

## Review article

## 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.**

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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, which may include psychotic symptoms, such as delusions and hallucinations. Typically it is an episodic illness, usually with full recovery between episodes. In all modern classifications, such as ICD10<sup>1</sup> or DSMIV<sup>2</sup>, the diagnosis of bipolar disorder requires that a person has suffered one or more episodes of mania with or without episodes of depression at other times during the life history. This requirement for the occurrence of an episode of mania at some time during the course of illness distinguishes bipolar disorder from the more common form of mood disorder in the population, namely unipolar disorder (also commonly known as unipolar major depression or simply unipolar depression) in which subjects suffer one or more episodes of depression without ever experiencing episodes of pathologically raised mood. Although bipolar and unipolar disorders are not completely distinct nosological entities, their separation for the purposes of diagnosis and research is supported in evidence from outcome, treatment, and genetic studies.<sup>3,4</sup> In DSMIV, bipolar disorder is subclassified into bipolar I disorder, in which episodes of clear cut mania occur, and bipolar II disorder, in which only milder forms of mania (so-called "hypomania") occur. However, this subclassification awaits robust validation.

Studies using modern operational diagnostic criteria suggest that lifetime prevalence of narrowly defined bipolar disorder is in the region of 0.5-1.5% with similar rates in males and females and a mean age of onset around the age of 21 years.<sup>5</sup> Currently there is no evidence that rates of bipolar disorder vary widely among different populations. Bipolar disorder is associated with high levels of service use and morbidity and it has been estimated that approximately 15% of patients eventually die by suicide.<sup>6</sup> Reasonably effective treatments are available for both manic and depressive phases of illness and lithium, and more recently a variety of anticonvulsants, have been used prophylactically as mood stabilisers to reduce recurrence of acute episodes of depression and mania.<sup>7</sup> However, current treatments have

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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.<sup>8 9</sup>

#### 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.<sup>10 11</sup> However, this effect may be an artefact of research methodology<sup>12</sup> 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

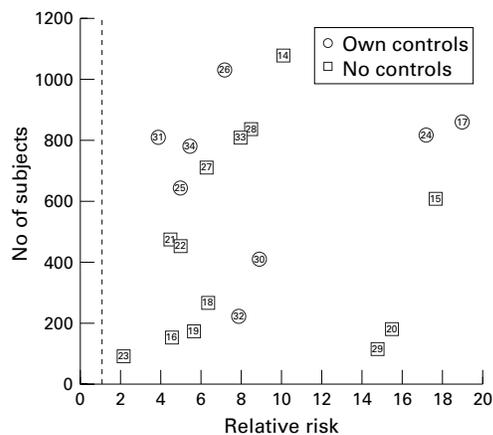
#### UNKNOWN DIAGNOSTIC VALIDITY

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,<sup>3 4</sup> 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.<sup>13</sup> 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,<sup>14-34</sup> of which eight included a sample of controls.<sup>17 24-26 30-32 34</sup> 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



**Figure 1** Family studies of bipolar disorder. The relative risk of narrowly defined bipolar disorder (equivalent to DSMIV bipolar I disorder) in first degree relatives of bipolar probands is shown 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% (see text for further details). Numbers refer to papers in reference list. All studies can be seen to give a relative risk of greater than one (dashed line) and therefore provide evidence of familial aggregation of bipolar disorder.

studies<sup>17, 24–26, 30–32, 34</sup> that included their own control groups, a meta-analysis<sup>35</sup> 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).<sup>36</sup> 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.<sup>37</sup> Bipolar II disorder has been shown to occur with increased frequency in relatives of bipolar I probands compared with the general population<sup>24, 27, 32</sup> and some workers believe it is the most common manifestation of the bipolar phenotype.<sup>38</sup> However, others have suggested it is a separate disorder.<sup>39</sup> 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.<sup>24, 27, 31, 34</sup>

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 al*<sup>17</sup> found the risk in sibs to be greater than that in parents and offspring but in a later study Gershon *et al*<sup>24</sup> 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 does not appear to vary with sex of relative or of the proband.<sup>27, 30, 32</sup> Lifetime risk of affective disorder in relatives with bipolar probands increases with early age of onset<sup>40</sup> and with number of ill relatives.<sup>24</sup> 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.<sup>13</sup> Six twin studies have used a modern concept of bipolar disorder and

