Genetics of bipolar disorder

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Abstract
Bipolar disorder (also known as manic depressive illness) is a complex genetic disorder in which the core feature is pathological disturbance in mood (affect) ranging from extreme elation, or mania, to severe depression usually accompanied by disturbances in thinking and behaviour. The lifetime prevalence of 1% is similar in males and females and family, twin, and adoption studies provide robust evidence for a major genetic contribution to risk. There are methodological impediments to precise quantification, but the approximate lifetime risk of bipolar disorder in relatives of a bipolar proband are: monozygotic co-twin 40-70%, first degree relative 5-10%; unrelated person 0.5-1.5%. Occasional families may exist in which a single gene plays the major role in determining susceptibility, but the majority of bipolar disorder involves the interaction of multiple genes (epistasis) or more complex genetic mechanisms (such as dynamic mutation or imprinting). Molecular genetic positional and candidate gene approaches are being used for the genetic dissection of bipolar disorder. No gene has yet been identified but promising findings are emerging. Regions of interest identified in linkage studies include 4p16, 12q23-q24, 16p13, 21q22, and Xq24-q26. Chromosome 18 is also of interest but the findings are confusing with up to three possible regions implicated. To date most candidate gene studies have focused on neurotransmitter systems influenced by medication used in clinical management of the disorder but no robust positive findings have yet emerged. It is, however, almost certain that over the next few years bipolar susceptibility genes will be identified. This will have a major impact on our understanding of disease pathophysiology and will provide important opportunities to investigate the interaction between genetic and environmental factors involved in pathogenesis. This is likely to lead to major improvements in treatment and patient care but will also raise important ethical issues that will need to be addressed.

Keywords: bipolar disorder; manic depressive illness
undesirable side effects, are not effective in all patients, and the pathogenesis of bipolar disorder remains poorly understood.

Clinicians have always known that bipolar disorder tends to run in families but recent advances in molecular genetics now provide the tools needed to identify genes influencing susceptibility. Although psychiatric and behavioural traits represent, perhaps, the greatest challenge to molecular investigation of complex genetic disorders, they also offer arguably the greatest potential reward. Identifying susceptibility genes for bipolar disorder will pinpoint biochemical pathways involved in pathogenesis, facilitate development of more effective, better targeted treatments, and offer opportunities for improving the validity of psychiatric diagnosis and classification. In this review article, we start by briefly considering methodological issues involved in genetic studies of bipolar disorder. We will then review the formal evidence that genes are involved in influencing susceptibility to bipolar disorder. We will consider the likely mode of inheritance before discussing current molecular genetic positional and candidate studies. Finally, we will discuss the implications of genetic investigation of bipolar disorder.

**Methodological issues**

Before reviewing available genetic data, it is important to be aware of several methodological issues that act as impediments to genetic research in bipolar disorder. It should be recognised that some of these apply equally to all complex genetic diseases.

**Lifetime diagnosis**

Although psychiatric diagnoses tend to remain stable, occasionally a change in diagnosis from one episode to another is observed. In genetic studies “lifetime diagnosis” is required in an attempt to classify subjects on the basis of a presumed diathesis for bipolar disorder. This requires that the sum of a person’s abnormal behaviour and experience over his/her lifetime be reduced to a small number of diagnostic categories, usually just one. Although this task is non-trivial, a relatively robust methodology of lifetime diagnosis has been developed which allows integration of information from different sources in an unbiased manner in order to produce acceptably reliable diagnoses.5 6

**Variable age at onset**

In common with many other diseases, subjects can develop the first episode of bipolar disorder at any time during his or her life. For this reason, unaffected subjects are much less useful in genetic studies than are affected subjects because they provide less information about genetic risk.

**Secular changes (for example, birth cohort effect)**

A change in the measured rate of mood disorder in successive birth cohorts has been described in some studies.10 11 However, this effect may be an artefact of research methodology12 and the effect has been less clearly shown in bipolar disorder than in unipolar disorder. This effect complicates prevalence dependent analysis of data that include differing birth cohorts, further reducing the usefulness of unaffected subjects.

