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Chromosomal Aberrations and Bipolar Affective Disorder

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Chromosomal abnormalities associated with bipolar disorder may help in the localisation of susceptibility genes for bipolar illness by pinpointing 'candidate' regions of the genome for further study using molecular genetic methods. We review descriptions of chromosomal abnormalities in association with bipolar and related affective disorders and evaluate their relevance for localising susceptibility genes for bipolar disorder, using standardised criteria. We found 28 reports. We identified four genomic regions of potential interest: 11q21-25; 15q11-13; chromosome 21; Xq28. It is important that clinicians are able to recognise patients who may have chromosome abnormalities which could help in the localisation of susceptibility genes for psychiatric disorders. We suggest referral for specialist investigation and karyotyping, to a psychiatric genetics research group, of any patient with functional psychosis and one or more of the following: (a) a strong family history of functional psychosis; (b) mental retardation; (c) another disease known to be caused by a single gene; or (d) congenital abnormalities.

There is compelling evidence from family, twin and adoption studies for the existence of important genetic factors determining susceptibility to bipolar affective disorder (Craddock & McGuffin, 1993). However, the mode of inheritance is unknown. Simple Mendelian transmission may occur in some families but cannot explain the majority of cases. With the advent of polymorphic DNA markers, linkage and association studies have become more useful methods for the genetic analysis of complex disorders such as affective illness. No consistent findings have yet emerged (Craddock & McGuffin, 1993). An important problem in performing molecular genetic studies in psychiatry is deciding which parts of the genome to search for susceptibility loci. A random or systematic 'genome search' may ultimately prove necessary but examining 'candidate' regions may be a particularly efficient search strategy. A region is a 'candidate' if there exists some *a priori* evidence that a susceptibility locus may be located within it. This evidence may come from the discovery of cytogenetic abnormalities associated with bipolar disorder. If bipolar disorder is associated with a chromosomal abnormality, the location of the chromosomal material disrupted by the aberration can be examined in linkage and association studies. This approach has been used successfully in helping to identify the genes for several disorders including Duchenne muscular dystrophy, familial polyposis coli and familial Alzheimer's disease (Collins, 1992).

Bassett (1992) reviewed autosomal chromosomal aberrations in schizophrenia. We present a review of both autosomal and sex chromosomal aberrations in bipolar disorder. We have used methodology similar to Bassett's in order to aid comparison between the reviews.

Method

We performed a Medline search from January 1966 to July 1992 using the search strategy 'bipolar disorder' or 'affective disorders' or 'depressive disorder' and 'chromosomal ab*'. We examined textbooks cataloguing chromosomal aberrations, textbooks of psychiatric disorders in mentally handicapped individuals and also Bassett's (1992) review article on chromosomal abnormalities in schizophrenia, for cases in which the most likely diagnosis for the psychiatric disorder was affective disorder. We assessed the relevance of each reported abnormality for localising major genes for bipolar disorder by assigning consensus ratings on each of four relevancy scales, using a modification of the arbitrary standardised criteria developed by Bassett (1992) for schizophrenia, namely, substituting bipolar disorder for schizophrenia and modifying the specificity criteria to allow a rating of 2 for bipolar probands with a *de novo* chromosome abnormality and no family history of psychiatric disorder, and a rating of 1 for bipolar probands with a *de novo* chromosome abnormality and a positive family history of psychiatric illness. (A detailed description of the criteria used in the current report is available from the authors.)

Results

We found reports of seven cytogenetic surveys of samples of psychiatric patients which included subjects with affective disorder. Six individuals with affective disorder and cytogenetic abnormality were found and these are included in Table 1. No consistent associations between cytogenetic abnormality in general or between any specific abnormality and affective disorder emerged from these surveys. In addition to these surveys we found 22 reports of

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Table 1
Relevancy ratings of reported chromosomal abnormalities associated with bipolar and related disorders