**Table 1** Lifetime rates of affective disorder in co-twins of bipolar twin probands

| Ref No | Sample  | Lifetime rates of affective illness in co-twin of bipolar twin probands (probandwise concordance rate) | Comment   |
|--------|---|--|---|
| 41     | Norway twin and psychosis register. 6 MZ pairs with BP proband                      | BP-BP: MZ: 67%   | Small sample and no operationalised diagnostic criteria   |
| 42     | USA Veteran twin register. 5 MZ, 15 DZ pairs (out of 15 909 twin pairs on register) | BP-BP: MZ: 20%   |   |
| 43     | Denmark twin and psychiatry registers. 34 MZ, 37 DZ pairs                           | BP-BP: MZ: 62%   | Despite lack of operationalised diagnostic criteria this is a detailed study and is the best available  |
|        |   | DZ: 8%   |   |
| 44     | Norway twin register. 4 MZ, 6 DZ pairs  | BP-BP/UP: MZ: 79%  | Small sample which may overlap partly with that of ref 41   |
|        |   | DZ: 19%  |   |
| 45     | Sweden twin and psychiatric registers. 13 MZ, 22 DZ pairs                           | BP-BP: MZ: 75%   | This has the strength of being a large epidemiological twin sample but the weakness of using questionnaire assessments. Likely to underestimate concordance |
|        |   | DZ: 0%   |   |
| 46     | UK psychiatric hospital twin register. 22 MZ, 27 DZ pairs                           | BP-BP/UP: MZ: 100%   | Diagnoses based on hospital notes. Likely to underestimate concordance  |
|        |   | DZ: 0%   |   |
| 45     | Sweden twin and psychiatric registers. 13 MZ, 22 DZ pairs                           | BP-BP: MZ: 39%   | This has the strength of being a large epidemiological twin sample but the weakness of using questionnaire assessments. Likely to underestimate concordance |
|        |   | DZ: 5%   |   |
| 46     | UK psychiatric hospital twin register. 22 MZ, 27 DZ pairs                           | BP-BP/UP: MZ: 62%  | Diagnoses based on hospital notes. Likely to underestimate concordance  |
|        |   | DZ: 14%  |   |
| 46     | UK psychiatric hospital twin register. 22 MZ, 27 DZ pairs                           | BP-BP: MZ: 36%   | Diagnoses based on hospital notes. Likely to underestimate concordance  |
|        |   | DZ: 7%   |   |

MZ: monozygotic; DZ: dizygotic. Sample size refers to number of twin pairs in which at least one twin suffered with bipolar disorder. BP-BP refers to twin pairs in 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 phenotype (including unipolar depression).

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

| Degree of relationship to bipolar proband | Risk of bipolar disorder (%) | (Additional) risk of unipolar depression (%) |
|---|------------------------------|--|
| Monozygotic co-twin                       | 40–70                        | 15–25  |
| First degree relative                     | 5–10                         | 10–20  |
| General population (ie, unrelated)        | 0.5–1.5                      | 5–10   |

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.

all show an increased probandwise concordance rate in monozygotic (MZ) twins when compared with dizygotic (DZ) twins<sup>41–46</sup> (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.*<sup>43</sup> 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.<sup>47</sup>

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 cotriplets of a bipolar proband have been described who have a diagnosis of schizoaffective disorder<sup>43</sup> or (very rarely) schizophrenia.<sup>48</sup> 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 Rainer<sup>49</sup> 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.*<sup>50</sup> 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<sup>51</sup> 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.<sup>52</sup> 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.<sup>53</sup> 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 3 Some regions of interest from molecular genetic linkage studies of bipolar disorder