**Unknown diagnostic validity**

Clinical, outcome, and genetic studies suggest that bipolar disorder is a relatively distinct nosological entity. However, in the absence of a clear understanding of the biology of psychiatric illnesses the most appropriate boundaries between bipolar disorder and other mood and psychotic disorders remain unclear. The bipolar-unipolar boundary has already been mentioned. At the psychotic end of the spectrum, there are a large number of patients who have illnesses with features both of schizophrenia and bipolar disorder (usually called “schizoaffective disorder”). Current diagnostic boundaries are based on best available evidence,5 6 but the extent to which they reflect genetic vulnerability will only become clear as susceptibility genes are identified.

Despite these challenges, methodological refinements in both psychiatric diagnosis and complex disease genetics have provided methods and approaches that in large part address most of the methodological issues. Currently the major problem is the unknown biological validity of current psychiatric classifications and it is worth bearing in mind that advances in molecular genetics are likely to be instrumental in providing the first robust validation of our diagnostic schemata.

**Family studies**

Many of the early studies of mood disorders failed to distinguish between unipolar and bipolar types of illness or failed to provide any description of the clinical features associated with the diagnostic categories used. A review of these early studies (almost all of which showed familial aggregation of mood disorder) can be found in Tsuang and Faraone.13 Over the last 30 years many studies using the modern concept of bipolar disorder have been conducted and Fig 1 provides a graphical summary of the findings. It includes all published studies (1) which use the modern concept of bipolar disorder, (2) measure lifetime risk of bipolar disorder in first degree relatives of a bipolar proband, and (3) in which at least some of the relatives were interviewed directly. There were 21 studies that met these criteria,14-34 of which eight included a sample of controls.17 24-26 30-32 34

Fig 1 shows the relative risk of narrowly defined bipolar disorder (equivalent to DSMIV bipolar I disorder) in first degree relatives of bipolar probands as a function of the number of subjects included in the study. Relative risk is defined as the ratio of risk of bipolar disorder in first degree relatives of bipolar probands to the risk in first degree relatives of controls or, for studies that did not include controls, to an assumed general population baseline risk of 1%. As can be seen, all of these studies showed an increased risk of bipolar disorder in the relatives of bipolar probands. Using the eight
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VHective disorder in co-twins of bipolar twin probands

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notype (including unipolar depression).

which both have narrowly defined bipolar disorder. BP-BP/UP refers to twin pairs in which one has bipolar disorder and the other has broadly defined bipolar phe-

MZ: monozygotic; DZ: dizygotic. Sample size refers to number of twin pairs in which at least one twin su-

43 Denmark twin and psychiatry registers. 34 MZ, 37 DZ pairs BP-BP: MZ: 62% Despite lack of operationalised diagnostic criteria this is

42 USA Veteran twin register. 5 MZ, 15 DZ pairs (out of 15 909

41 Norway twin and psychosis register. 6 MZ pairs with BP proband and sibs, several studies have reported only the pooled estimate of risk for all types of first degree relatives. The lifetime risk of affective disorder in relatives of a bipolar proband does not appear to vary with sex of relative or of the proband.27 30 32 Lifetime risk of affective disorder in relatives with bipolar probands increases with early age of onset28 and with number of ill relatives.24 There are no adequate data to provide meaningful estimates of the rates of affective disorder in second degree relatives of bipolar probands but available evidence suggests that the rates lie between those for first degree relatives and those for the general population.

