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 SETS 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 phenotype. 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
the genes do. Currently the functional
effects of common polymorphisms in genes
in candidate pathways such as the serotonia
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
depression is not yet understood. Do
gene predisposes 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; Rijndijk
et al, 2001). In a nearest-aged sib-pair study
of depression, Farmer et al (2000) found no
significant difference between the number
of depressed relatives of individuals
with depression and the siblings of healthy controls. How-
ever, 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. Ex-
amination 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 inter-
action effects (not just simple additive
effects) between genes and environment
are probably more common than previ-
ously thought. Caspi et al (2003) demon-
strated that a functional polymorphism in
the promoter region of the 5-hydroxytryp-
tamine transporter gene (SHTTLPR)
moderates the impact of adversity. This
finding concerning SHTTLPR has recently
been replicated in a sample of adolescent fe-
males (Eley et al, 2004b), 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 adverse-
ity and mood states throughout childhood
into adult life is to conduct longitudinal
cohort studies. The Twins Early Develop-
ment Study (TEDS) (Trouton et al, 2002)
the largest-ever twin study of its kind, has
undertaken regular assessments of twins
Several ‘spin-off’ studies have been per-
formed, one of which examined the pheno-
typic and genetic structure of anxiety in young
children (Eley et al, 2003). Another study
currently being undertaken will ex-
amine mother–twin and twin–twin social
interactions during slightly stressful or
mildly anxiety-provoking tasks. Emotional
responses and measures of anxious cogni-
tive 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) re-
cruited the study participants’ adolescent
offspring (around 1900 children, of whom
half are sibling pairs), who have been
examined at three time points in adoles-
cence. 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, edu-
cation, employment, parenting style and
friendships. As this age group is at increas-
ing risk of developing depression, the evolu-
tion 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 depres-
sion and parental lack of education (Eley
et al, 2004a). They also found an interac-
tion between negative life events, parental
disciplinary style and genetic risk for de-
pression (Lau et al, 2004a). Furthermore,
attributional style – a cognitive risk factor
for depression traditionally thought of as
a learned trait – has been shown to be heri-
table, and to share genetic influence with
both depression and parental disciplinary
style (Lau et al, 2004b).

**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 affec-
tive disorders remains a major research pre-
occupation. However, many geneticists as
well as researchers from other disciplines
are now turning their attention to environ-
mental risk factors and how these interact
and co-act with genes to lead to the expres-
sion 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 manipula-
tion of the environment of human subjects
is clearly not possible. Consequently, alter-
native methods are required to measure the
’environome’. One is to examine the geno-
types of individuals who have all been ex-
posed to a specific risk factor, such as
childhood adversity or severe threatening
life events, comparing those who have ex-
pressed the phenotype, for example by be-
coming depressed, and those who have
not (resilient individuals). Some of the longi-
itudinal 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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