Reference	Chromosomal site	Details	Total score	Diagnosis	Family history	Specificity	Weight of evidence
St Clair *et al* (1990)	1q43	See 11q21	7	3	2	1	1
Holland & Gosden (1990)	6q14.2	See 11q25	6	2	1	2	1
Smith *et al* (1989)	9p22	See 11q22.3	8	3	2	2	1
Crandall *et al* (1970); Adams *et al* (1970) (same patient)	10 or 11	46, XX, t(Cq−;Gp+)	3	2	0	1	0
St Clair *et al* (1990)	11q21	Balanced translocation (1q43;11q21)	7	3	2	1	1
Smith *et al* (1989) and personal communication	11q22.3	Balanced translocation (9p22;11q22.3)	8	3	2	2	1
Craddock *et al* (1993)	11q23.3-11q25	Duplication 11q23.3-25	3	1	0	1	1
Holland & Gosden (1990)	11q25	Balanced translocation (6q14.2;11q25)	6	2	1	2	1
Nielsen *et al* (1973)	13	Balanced ('Robertsonian') translocation (13;14)	1	0	1	0	0
Roberts *et al* (1986)	13q31-32	Balanced intra-chromosomal insertion of 13q31-32 between bands 13q21.2 and 13q21.3	5	1	3	1	0
Nielsen *et al* (1973)	14	See 13	1	0	1	0	0
Clarke (1993) (case 1)	15q11-13	Deletion (15q11-13)	4	2	0	1	1
Clarke (1993) (case 2)	15q11-13	Deletion (15q11-13)	7	2	2	2	1
Clarke (1993) (case 3)	15q11-13	Deletion (15q11-13)	1	0	0	0	1
Kerbeshian *et al* (1990)	15q12	Deletion (15q12)	2	1	0	0	1
Krag-Olsen *et al* (1981) (case 8)	18	Ring chromosome 18	2	1	0	0	1
Krag-Olsen *et al* (1981) (cases 9 & 10); Christensen *et al* (1970) (same cases)	18	Ring chromosome 18	2	1	0	0	1
Cook & Leventhal (1987)	21	Trisomy 21	5	1	2	2	0
McLaughlin (1987)	21	Trisomy 21	5	1	2	2	0
Sovner (1991)	21	Trisomy 21	5	1	2	2	0
Cooper & Collacott (1991) (case 1)	21	Trisomy 21	5	1	2	2	0
Cooper & Collacott (1991) (case 2)	21	Trisomy 21	3	1	1	1	0
Crandall *et al* (1970); Adams *et al* (1970) (same patient)	21	Balanced translocation (Cq−;Gp+)	3	2	0	1	0
El-Badramany *et al* (1989)	21p	Deletion 21p (pcen-pter)	5	3	2	0	0
Jancar (1968)	Y	XXYY	6	2	2	2	0
Woodhouse *et al* (1992)	X	XXX	5	2	2	0	1
Reid (1972)	X	XXX	2	1	0	0	1
Panzer & Tandon (1991)	X	86% XO, 14% 46, X iso (Xq)	5	2	1	1	1
Fishbain & Vilasuso (1981)	X	10% XO, 90% XX	5	3	0	1	1
Reiss *et al* (1986)	Xq27-28	Fragile X	8	3	1	2	2
Reiss *et al* (1988)	Xq27-28	Fragile X	5	3	0	0	2
Tranebjaerg & Orum (1991)	Xq27-28	Fragile X	3	1	0	0	2
Mendlewicz & Hirsch (1991)	Xq27-28	Fragile X	3	1	0	0	2

Note: Several reports appear twice in the table because often the cytogenetic abnormality affects two chromosomal regions.

chromosome abnormalities co-occurring with affective disorder (Table 1). Eight of Bassett's reports are included in our own total of 28 reports.

The relevancy rating system sorted the reported associations reviewed ($n = 28$) into three of Bassett's four relevance categories (Bassett, 1992). Results of the consensus relevance ratings are given in Table 1. Twelve of the reports had 'low' relevance scores of 3 or less; eight had 'possible modest' relevance scores of 4–5 and seven had 'possibly relevant' scores between 6 and 8. No report

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scored higher than 8 out of the maximum possible score of 12.

Discussion

Our review leads us to the following conclusions.

(1) There are very few reports of cytogenetic abnormalities associated with affective disorder. Significant chromosomal abnormalities, such as aneuploidies, translocations and other structural abnormalities, occur in approximately 1 in 200 live births (Therman & Susman, 1993) so one would expect co-occurrence of affective disorder and a significant chromosomal abnormality once in every 200 bipolar patients merely by chance association. This could easily explain many of the single case reports in the literature. However, some of these single cases *may* represent chromosomal abnormalities which increase susceptibility to affective disorder. This will only become apparent if several cases with abnormalities involving the same locus are discovered, or if other evidence emerges such as the presence of a strong 'candidate' gene for affective disorder at that chromosomal location. Extended pedigrees with co-segregation of affective disorder and the chromosomal abnormality in several members provide the most convincing evidence that an observed association is not due simply to chance.