Twin studies

Early twin studies, which did not distinguish between bipolar and unipolar illness, supported the involvement of genes in broadly defined mood disorders and are reviewed by Tsuang and Faraone.13 Six twin studies have used a modern concept of bipolar disorder and

It is an unresolved question as to whether the lifetime rates of illness in first degree relatives of bipolar probands vary according to type of relative (parent, offspring, or sib). Gershon et al27 found the risk in sibs to be greater than that in parents and offspring but in a later study Gershon et al41 found the difference to be reversed. Perhaps because of small sample sizes or because there appears to be no consistent difference between risks in parents, offspring, and sibs, several studies have reported only the pooled estimate of risk for all types of first degree relatives. The lifetime risk of affective disorder in relatives of a bipolar proband increases with early age of onset40 and with number of ill relatives.42 There are no adequate data to provide meaningful estimates of the rates of affective disorder in second degree relatives of bipolar probands but available evidence suggests that the rates lie between those for first degree relatives and those for the general population.

... that included their own control groups, a meta-analysis25 showed no evidence of heterogeneity between studies and provided an overall estimate of risk (as measured by odds ratios, OR, and 95% confidence intervals, CI) in first degree relatives of bipolar I probands of OR=7 (CI 5-10).

Family studies are also consistent in showing that first degree relatives of bipolar probands are at increased risk of unipolar major depression when compared with first degree relatives of controls. Indeed, the absolute risk of unipolar depression is higher than the absolute risk of bipolar disorder in the first degree relatives of a bipolar proband. However, because the background population lifetime prevalence of unipolar depression is substantially greater than that of bipolar disorder (of the order of 10% versus 1%), the relative increase in risk is much lower for unipolar disorder (of the order of a doubling of risk).34 It has been estimated that approximately 2/3-3/4 of cases of unipolar depression in the family of a bipolar proband are genetically bipolar, that is, share a common genetic susceptibility.35 Bipolar II disorder has been shown to occur with increased frequency in relatives of bipolar I probands compared with the general population24 27 32 and some workers believe it is the most common manifestation of the bipolar phenotype.36 However, others have suggested it is a separate disorder.37 Family studies have not shown an increase in the risk of schizophrenia in the relatives of bipolar probands, but have consistently shown familial aggregation of bipolar disorder and schizoaffective disorder in which manic features occur.

..
all show an increased probandwise concordance rate in monozygotic (MZ) twins when compared with dizygotic (DZ) twins\(^{41-46}\) (table 1). Pooling the data from these studies provides an estimate of probandwise MZ concordance for narrowly defined bipolar disorder of 50% (95% confidence intervals 40%-60%). However, three of the studies almost certainly underestimate the concordance so the true MZ concordance is likely to be >50%, probably close to the 60% found in the study of Bertelsen et al.\(^{41}\) Longitudinal study of the offspring of the unaffected members of discordant MZ twin pairs ascertained through a bipolar proband has shown an increase in risk of bipolar illness indistinguishable from that in the offspring of subjects affected by bipolar disorder.\(^{47}\)

Studies of genetically identical subjects illustrate the phenotypic spectrum that may be associated with bipolar susceptibility genes. In addition to bipolar disorder, unipolar disorder, or absence of illness, MZ co-twins or co-triplets of a bipolar proband have been described who have a diagnosis of schizoaffective disorder\(^{48}\) or (very rarely) schizophrenia.\(^{48}\) It should also be recognised that the incomplete phenotypic concordance in MZ twins has provided the most robust evidence that non-genetic factors play an important role in determining susceptibility to bipolar disorder.

### Adoption studies

Only two adoption studies have used a modern concept of bipolar disorder. Mendlewicz and Raine\(^{49}\) investigated the biological and adoptive parents of 29 bipolar and 22 normal adoptees and the biological parents of 31 bipolar non-adoptees and found significantly (p<0.05) greater risk of affective disorder (bipolar, schizoaffective, and unipolar) in the biological parents of bipolar adoptees (18% risk) compared with the adoptive parents (7% risk). This risk in biological relatives of bipolar adoptees was similar to that in the biological relatives of bipolar non-adoptees. The study of Wender et al.\(^{50}\) included only 10 bipolar probands but showed a similar (but non-significant) trend for biological relatives of probands to be at increased risk compared with adoptive relatives.

