

Genomewide Linkage Scan in Schizoaffective Disorder

Significant Evidence for Linkage at 1q42 Close to DISC1, and Suggestive Evidence at 22q11 and 19p13

Marian L. Hamshere, PhD; Phil Bennett, PhD; Nigel Williams, PhD; Ricardo Segurado, PhD; Alastair Cardno, PhD, MRCPsych; Nadine Norton, PhD; David Lambert, PhD; Hywel Williams, PhD; George Kirov, MD, MRCPsych; Aiden Corvin, MD, MRCPsych; Peter Holmans, PhD; Lisa Jones, PhD; Ian Jones, PhD, MRCPsych; Michael Gill, MD, MRCPsych; Michael C. O'Donovan, PhD, FRCPSych; Michael J. Owen, PhD, FRCPSych; Nick Craddock, PhD, FRCPSych

Context: Traditionally, the search for genes involved in predisposition to major psychoses has proceeded with separate studies of schizophrenia and bipolar disorder. However, twin data suggest that, in addition to genes with specificity for these phenotypes, there exist genes that simultaneously influence susceptibility to schizophrenia, bipolar disorder, and schizoaffective disorder.

Objective: To undertake, to our knowledge, the first systematic search for such loci.

Design: Genomewide linkage scan.

Setting: Affected individuals were ascertained in the United Kingdom and Ireland from general psychiatric inpatient and outpatient services.

Participants: The families were selected for linkage studies of either schizophrenia or bipolar disorder. Pedigrees were selected for the current analysis where there was at least 1 member with DSM-IV schizoaffective disorder, bipolar type. Within these pedigrees, individuals were coded as affected if they had been diagnosed with DSM-IV schizophrenia, schizoaffective disorder of bipolar type, or bipolar I disorder. A total of 24 pedigrees

contributed 35 affected sibling pairs to the sample.

Method: A 10-centimorgan genome scan using microsatellite markers was analyzed using MAPMAKER/SIBS software.

Results: A genomewide significant signal (LOD=3.54) was observed at chromosome 1q42 (near *DIS2800*), and suggestive LOD scores were observed at chromosomes 22q11 (LOD=1.96) and 19p13 (LOD=1.85). No linkage was observed in these regions in our original schizophrenia or bipolar scans in individuals from the United Kingdom.

Conclusions: Our linkage findings strongly support the existence of loci that influence susceptibility across the functional psychosis spectrum. The *DISC1* gene lies within 2.5 megabases of our peak marker on chromosome 1q42 and has been previously implicated in schizophrenia, bipolar disorder, and, recently, schizoaffective disorder. Follow-up of this region should use samples enriched for cases of schizoaffective disorder. Our findings have similar implications for the search for genetic variation on chromosome 22q11 that influences susceptibility to psychosis.

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Author Affiliations: Department of Psychological Medicine (Drs Hamshere, N. Williams, Cardno, Norton, H. Williams, Kirov, I. Jones, O'Donovan, Owen, and Craddock) and Biostatistics and Bioinformatics Unit (Drs Hamshere and Holmans), School of Medicine, Cardiff University, Cardiff, Wales; Division of Neuroscience, University of Birmingham, Queen Elizabeth Psychiatric Hospital, Birmingham, England (Drs Bennett and L. Jones); and Departments of Psychiatry and Genetics, Trinity College, Dublin, Ireland (Drs Segurado, Lambert, Corvin, and Gill).