(2) In many of the reports of cytogenetic abnormalities associated with affective disorder, the abnormalities are common in the general population. Examples include trisomy 21, fragile X syndrome and sex chromosome aneuploidies. The relatively high prevalence of these chromosome abnormalities increases the likelihood that these reports reflect chance association.

(3) Consideration of the number and quality of individual reports, together with evidence from other sources, suggests that the following chromosomal regions are of potential interest in localising susceptibility genes for affective disorder. (Note the use of the following terminology: '11q21-25' denotes subbands 21-25 of the long arm (q) of chromosome 11; the short arm (p) of chromosome 11 is denoted by '11p'.)

(a) 11q21-25. There are four reports of abnormalities involving distal 11q in association with affective disorder, including three extended pedigrees segregating balanced translocations (Smith *et al*, 1989; St Clair *et al*, 1990; Holland & Gosden, 1990; Craddock *et al*, 1993). However, it seems unlikely that a single susceptibility locus for affective disorder could be in linkage with, or have been disrupted by, all of the chromosomal abnormalities observed. Nonetheless, the region is undoubtedly worthy of further investigation.

(b) 15q11-13. There are three cases in which deletions in this region are associated with bipolar or cycloid psychoses (Kerbeshian *et al*, 1990; Clarke, 1993) and a further case in which a deletion of 15q11-13 is associated with chronic psychosis (Clarke, 1993). Prader-Willi syndrome results from loss of the paternal 15q11-13 region (Therman & Susman, 1993). Bipolar disorder and psychosis are not recognised features of Prader-Willi syndrome (Clarke, 1993) and are therefore not an inevitable consequence of the genetic process causing the syndrome. However, under the assumption of the existence of an affective psychosis susceptibility locus within the 15q11-13 region, several possible genetic mechanisms including dominant or recessive major loci or somatic mutation could explain an increased rate of psychosis in individuals with Prader-Willi syndrome above that in the general population.

(c) 21. Chromosome 21 is of potential genetic interest because of the possibility that mania is less common in patients with trisomy 21 than in other mentally retarded patients or in the general population. In a review of the literature relating to affective disorder in Down's syndrome, Sovner *et al* (1984) found 28 cases of major depression but no cases of mania. The authors speculated that Down's syndrome may be incompatible with mania. In our review, we found six cases of bipolar disorder occurring in patients with Down's syndrome (Table 1). After the earlier authors' implied challenge to find such cases, the appearance of only six cases in the world literature in the last nine years seems surprisingly few if mania is as common in Down's syndrome as in the general population. There have been three surveys of psychiatric disorder in Down's syndrome adults, which have included a total sample of 579 Down's patients over 20 years of age (Lund, 1988; Myers & Pueschel, 1991; Collacott *et al*, 1992). Only two cases of mania were found, both reported by Cooper & Collacott (1991). In similar studies of non-Down's mentally retarded adults, Lund (1985) and Collacott *et al* (1992) found eight manic patients out of 671 subjects studied. The numbers are too small to allow statistically meaningful conclusions, but these results are consistent with the rate of bipolar disorder in Down's syndrome being less than in other mentally retarded subjects and in the general population. Psychiatric investigation of a large sample of Down's subjects and a control sample of subjects matched for age and level of intellectual functioning will be necessary to confirm the existence of a true reduction in prevalence of the disorder. However, the available evidence suggests that bipolar disorder

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may be less common in Down's syndrome than in other mentally retarded adults or in the general population.

A reduced rate of bipolar disorder in Down's syndrome adults could be the result of non-specific effects of the chromosomal abnormality upon the control or expression of affective responses. Although mania clearly *can* occur in trisomy 21, a plausible and potentially important alternative to the 'non-specific' effect hypothesis for explaining a reduced rate of bipolar disorder in Down's syndrome is the hypothesis that possession of an extra copy of chromosome 21 confers some protection against bipolar disorder.

Hypotheses invoking either dominant or recessive disease susceptibility alleles acting at a major locus on chromosome 21 can be advanced to explain a reduced rate of bipolar disorder in subjects with trisomy 21 compared with individual's possessing two copies of chromosome 21. Moreover, testable genetic hypotheses result from the alternative explanations. (These ideas will be developed further in a forthcoming paper.) On the basis of the available evidence, chromosome 21 may be an interesting chromosome at which to start any systematic genome mapping. It has the additional merit of being the smallest autosome!