### Summary of epidemiological, family, twin, and adoption studies

Family, twin, and adoption studies provide an impressive and consistent body of evidence supporting the existence of genes determining predisposition to bipolar disorder and show a gradation in risk of mood disorder in relatives of bipolar probands in the order (highest to lowest risk) of: monozygotic co-twin, first degree relative, unrelated member of the general population. Although there are many methodological impediments to producing a consistent quantification of risk, the figures given in table 2 may be taken as an “order of magnitude” guide to risk in different classes of relative\(^{51}\) and, provided appropriate caveats are made, are suitable for providing information to patients and their relatives.

### Chromosome studies

Bipolar disorder is not consistently associated with chromosome abnormalities although a number of such published reports have appeared.\(^{52}\) Perhaps the most interesting observation is that subjects with trisomy 21 appear to be less susceptible to mania than are members of the general population.\(^{53}\) This is consistent with the existence of a bipolar susceptibility gene on chromosome 21, a possibility that finds support from recent molecular genetic studies (see table 3).

### Mode of inheritance

Early linkage studies were predicated on the assumption of single gene inheritance and attempts were made to recruit large unilineal apparently autosomal dominant pedigrees.

### Table 2: Approximate lifetime rates of mood disorder in various classes of relative of bipolar probands

<table>
<thead>
<tr>
<th>Degree of relationship to bipolar proband</th>
<th>Risk of bipolar disorder</th>
<th>(Additional) risk of unipolar depression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygotic co-twin</td>
<td>40–70</td>
<td>15–25</td>
</tr>
<tr>
<td>First degree relative</td>
<td>5–10</td>
<td>10–20</td>
</tr>
<tr>
<td>General population (ie, unrelated)</td>
<td>0.5–1.5</td>
<td>5–10</td>
</tr>
</tbody>
</table>

The lifetime risk of major mood disorder in a relative is obtained by adding the risk of bipolar disorder and the risk of unipolar depression. General population lifetime risk of unipolar depression is notoriously difficult to quantify but the figures in the table are based on a definition of clinically significant depression comparable to that used in the genetic studies.

<table>
<thead>
<tr>
<th>Chromosomal location</th>
<th>Study reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4p16</td>
<td>117</td>
<td>Single large UK pedigree with max lod = 4.8</td>
</tr>
<tr>
<td>12q23-2q24</td>
<td>119</td>
<td>Single moderate size UK pedigree (schizoaffective disorder) with max lod =1.9</td>
</tr>
<tr>
<td>12p22</td>
<td>122</td>
<td>Single UK pedigree in which Darin’s disease(^{50-51}) and bipolar disorder cosegregate. Max lod = 2.1</td>
</tr>
<tr>
<td>12q12</td>
<td>123</td>
<td>Single very large pedigrees from an isolated French Canadian community. Max lod = 4.9</td>
</tr>
<tr>
<td>18 centromeric</td>
<td>125</td>
<td>22 moderate size US pedigrees. Max non-parametric evidence p&lt;0.0001</td>
</tr>
<tr>
<td>18q11</td>
<td>126</td>
<td>28 moderate size US pedigrees (particularly those showing paternal transmission). Max non-parametric evidence p&lt;0.001</td>
</tr>
<tr>
<td>18q22</td>
<td>127</td>
<td>2 large Costa Rican pedigrees. Max lod for combined linkage association = 4.06</td>
</tr>
<tr>
<td>21q22</td>
<td>128</td>
<td>Single large US pedigree. Max lod = 3.4</td>
</tr>
<tr>
<td>22q13</td>
<td>129</td>
<td>22 moderate size US pedigrees (particularly those showing maternal transmission). Max lod = 2.2</td>
</tr>
</tbody>
</table>