WITHIN THE SET OF SEVERE psychiatric disorders of adult onset, the 2 diagnostic categories that have been the focus of most genetic analyses to date are schizophrenia and bipolar disorder. There is substantial evidence from family, twin, and adoption studies for the importance of genes in influencing susceptibility to schizophrenia¹ and bipolar disorder,^{2,3} and replicated findings for each disorder are emerging from molecular genetic studies.⁴⁻¹⁰

Traditionally, psychiatric research in general, and the search for predisposing genes in particular, has proceeded under

the assumption that schizophrenia and bipolar disorder are separate disease entities with separate underlying etiologies (and treatments)—the so-called “Kraepelinian dichotomy.” This distinction has pervaded Western psychiatry since Emil Kraepelin’s influential nosological writings,¹¹ and it remains enshrined in current operational classification systems such as DSM-IV¹² and the ICD-10 *Classification of Mental and Behavioural Disorders*,¹³ although some workers, such as Crow,¹⁴ have argued for a continuum approach to psychosis. The clinical reality is that many individuals with severe psychiatric illness have features that fall between these 2 extremes and have both

mood and psychotic features; such cases are often classified as “schizoaffective disorder” or some similar atypical diagnosis. The existence of these cases raises the possibility, or perhaps the likelihood, that there is not a neat biological distinction between schizophrenia and bipolar disorder. This possibility finds support in several observations from genetic research.¹⁰ First, although family studies¹⁵⁻¹⁷ have shown substantial consistency in demonstrating that schizophrenia and bipolar disorder tend to “breed true,” some studies have also shown that bipolar disorder occurs at an increased frequency in the relatives of probands with schizophrenia¹⁸ and that schizophrenia occurs at an increased frequency in the relatives of probands with bipolar disorder.¹⁹ Some studies have shown that schizoaffective disorder occurs at an increased rate in the families of probands with schizophrenia²⁰ and bipolar disorder.²¹ Both schizophrenia and bipolar disorder have been shown to occur at increased rates in the families of probands with schizoaffective disorder.²¹ A recent twin study²² that used an analysis unconstrained by the diagnostic hierarchy inherent in current classification systems (ie, the principle that schizophrenia trumps mood disorder in diagnosis) demonstrated an overlap in the genetic susceptibility to mania and schizophrenia. Genetic linkage studies^{9,23} have identified convergent or overlapping regions of interest in both disorders—including regions of chromosomes 13q, 22q, and 18, although some meta-analyses^{7,8} of linkage studies have not shown this. Positive association findings at the *G72(DAOA)/G30* locus on chromosome 13q in both schizophrenia^{24,25} and bipolar disorder²⁵⁻²⁷ have been described (although there have also been negative reports). The schizophrenia susceptibility gene, *NRG1*, has been described to show association with bipolar disorder.²⁸ These genetic data argue for a more complex relationship between the psychoses than is reflected in the conventional dichotomous view.

The twin study by Cardno et al²² mentioned earlier provides evidence for the existence of some genes that have relative specificity for either schizophrenia or bipolar disorder. This is the assumption underpinning the designs used to date in which bipolar disorder and schizophrenia have been studied as separate phenotypes. However, the study also provides evidence that there are genes that confer risk across the Kraepelinian extremes and simultaneously affect the risk of schizophrenia, bipolar disorder, and illnesses in which both mood and psychotic features are prominent. Here we describe, to our knowledge, the first systematic genome search for such loci in a set of pedigrees that are multiply affected by illness in the schizophrenia–bipolar disorder spectrum and in which there is at least 1 family member that has *DSM-IV* schizoaffective disorder of bipolar type (ie, an illness characterized by a balanced mix of prominent bipolar mood features and schizophrenia-like psychotic features).

METHOD

All of the subjects in these studies were white and of United Kingdom or Irish origin, and they all provided written informed consent to participate in genetic studies. Protocols and procedures were approved by the relevant ethical review panels.²⁹⁻³¹