(d) Xq28. Several cytogenetic surveys and literature reviews have suggested that possession of additional X chromosomes is associated with increased rates of psychosis (Crow, 1988). However, none has suggested an increased rate of bipolar disorder. Over the last 20 years there have been several reports of co-segregation of affective disorder with the X-linked traits colour blindness and glucose-6-phosphate dehydrogenase deficiency (Craddock & McGuffin, 1993). The genes for both these conditions lie in the Xq28 region. Other workers have failed to find evidence for linkage between susceptibility to affective disorder and Xq28 markers, and the methodology of the studies showing linkage has been criticised (Craddock & McGuffin, 1993). However, it remains possible that a susceptibility locus for affective disorder lies in the Xq28 region. The reports of an association between fragile X and affective disorder, both within families and in unrelated individuals, compared with a control group (Table 1), support this possibility. It may be that the fragile X locus itself plays some role in determining disease susceptibility ('pleiotropy') or that it is closely genetically linked to a susceptibility locus for affective disorder ('linkage disequilibrium'). An alternative possibility is that the families and cases reported simply represent ascertainment bias – Xq28 is a well-known candidate region in bipolar disorder and fragile X has been studied intensively, so any potentially interesting cases supporting the hypothesis have a high probability of being reported and published. In favour of this view are the recent reports of Jeffries *et al* (1993) and Reiss and colleagues (1993), which do not support an association between bipolar disorder and fragile X. On balance the evidence for the existence of an association between fragile X and affective disorder is not compelling.

In any review, arbitrary thresholds must be used for inclusion or exclusion of reports and for the amount of discussion given to each report. We have attempted to review all relevant reports in the English literature but it is possible that our review is incomplete.

Bassett (1992) has discussed possible reasons for the low number of reports of cytogenetic abnormality in association with psychiatric disorder and has made suggestions for future studies and reports: "(a) standardised psychiatric diagnoses, (b) reporting segregation patterns of both psychiatric illness and chromosomal abnormality, (c) cytogenetic surveys of dysmorphic or mentally handicapped psychiatric patients, (d) judicious use of high-resolution cytogenetic techniques, and (e) increased consultation between psychiatrists and geneticists". We would unreservedly support these recommendations and would like to add to the list of suggestions: (f) psychiatric surveys of adults with chromosomal abnormalities involving candidate chromosomal regions, and (g) screening of families with a high density of functional psychosis for cytogenetic abnormality.

It is important to bear in mind that the phenotypic effects of a chromosome abnormality may manifest themselves through their influence on the expression of one or more genes located in parts of the genome distant from the site of the chromosomal abnormality. Thus, a whole chain of events may be involved between the chromosomal lesion and the expression of the disorder, making it difficult to establish a direct link between a gene at the site of the chromosome abnormality and the ultimate disease phenotype. Furthermore, the phenotypic effects of a chromosomal abnormality may result from psychologically mediated mechanisms, such as stress resulting from mental impairment or physical handicap. Caution is therefore required when interpreting the nature of any observed association between chromosomal abnormalities and psychiatric illness. However, the cytogenic approach has already proved successful in localising genes for several disorders, including Duchenne muscular dystrophy, familial polyposis coli and familial Alzheimer's

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disease (Collins, 1992). Cytogenetic studies of psychiatric patients have not yet produced tangible benefits. However, there have been recent major improvements in the ability to detect small abnormalities (Therman & Susman, 1993) and these may eventually prove to be of help in detecting susceptibility loci for bipolar disorder and schizophrenia.

It is important that clinicians recognise from among their caseload patients who may have chromosomal abnormalities. Unfortunately, with the high workload of Regional Cytogenetics Services in the context of current funding constraints, many cytogenetics laboratories may be reluctant to karyotype psychiatric patients for research-oriented indications. Nonetheless, in order to identify chromosomal abnormalities of potential relevance for localising susceptibility genes for major psychiatric disorders, it is vital to examine the chromosomes of appropriate psychiatric patients. We suggest that clinicians should refer to a research group interested in psychiatric genetics any patient with functional psychosis and one or more of: (a) a strong family history of functional psychosis (particularly if this is only on one side of the family), or (b) mental retardation, or (c) another disease known to be caused by a single gene, or (d) congenital physical abnormalities. These indications increase the probability of detecting a cytogenetic abnormality of potential relevance. The psychiatric genetic research group can further investigate the patient and his or her family and arrange appropriate specialist karyotyping.

A fuller manuscript is available from the authors, containing more technical information and discussion, six tables and 75 references.

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