective disorder and major depressive disorder lie on the same severity of liability continuum contributed to by the (mainly) additive effects of genetic and environmental risk factors. The theory suggests that the two phenotypes differ only in respect of severity of liability, with bipolar affective disorder representing the more severe, less common subtype and major depressive disorder the more common, less severe subtype. However, this model has been recently refuted by McGuffin and colleagues, who also applied structural equation model-fitting methods to explore further the aetiological overlap between the two disorders, using a twin design (McGuffin *et al*, 2003). These authors showed that although there is a substantial genetic correlation between mania and depression, most of the genetic variance in liability to mania is specific to the manic syndrome. That is, the main clinically relevant subtypes of affective disorder show a large overlap in their genetic aetiology, but bipolar disorder is also contributed to by a set of genes that are specific to the manic state.

A similar model-fitting approach has been applied to the genetic and environmental overlap between schizophrenia, schizoaffective disorder and bipolar disorder (Cardno *et al*, 2002). Although there was evidence of genetic overlap between the three disorders there was also evidence for specific genetic components for schizophrenia and bipolar disorder (but not schizoaffective disorder). This goes some way towards explaining the (otherwise puzzling) findings from linkage studies that have implicated some of the same genomic regions in schizophrenia and bipolar disorder and studies that have implicated a positional candidate gene *G72* in both disorders (Elkin *et al*, 2004). Thus, the molecular and the quantitative genetic findings appear to be convergent in suggesting three sets of genes: one conferring liability to both schizophrenia and bipolar disorder, and two that are specific for each of the two main Kraepelinian syndromes. Interestingly, in the quantitative analyses the environmental risk factors appeared to be specific to each psychotic disorder.

A rather different type of analysis seeks to tease out dimensions within the broad category of recurrent depression. Using phenotypic data from participants in current large-scale genetic studies of depression (see below), this has produced some interesting early results. Factor analysis of psychopathology from worst and second-worst episodes of depression in sibling pairs has shown that a four-factor solution provides the best fit for the data. Three of the factors were found to be familial by examining the sib-pair correlations, and a confirmatory factor analysis of a large sample of unrelated patients suggested that the factor structure is stable, replicable and potentially useful for analyses exploring the relationship with genetic markers (Korszun *et al*, 2004).

FINDING GENES AND EXPLORING FUNCTION

Linkage studies use genetic marker allele sharing between family members (most commonly, affected siblings) to find regions within the genome where susceptibility genes might be located. Once such regions have been found, they can then be explored in greater detail using association studies (either case–control or within-family designs). Both approaches require large datasets, drawn from hundreds or thousands of subjects, and the application of these methods to affective disorders has somewhat lagged behind other disorders such as schizophrenia. However, several large affected sib-pair and case–control collections of DNA for recurrent major depression and bipolar affective disorder, as well as depressive and anxiety symptoms that occur in the general population, have now been collected and results of genome scans are beginning to emerge (Nash *et al*, 2004).

Finding genetic polymorphisms associated with affective disorders is only the first step on the path to understanding what

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the genes do. Currently the functional effects of common polymorphisms in genes in candidate pathways such as the serotonin pathway are under investigation. This includes studies of gene expression in post-mortem human brain tissue (Sugden *et al*, 2004) and in animal models (Fernandes *et al*, 2004).

GENE–ENVIRONMENT INTERPLAY

Although the relationship between adverse life events and the onset of depression is well established, the nature of the relationship between this and genetic vulnerability to depression is not yet understood. Do genes predispose some individuals to encounter adversity or do genes make some individuals more susceptible to the effects of adversity when it occurs? Several studies have shown that life events aggregate in families (e.g. McGuffin *et al*, 1988; Rijsdijk *et al*, 2001). In a nearest-aged sib-pair study of depression, Farmer *et al* (2000) found no significant difference between the number of threatening life events experienced by the siblings of individuals with depression and the siblings of healthy controls. However, the siblings of probands with depression who had experienced a threatening event were significantly more likely to develop depression than the siblings of controls. These findings suggest that genes make individuals susceptible to adversity rather than influence their exposure to it. Nevertheless, many individuals exposed to adversity do not develop depression. Examination of resilience, whatever protects individuals from developing psychopathology in the presence of environmental risk factors, can also be informative (Farmer & McGuffin, 2003).