This table illustrates some current regions of interest. Readers seeking a systematic overview of findings including both negative and positive reports should consult Chromosome Workshop reports (see text).
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Although rare, a number of such pedigrees have been identified and it seems likely that in at least some of these a single gene may play a major role in determining disease susceptibility. Some segregation analyses on systematically ascertained pedigree sets have produced results consistent with single gene models, while others have been unable to show major locus transmission. However, caution is required in interpreting these results because of the limited power of the studies to distinguish between single gene and oligogenic models and because of the failure to take account of an important parameter, the recurrence risk in MZ cotwins of a bipolar proband. The observed very rapid decrease in recurrence risk from identical co-twins to first degree relatives and back to the general population (as shown in table 2) is not consistent with single gene modes of inheritance. The recurrence risk data are consistent with epistatic interaction of multiple genes or with more complex genetic mechanisms. Several genetic mechanisms that are known to produce complex patterns of inheritance and which have been suggested as possible explanations for bipolar disorder are shown in table 4.

### Molecular genetic studies

Linkage and association studies using DNA markers are, of course, the cutting edge of modern approaches to complex genetic diseases. Conceptually, molecular genetic studies can be divided into positional and candidate gene approaches. In positional approaches, chromosomal locations of susceptibility genes are determined, usually by linkage studies. This requires no knowledge of disease pathophysiology and can be considered a purely genetic approach. In contrast, the candidate gene approach presupposes that the researcher has sufficient understanding of disease biology to be able to recognise genes that may be involved in bipolar disorder. These are then examined in linkage or, more usually, association studies. In practice both positional and candidate approaches are often combined. The principles behind, and applications of, these approaches are discussed in detail elsewhere.

#### LINKAGE STUDIES

Early linkage studies of bipolar disorder used very large families and were based on the implausible assumption that all illness was caused by a single major gene. In the late 1980s there were two high profile claims of linkage published in *The New England Journal of Medicine*: Baron et al. reported linkage to X chromosome markers in several Israeli pedigrees and Egeland et al. reported linkage to markers on chromosome 11p in a large pedigree of the Old Order Amish community in Pennsylvania. Other workers were unable to replicate these findings and eventually in both cases the original groups published updated and extended analyses of their own data in which the significant evidence of linkage all but vanished. The reasons for these dramatic reversals in findings included: (1) family members originally diagnosed as unaffected became ill for the first time during follow up; (2) new family members were examined who did not show evidence for linkage; and (3) additional DNA markers were examined which reduced the evidence for linkage. After initial pessimism following these disappointments, the field has moved forward with the development and use of research methodologies more appropriate for the investigation of complex genetic traits. There has been a trend towards use of smaller families (particularly affected sib pairs) and of analytic methods that are less sensitive to diagnostic changes or errors (reviewed by Craddock and Owen).

Several groups around the world are undertaking large scale molecular genetic linkage studies of bipolar disorder and promising findings are beginning to emerge. A variety of different types of sample set are being used ranging from single large densely affected pedigrees in genetic isolates to large numbers of affected sib pairs and systematic genome screens are being undertaken in many of these samples. The pattern of results emerging from these linkage studies supports the view that no single major gene exists that explains the majority of cases of bipolar disorder. Several features are emerging that are to be expected in the search for genes involved in a complex genetic

#### Table 4 Complex genetic mechanisms that have been suggested in bipolar disorder

<table>
<thead>
<tr>
<th>Genetic mechanism</th>
<th>Authors</th>
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<tbody>
<tr>
<td>Locus heterogeneity</td>
<td>Hodgkinson et al.</td>
</tr>
<tr>
<td>Allelic heterogeneity</td>
<td>Sandhui and Ort</td>
</tr>
<tr>
<td>Epistasis</td>
<td>Craddock et al.</td>
</tr>
<tr>
<td>Dynamic mutation</td>
<td>McAlpin et al.</td>
</tr>
<tr>
<td>Imprinting</td>
<td>McMahon et al.</td>
</tr>
<tr>
<td>Mitochondrial inheritance</td>
<td>McMahon et al.</td>
</tr>
</tbody>
</table>