| Chromosomal location | Study reference | Comment   |
|----------------------|-----------------|---|
| 4p16                 | 117             | Single large UK pedigree with max lod = 4.8   |
|                      | 118             | Single moderate size UK pedigree (schizoaffective disorder) with max lod = 1.9  |
| 12q23–q24            | 119             | Single UK pedigree in which Darier's disease <sup>120 121</sup> and bipolar disorder cosegregate. Max lod = 2.1           |
|                      | 122             | 29 small-moderate UK pedigrees. Max lod = 2.0. No evidence in 16 German families  |
|                      | 123             | Single very large pedigree from an isolated French Canadian community. Max lod = 4.9                                      |
|                      | 124             | 2 moderate size Danish pedigrees. Max lod = 3.4   |
| 18 centromeric       | 125             | 22 moderate size US pedigrees. Max non-parametric evidence $p < 0.0001$   |
|                      | 126             | 28 moderate size US pedigrees (particularly those showing paternal transmission). Max non-parametric evidence $p < 0.001$ |
| 18q22                | 126             | 28 moderate size US pedigrees (particularly those showing paternal transmission). Max sib pair evidence $p < 0.001$       |
|                      |                 | 2 large Costa Rican pedigrees. Max lod for combined linkage association = 4.06  |
| 18q22–q23            | 127             | Single large US pedigree. Max lod = 3.4   |
|                      | 128             | 22 moderate size US pedigrees (particularly those showing maternal transmission). Max sib pair evidence $p < 0.001$       |
| 21q22                | 129             | 22 moderate size US pedigrees (particularly those showing maternal transmission). Max sib pair evidence $p < 0.001$       |
|                      | 130             | 97 moderate size US pedigrees. Max sib pair evidence $p < 0.001$  |
|                      | 131             | 23 UK & Icelandic pedigrees. Max lod = 2.2  |

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).

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

| Genetic mechanism         | Authors                                |
|---------------------------|--|
| Locus heterogeneity       | Hodgkinson <i>et al</i> <sup>132</sup> |
| Allelic heterogeneity     | Sandkuyl and Ott <sup>133</sup>        |
| Epistasis                 | Craddock <i>et al</i> <sup>60</sup>    |
| Dynamic mutation          | McInnis <i>et al</i> <sup>134</sup>    |
| Imprinting                | McMahon <i>et al</i> <sup>135</sup>    |
| Mitochondrial inheritance | McMahon <i>et al</i> <sup>135</sup>    |

Genetic mechanisms causing complex patterns of inheritance and authors who have invoked the mechanisms to explain the inheritance of bipolar disorder.

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,<sup>27 30 54 55</sup> while others have been unable to show major locus transmission.<sup>56-58</sup> 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.<sup>59</sup> 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.<sup>60</sup> 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.

#### X LINKAGE

The idea that X linkage may explain some forms of affective disorder goes back over half a century<sup>61</sup> and has been debated vigorously over the last 25 years because of several reports of families showing cosegregation between X linked markers (such as colour blindness or glucose-6-phosphate dehydrogenase deficiency) and bipolar disorder, suggesting the possibility of an X linked dominant susceptibility gene.<sup>62-64</sup> However, these reports have been criticised on methodological grounds,<sup>65</sup> particular problems being ascertainment bias and non-blinding to marker status. If X linkage does occur, analyses suggest that it can account for only a minority of cases.<sup>56 66</sup>

In summary, as clinical psychiatrists are well aware, although bipolar disorder tends to aggregate in families, the pattern of inheritance in most pedigrees is not simple. Although it seems likely that occasional families exist in which a single gene plays a major role in determining susceptibility to illness, the evidence indicates that single gene transmission does not occur in most cases. This observation is consistent with the failure to identify genes of major effect in linkage studies predicated on single gene models.

#### 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.<sup>67</sup> The principles behind, and applications of, these approaches are discussed in detail elsewhere.<sup>68</sup>

#### 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 journal *Nature*: Baron *et al*<sup>64</sup> reported linkage to X chromosome markers in several Israeli pedigrees and Egeland *et al*<sup>69</sup> 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.<sup>70 71</sup> 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<sup>68</sup>).