These findings also suggest that interaction effects (not just simple additive effects) between genes and environment are probably more common than previously thought. Caspi *et al* (2003) demonstrated that a functional polymorphism in the promoter region of the 5-hydroxytryptamine transporter gene (*5HTTLPR*) moderates the impact of adversity. This finding concerning *5HTTLPR* has recently been replicated in a sample of adolescent females (Eley *et al*, 2004*b*), and the detection of gene–environment interactions will be the subject of a later editorial.

DEVELOPMENTAL ASPECTS: SAD AND ANXIOUS CHILDREN

One of the methods for disentangling the changes in the relationship between adversity and mood states throughout childhood into adult life is to carry out longitudinal cohort studies. The Twins Early Development Study (TEDS) (Trouton *et al*, 2002) the largest-ever twin study of its kind, has undertaken regular assessments of twins born in the UK between 1994 and 1995. Several 'spin-off' studies have been performed, one of which examined the phenotypic and genetic structure of anxiety in young children (Eley *et al*, 2003). Another study currently being undertaken will examine mother–twin and twin–twin social interactions during slightly stressful or mildly anxiety-provoking tasks. Emotional responses and measures of anxious cognitive style in both twins as well as the quality of the interactions are being identified. As the study design crosses two time points in middle childhood, a developmental hypotheses regarding aspects of cognitive style and anxiety symptoms can be tested (Eley *et al*, 2003).

Another 'spin-off' study from a large sib-pair study of depression and anxiety in a general population adult sample (The GENESiS study) (Sham *et al*, 2000) recruited the study participants' adolescent offspring (around 1900 children, of whom half are sibling pairs), who have been examined at three time points in adolescence. The sib-pair sample was combined with a sample of adolescent twins identified by the Office for National Statistics, and a comprehensive series of assessments have investigated socio-economic factors, education, employment, parenting style and friendships. As this age group is at increasing risk of developing depression, the evolution of affective symptoms and disorder has been evaluated along with cognitive risks associated with these disorders. The study team has shown that regarding risk of depression, there is an interaction between familial vulnerability to adolescent depression and parental lack of education (Eley *et al*, 2004*a*). They also found an interaction between negative life events, parental disciplinary style and genetic risk for depression (Lau *et al*, 2004*a*). Furthermore, attributional style – a cognitive risk factor for depression traditionally thought of as a learned trait – has been shown to be heritable, and to share genetic influence with both depression and parental disciplinary style (Lau *et al*, 2004*b*).

CONCLUSIONS

With the completion of the sequencing of all the base pairs in the human genome earlier in the decade, we are now entering a 'post-genomic' era, although identifying the genes involved in the aetiology of affective disorders remains a major research preoccupation. However, many geneticists as well as researchers from other disciplines are now turning their attention to environmental risk factors and how these interact and co-act with genes to lead to the expression of pathological phenotypes such as depression. Although genetic variation in humans can now be determined relatively easily from a single DNA sample derived from blood or even scrapings from the inside of the cheek, experimental manipulation of the environment of human subjects is clearly not possible. Consequently, alternative methods are required to measure the 'environome'. One is to examine the genotypes of individuals who have all been exposed to a specific risk factor, such as childhood adversity or severe threatening life events, comparing those who have expressed the phenotype, for example by becoming depressed, and those who have not (resilient individuals). Some of the longitudinal and twin studies described above, as well as others currently being conducted by various research groups around the world, will lend themselves to this type of analysis.

DECLARATION OF INTEREST

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