Genetic mechanisms causing complex patterns of inheritance and authors who have invoked the mechanisms to explain the inheritance of bipolar disorder.
disorder.23–25 (1) No finding replicates in all data sets. (2) Levels of statistical significance and estimated effect sizes are usually modest. (3) Chromosomal regions of interest are typically broad (often >20-30 cM). (4) The same region may be implicated as (a) containing a susceptibility gene in large samples comprised of small families, and (b) harbouring a potential major locus within one or more large multiply affected pedigrees. (5) Some chromosome regions have been implicated in linkage studies of different psychiatric phenotypes. For example, 15q11-q13 is implicated in studies of both bipolar disorder and schizophrenia.26

Table 3 provides information about four regions that are attracting a great deal of interest in linkage studies of bipolar disorder. Of these 12q23-q24 and 21q22 are, perhaps, the most promising (as already mentioned, the reduced incidence of mania in trisomy 21 is consistent with a chromosome 21 locus27). Chromosome 18 is the most confusing with positive reports scattered throughout the chromosome in a pattern that is not consistent with a single susceptibility gene.28 Other regions of interest include 16p13,29 1q24-q26,30 and 15q11-q13.30 Detailed reviews of linkage data for each chromosome can be found in the chromosome workshop reports of the World Congress of Psychiatric Genetics, held annually. Reports from the Fifth World Congress held in Santa Fe, New Mexico, in 1997 were published in *Psychiatric Genetics* 1998;8(2). The report from the Sixth World Congress held in Bonn, Germany, in 1998 will be reported in *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 1999;88(3).

As is the case for most complex genetic disorders, methodological differences between linkage studies make conventional meta-analysis all but impossible. However, new methods of meta-analysis are being developed in which the comparison of genome scan results is based on ranking of chromosomal regions according to linkage evidence rather than absolute values of linkage statistics. The application of such approaches to bipolar disorder will provide a more systematic and unified overview of the evidence.

This is a rapidly moving field and new data are becoming available regularly. The reader who is interested in a specific chromosomal region is recommended to consult the most recent chromosome workshop reports and bibliographic databases.

**ASSOCIATION STUDIES**

For complex genetic disorders such as bipolar disorder, association studies represent an important experimental approach both to follow up regions of interest detected in linkage studies (using both systematic linkage disequilibrium mapping and positional candidate studies) as well as for pure functional candidate gene studies. Important advantages of the association paradigm are relative robustness to genetic heterogeneity and the ability to detect much smaller effect sizes than are detectable using feasible sample sizes in linkage studies.31

Several research groups are assembling large samples of unrelated probands and appropriate comparison subjects for use in linkage disequilibrium and candidate gene studies but robust positive findings have yet to emerge.

The candidate gene association approach is potentially very powerful, particularly when used within the context of a VAPSE (Variation Affecting Protein Sequence or Expression) paradigm.32 This approach involves systematic mutation/polymorphism detection in coding and control regions of candidate genes followed by association studies in disease comparison samples. Conventional association studies are susceptible to spurious associations resulting from inadequate matching of cases and controls, especially when there is population stratification. However, the recent development of family based association methods helps overcome this problem by allowing an artificial well matched notional control sample to be constructed from marker data from the family of each proband.33 Although several statistical approaches can be used in this design,34 the transmission disequilibrium test (TDT) has gained popularity.35 This advance has increased the attractiveness of association studies for genetic dissection of complex diseases and such samples are being developed for investigation of bipolar disorder.

