

Genetic studies of bipolar affective disorder in large families

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Background Genetic factors are known to be important in the aetiology of bipolar disorder.

Aims To review linkage studies in extended families multiply affected with bipolar disorder.

Method Selective review of linkage studies of bipolar disorder emphasising the gains and drawbacks of studying large multiply-affected families and comparing the statistical methods used for data analysis.

Results Linkage of bipolar disorder to several chromosome regions including 4p, 4q, 10p, 12q, 16p, 18q, 21q and Xq has first been reported in extended families. In other families chromosomal rearrangements associated with affective illnesses provide signposts to the location of disease-related genes. Statistical analyses using variance component methods can be applied to extended families, require no prior knowledge of the disease inheritance, and can test multilocus models.

Conclusion Studying single large pedigrees combined with variance component analysis is an efficient and effective strategy likely to lead to further insights into the genetic basis of bipolar disorders.

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LINKAGE IN LARGE FAMILIES

Linkage analysis has been highly effective when used to identify the genes responsible for monogenic disorders, such as cystic fibrosis and Huntington's disease, but has been less consistent when applied to genetically complex conditions such as bipolar disorder, which are likely to be influenced by multiple genetic loci and by non-genetic environmental effects (Risch & Botstein, 1996). The lack of consistent findings from genome-wide linkage studies in bipolar disorder may be due to non-significant effects being reported or because different genes and/or different alleles at these genes are causing illness in different families and populations. Indeed, the hypothesis that different relatively uncommon alleles are segregating in different families would predict a lack of consistent findings across linkage studies based on sibling pairs or small families, since the power of the linkage approach is greatly reduced for diseases that show genetic heterogeneity (Terwilliger & Weiss, 1998). Bipolar disorder is likely to be genetically heterogeneous; mutations in one of several independent genes may produce a similar clinical phenotype and different mutations in the same gene may cause a variety of related symptoms. Another possible model is that the clinical symptoms of the affective disorders can be viewed as continuous variables, called quantitative traits, that are produced by the additive or interactive effects of mutations in two or more genes. Under this model, each gene – termed a quantitative trait locus (QTL) – has only a small effect on the trait, and symptoms develop as a result of the cumulative effects of mutations in several genes, probably combined with other internal and external environmental risk factors. In these situations there is also an advantage in studying single large pedigrees where the disease is likely to be caused by a more limited number of interacting genes and environmental factors.

The study of multiply-affected families with sufficient power on their own to generate significant evidence for linkage remains one of the most promising strategies to find genes implicated in bipolar disorder and other psychiatric conditions that may be characterised by extreme allelic complexity. Several chromosomal regions have been initially identified by linkage analysis in single families. These include chromosome 4p, reported in three studies of four extended pedigrees (Blackwood *et al*, 1996; Asherson *et al*, 1998; Ewald *et al*, 1998a); chromosome 4q (Adams *et al*, 1998); chromosome 10p (Armstrong *et al*, 1997); chromosome 12q, where bipolar disorder, initially found to associate with Darier's disease (Craddock *et al*, 1994), was found to show linkage in large pedigrees studied independently (Barden *et al*, 1996; Ewald *et al*, 1998b; Morissette *et al*, 1999); chromosome 16p (Ewald *et al*, 1995); chromosome 18q (Freimer *et al*, 1996); chromosome 21q (Straub *et al*, 1994); and chromosome Xq (Pekkarinen *et al*, 1995). The Old Order Amish, one of the largest extended families studied so far, has yielded several regions of suggestive linkage (Ginns *et al*, 1996; LaBuda *et al*, 1996) and the intriguing finding on chromosome 4p of an apparent 'protective' locus in the same region where linkage to a susceptibility locus has been identified in other families (Ginns *et al*, 1998). All of these studies illustrate some of the advantages of working with large families. The penetrance and mode of inheritance may vary between different populations but can often be defined more clearly within one family where information about the presence of anticipation, imprinting and other factors is also likely to be available. It is likely that within a single family the influence of one or a small number of genes will be paramount and hence detectable. However, there are limitations to using large families. Disease in a family may be derived not from one but from several founders, or the disease may be the result of rare genetic causes that explain an insignificant fraction of the condition in a wider population. Despite these limitations, identifying any gene contributing to bipolar illness would be a significant advance and would point to other genes related by sequence or function.