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<sup>69</sup> to large numbers of affected sib pairs<sup>72</sup> 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

disorder.<sup>73-75</sup> (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.<sup>76</sup>

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 locus<sup>53</sup>). 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.<sup>77</sup> Other regions of interest include 16p13,<sup>78</sup> Xq24-q26,<sup>79</sup> and 15q11-q13.<sup>76</sup> 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.<sup>80</sup> 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.<sup>81</sup> 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.<sup>82</sup> Although several statistical approaches can be used in this design,<sup>83</sup> the transmission disequilibrium test (TDT) has gained popularity.<sup>84</sup> 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 noradrenalin. No convincing positive findings have yet emerged although several studies have provided tantalising, albeit modest, evidence implicating the serotonin transporter gene (*hSERT*).<sup>85-89</sup> 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<sup>TM</sup>) 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 clear<sup>90-94</sup> 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-

tunity to explore their role in the pathogenesis of bipolar disorder.

#### TRINUCLEOTIDE REPEAT EXPANSION (DYNAMIC MUTATION)

For several neurological/neuropsychiatric diseases, such as Huntington's disease, myotonic dystrophy, and fragile X syndrome, the clinical phenomenon of anticipation (progressively more severe disease/earlier age at onset as the disease is transmitted through successive generations) occurs and is caused by DNA sequences of trinucleotide repeats that expand as they are passed from parent to offspring.<sup>95</sup> Anticipation has been reported in some recent studies of bipolar disorder and it has been hypothesised that trinucleotide repeat expansion may play a role in the pathogenesis of bipolar disorder (reviewed by O'Donovan and Owen<sup>95</sup>). In agreement with this hypothesis, four independent association studies using the repeat expansion detection (RED) method<sup>96</sup> have shown trinucleotide repeat sequences to be significantly larger in bipolar patients compared with controls.<sup>97-100</sup> However, some studies have failed to find this association.<sup>101</sup> 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,<sup>102</sup> and that CTG18.1 shows a modest association with bipolar disorder. 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 complicated than is the case for trinucleotide repeat diseases previously described (for example, Huntington's disease), and (2) that trinucleotide repeat containing genes involved in bipolar disorder may operate as susceptibility genes rather than as a single gene of major effect.<sup>103</sup>

#### 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.<sup>74</sup> A number of such potentially useful subtypes are known in bipolar disorder and researchers are beginning to take an interest in these.

#### RAPID CYCLING

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 antidepressants. Although family studies have produced inconclusive results regarding the familiarity of rapid cycling,<sup>104-106</sup> recent candidate gene association 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.<sup>107-109</sup>

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 requires confirmation in large independent samples and, even if confirmed, makes only a modest 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<sup>110</sup> and SAD has been shown to aggregate in families.<sup>111</sup> Biological systems that have been implicated in the pathogenesis of SAD include systems involved in serotonergic neurotransmission and circadian and circannual clocks.<sup>112</sup>

#### PUERPERAL PSYCHOSIS

Puerperal psychosis refers to severe (usually psychotic) psychiatric disorder occurring within a few weeks of parturition.<sup>113</sup> The vast majority of subjects who suffer episodes of puerperal psychosis have a bipolar disorder diathesis together with a susceptibility to puerperal triggering of episodes (frequently manic). There is strong evidence that the puerperal trigger is familial (Jones and Craddock, unpublished data) and plausible biological systems include steroid hormone pathways.<sup>114</sup>

#### The future

Several groups around the world are assembling the large clinical samples needed for the genetic dissection of bipolar disorder using currently available methodologies and collaboration will undoubtedly be necessary to identify genes of relatively modest effect. The trend for genotyping methods to become increasingly automated with dramatic increases in efficiency will undoubtedly continue and novel molecular methods may become available that will eventually supersede current linkage and association studies. Such technological advances, in the context of completion of the Human Genome Project in the first years of the next millennium, should facilitate the identification 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 discovered, it should prove feasible to breed transgenic mice (or other species) that include the abnormal form of the gene, thereby providing a model in which the disease process can be studied *in vivo*.

Identification of genetic mechanisms conferring susceptibility to bipolar disorder will, of course, be a major achievement. However, this will not be an end in itself but rather the beginning of a path that will lead towards an understanding 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.<sup>115</sup>

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 bipolar 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.<sup>116</sup> 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.

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