The main problem with candidate gene approaches is that efficiency in the choice of candidates is inevitably a function of the level of previous understanding of disease pathophysiology. To date, most candidate gene studies in bipolar disorder (and in other psychiatric phenotypes) have focused on the major neurotransmitter systems that are influenced by medication used in clinical management of the disorder. Thus, studies of known polymorphisms have been conducted for several genes encoding receptors or proteins and enzymes involved in metabolism or re-uptake of dopamine, serotonin (5HT), and noradrenaline.

No convincing positive findings have yet emerged although several studies have provided tantalising, albeit modest, evidence implicating the serotonin transporter gene (*hSERT*).36–40 This gene is undoubtedly an excellent functional candidate because it is the site of action of selective serotonin re-uptake inhibitors, a major class of antidepressants of which fluoxetine (Prozac™) is a well known member, which are effective in treatment of bipolar depression and can also induce mania in bipolar subjects. The picture is still far from clear36–44 and *hSERT* is certainly not a gene of major effect, but results are consistent with a modest influence on disease susceptibility. Confirmation of such an effect will require replication in large independent samples from different populations and will ultimately require demonstration of the pathogenic relevance of polymorphisms within tissue and animal systems.

A deeper understanding of the pathogenesis of bipolar disorder will almost certainly include systems involved in signal transduction and modulation of gene expression and, as genes involved in these systems are cloned, candidate gene association studies will offer the oppor-
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inconclusive results regarding the familiality of
sants. Although family studies have produced
by some medications, including antidepres-
more common in females, and may be induced
disorder within a 12 month period, occurs in a
four or more discrete episodes of mood
RAPID CYCLING
forms of the disorder. A number of such
represent more genetically homogeneous
specific phenotypic subtypes known or thought
to rapid cycling within bipolar patients.107–109
One of the groups with the positive RED find-
compared with controls.106 However, some
have shown trinucleotide repeat sequences to
be significantly larger in bipolar patients
in agreement with this hypothesis, four independent association studies using the
repeat expansion detection (RED) method have
trinucleotide repeat sequences to
be significantly larger in bipolar patients
controlled.26 However, some
studies have failed to find this association.108 One
of the groups with the positive RED finding has reported that most of the large RED
products may be explained by two specific loci,
CTG18.1 and ERDA7,102 and that CTG18.1 shows a modest association with bipolar disor-
however, this finding awaits confirmation.
Furthermore, if one or more trinucleotide repeat containing loci are confirmed as playing a role in bipolar disorder, it appears likely (1) that the genotype-phenotype correlation in bipolar disorder will prove to be more compli-
cated than is the case for trinucleotide repeat
diseases previously described (for example, Huntington’s disease), and (2) that trinucleo-
tide repeat containing genes involved in bipolar
disorder may operate as susceptibility genes
rather than as a single gene of major effect.105
Subtypes of bipolar disorder
One of the principles that can be used to
increase the power to detect genes involved in
complex diseases is to focus investigation on
specific phenotypic subtypes known or thought
to represent more genetically homogeneous
forms of the disorder. A number of such
potentially useful subtypes are known in bipol-
ard disorder and researchers are beginning to
take an interest in these.
Rapid cycling, defined as the occurrence of
four or more discrete episodes of mood
disorder within a 12 month period, occurs in a
substantial proportion of bipolar patients, is
more common in females, and may be induced
by some medications, including antidepres-
sants. Although family studies have produced
inconclusive results regarding the familiality of
rapid cycling, recent candidate gene associa-
tion studies suggest that the low activity
allele at a common polymorphism within the
catechol-o-methyl transferase (COMT) gene
may be associated with increased susceptibility
to rapid cycling within bipolar patients.
This observation has biological consistency with the observed tendency for antidepressants
to induce rapid cycling in that both increase
availability of catecholamines at neuronal
synapses. However, this genetic finding re-
quires confirmation in large independent sam-
ple and, even if confirmed, makes only a mod-
est contribution to rapid cycling.
SEASONAL AFFECTIVE DISORDER
Seasonal affective disorder (SAD) describes
mood disorder with a characteristic seasonal
variation. Many subjects with SAD are bipolar.
Genes have been shown to influence seasonal
variation in mood and SAD has been shown to
gather in families. Biological systems that have been implicated in the pathogenesis
of SAD include systems involved in serotoner-
gic neurotransmission and circadian and cir-
cannual clocks.
PUERPERAL PSYCHOSIS
Puerperal psychosis refers to severe (usually
psychotic) psychiatric disorder occurring
within a few weeks of parturition.113 The vast
majority of subjects who suffer episodes of
puerperal psychosis have a bipolar disorder
diathesis together with a susceptibility to puer-
peral triggering of episodes (frequently manic).
There is strong evidence that the puerperal
trigger is familial (Jones and Craddock, unpub-
lished data) and plausible biological systems
include steroid hormone pathways.
The future
Several groups around the world are assem-
bbling the large clinical samples needed for the
genetic dissection of bipolar disorder using
currently available methodologies and collabo-
ration will undoubtedly be necessary to identify
genes of relatively modest effect. The trend for
fing methods to become increasingly
automated with dramatic increases in ef-
ciency will undoubtedly continue and novel
molecular methods may become available that
will eventually supersede current linkage and
association studies. Such technological ad-
ances, in the context of completion of the
Human Genome Project in the first years of the
next millennium, should facilitate the identifi-
cation of bipolar susceptibility genes of even
small effect. Current biological research in
bipolar disorder is constrained by the lack of
an animal model. Once susceptibility genes are
covered, it should prove possible to breed
transgenic mice (or other species) that include
the abnormal form of the gene, thereby provid-
ing a model in which the disease process can be
studied in vivo.
Identification of genetic mechanisms confer-
rung susceptibility to bipolar disorder will, of
course, be a major achievement. However, this
will not be an end in itself but rather the begin-
ing of a path that will lead towards an under-
standing of the biological underpinnings of
bipolar and related mood disorders. It is quite
likely that along this path we will learn much
about the biological basis of normal affective
responses. In this regard it is interesting to note
that a recent twin study showed that normal happiness is in large part under genetic influence.15