FAMILIES WITH CHROMOSOME ABNORMALITIES

Karyotype abnormalities associated with the development of a medical illness can

point directly to chromosomal regions that contain candidate disease genes and have played a key role in the search for genes for many genetic conditions. If the anomaly is inherited, its co-segregation with a specific illness can be tested by linkage. Moreover, if the size of available pedigree is small then the chance of true association is increased if the chromosomal abnormality lies within a region where linkage or association has been previously reported in other families.

A balanced reciprocal chromosomal translocation t(1;11)(q42.1;q14.3) has been found to co-segregate with several major psychiatric disorders, including severe recurrent major depressive disorder and schizophrenia, in a large Scottish pedigree (St Clair *et al*, 1990). A recent follow-up of this family has identified additional subjects with the translocation who have developed major psychotic illness, including bipolar disorder (Blackwood *et al*, 1998). Systematic physical mapping of the break-points of this translocation has revealed disrupted coding sequences on chromosome 1 that represent candidate genes for the psychoses within this family (Muir *et al*, 1995; Millar *et al*, 2000, 2001).

A rare chromosomal abnormality, inv(18)(p11.3;q21.1), has been described in separate Danish and Scottish families (Mors *et al*, 1997). The inversion is associated with bipolar disorder in one family and schizophrenia in the other. The break-points lie within the linkage regions on the long and short arms of chromosome 18 and it may be hypothesised that they have disrupted genes at one or both breakpoints (Hampson *et al*, 1999).

STATISTICAL ANALYSES

Model-based linkage analysis in single extended pedigrees requires prior specification of the mode of inheritance, penetrance and population frequency of the trait. Since none of these variables in bipolar disorder is known for certain, a high rate of false positive or negative linkage findings are likely. Recently, there has been renewed interest in variance-based methods to detect QTLs for complex traits (Almasy & Blangero, 1998). These methods do not specify any particular genetic model but identify regions of the genome which explain a significant amount of the phenotypic variation in the trait. These regions are then the best

CLINICAL IMPLICATIONS

- Understanding genetic risk factors in bipolar disorder may:
- Form the basis of a biological classification of the disorder.
- Guide the search for new drug therapies.
- Suggest preventative measures.

LIMITATIONS

- A single family may express an uncommon form of a disease and give findings of limited application to the general population. An example is that of the *BRCA* genes which explain much of the variance in breast cancer in some affected families but less of the variance in the population as a whole.
- The resolution for linkage in single families is limited by the relatively small number of meioses available for study: a typical linkage region will be 5–30 centimorgans. Linkage disequilibrium methods which essentially use historical meioses may reduce the mapping resolution to less than 1 centimorgan.
- Linkage results in extended pedigrees may be confounded by inbreeding or the presence of several founders.

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estimates for the location of a QTL. When data from a single large pedigree that showed significant linkage between bipolar disorder and markers on chromosome 4p were re-analysed using a variance component method, the results confirmed that this more robust approach can be successfully used for the analysis of data from a single pedigree (Visscher *et al*, 1999). The variance component method, unlike linkage analysis, can distinguish between polygenic variation and single-gene effects. In addition, this model can include factors and covariates such as cohort or gender effects and allow other random effects which cause the observations to be correlated, such as a common environmental effect. Furthermore, variance models can be extended to multiple QTLs, making it possible to examine for epistatic interactions between loci in a family, and can be applied also to multiple traits simultaneously.

CONCLUSION

The dramatic successes of linkage studies in identifying genes for neuropsychiatric disorders, such as Huntington's disease and Alzheimer's disease, have not yet been matched in the affective disorders. Linkage strategies based on affected sibling pairs or many small families have limited power if the disease phenotype can be caused by variation in one of many genes in a population. In diseases with marked allelic complexity much can be learned by examining single large families, even when these show atypical clinical phenotypes. These include inbred or geographically isolated pedigrees, families with chromosomal abnormalities co-segregating with illnesses, and families with mental illness and comorbid conditions such as learning disabilities or deafness. In these families the search for linkage is facilitated because only one or a

few loci may be responsible for the trait. To identify even a rare locus could point the way to other causes of bipolar disorder.

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