Major benefits will accrue from the research that will follow identification of genes involved in the pathogenesis of bipolar disorder. Knowledge of a gene that confers susceptibility to illness will allow identification of its gene product which will in turn lead to an understanding of the role of the individual protein in disease causation, including its interaction with other substances and the effect of environmental changes on protein level and function. This level of understanding will allow the development of therapeutic agents that are much more specifically targeted at the biochemical lesions involved in disease. It will be possible to develop a rational, aetiology based classification of bipolar and related disorders which will almost certainly provide a much better guide to treatment and prognosis than do current classifications. A new generation of psychiatrists will learn not only to recognise clinical syndromes, as at present, but will be able to perform laboratory tests that will help determine the pathogenesis of the psychopathology which will in turn guide the clinician towards the most appropriate therapy. Importantly, identification of these susceptibility genes will facilitate identification of environmental factors that confer risk or are protective, both in people who are not genetically susceptible and in those who have a high level of genetic risk. Once these environmental factors are characterised, it may prove possible to provide helpful occupational, social, and psychological advice to those at genetic risk of bipolar disorder.

It must not be forgotten that major advances raise major ethical issues. Although many of the issues in psychiatric genetics are no different from those for other common familial disorders, this combination of genetics and mental illness justifiably excites and receives particularly close scrutiny of ethical and psychosocial issues.16 Areas that will need to be addressed include the availability of services, the right to information, and the possibility of testing of subjects below the age of consent. The challenge to psychiatrists in the 21st century is to ensure that a revolution in understanding of the biology of bipolar disorder is translated into a revolution in clinical care. Our patients deserve nothing less.

Ian Jones is a Wellcome Trust Research Fellow in Mental Health. Nick Craddock is a Wellcome Trust Senior Research Fellow in Clinical Sciences.


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