FAMILIES

Families for study were selected from those families recruited by our research grouping for our ongoing molecular genetic, affected sibling-pair studies of schizophrenia and bipolar disorder. Our programs of research in these phenotypes have used consistent recruitment and assessment methodologies and have benefited from ongoing interaction between the field teams undertaking the phenotypic assessments. All of the families were recruited in the United Kingdom and the Republic of Ireland through mental health services, patient support groups, and articles in the national media. Families originally identified in our schizophrenia pedigree set were ascertained through a proband with *DSM-IV* schizophrenia; those originally identified in our bipolar disorder pedigree set were ascertained through a proband with *DSM-IV* bipolar I disorder. Families were selected for inclusion in the current analysis according to the following criteria: (1) at least 1 member had an illness that met *DSM-IV* criteria for schizoaffective disorder, bipolar type; (2) at least 1 additional family member had an illness that met *DSM-IV* criteria for schizophrenia, bipolar I disorder, or schizoaffective disorder, bipolar type; and (3) the family was informative for affected sibling-pair linkage analysis. Our sample comprised 24 nuclear families, 11 of whom came from our schizophrenia pedigree series and 13 of whom came from our bipolar series. In total, there were 35 independent sibling pairs (counted according to the all-possible-pairs method) who were available for linkage analysis. The breakdown of *DSM-IV* diagnoses among members of these pairs was as follows: schizoaffective disorder, bipolar type, 23 individuals; schizophrenia, 12 individuals; and bipolar I disorder, 18 individuals. Further details relating to the family sample set are shown in **Table 1**.

DIAGNOSIS

Details of the phenotypic assessment and diagnostic methods are provided in articles by Williams et al^{30,31} and Bennett et al.²⁹ Briefly, following receipt of multicenter research ethics approval, written informed consent was obtained from all of the participating individuals. Participants were interviewed by trained investigators (psychiatrists or psychologists) using a semistructured research interview (Schedule for Clinical Assessment in Neuropsychiatry³²), and case note information was obtained. The OPCRIT checklist³³ was completed for each participant. Lifetime best-estimate psychiatric diagnoses were made according to *DSM-IV* criteria by 2 independent raters using all of the available information. Any disagreements were rated by a third investigator and discussed to reach a consensus. Regular meetings were held between all of the interviewers and raters to maximize clinical consistency and reliability. Interrater reliability was assessed using clinical data from 20 cases (chosen to represent a typical cross section of subjects recruited within the study), which were rated by each investigator and compared against consensus to obtain individual κ coefficients of reliability. Reliability was measured during the studies and was shown to be excellent, with a mean κ value greater than 0.80 (range, 0.81-1.00) for *DSM-IV* diagnoses.

MARKERS

A total of 426 microsatellite markers were included in this study. There were 394 markers that were selected from the ABI PRISM linkage mapping set, version 2 (since renamed the Medium Density 10-centimorgan [cM] mapping set; Applied Biosystems, Foster City, Calif), with an additional 32 markers being added from the Marshfield genetic map.³⁴ The marker order and the distances between them were determined according to the Marsh-

field genetic map,³⁵ resulting in an average intermarker distance of 8.7 cM across the genome.

GENOTYPING

Laboratory work was undertaken using consistent methodologies in 3 participating laboratories: the Neuropsychiatric Genetics laboratory at Cardiff University (M.J.O. and M.C.O.), the Molecular Psychiatry laboratory at the University of Birmingham (N.C.), and the Psychiatric Genetics laboratory at Trinity College (M.G.). The consistency and reliability of cross-center genotyping strategies was validated by way of a joint pilot study³⁶ using markers on chromosome 21.

All of the DNA samples were extracted either from whole blood or from saline mouthwash samples using standard procedures. After quantification by UV spectroscopy, working solutions at approximately 5 ng/μL were prepared for each participant and stored at 4°C in standard 96-deep well plates. The polymerase chain reactions were performed with thermal cyclers from MJ Research Inc, Waltham, Mass, using an initial denaturation temperature of 95°C for 12 minutes, followed by either 10 cycles (15 seconds at 94°C, 15 seconds at 55°C, and 30 seconds at 72°C) and then 25 cycles (15 seconds at 89°C, 15 seconds at 55°C, and 30 seconds at 72°C), or a touchdown procedure of 11 cycles (5 seconds at 94°C, 5 seconds at 60°C, and 10 seconds at 72°C minus 0.5°C per cycle), which was then followed by 27 cycles (5 seconds at 94°C, 5 seconds at 54°C, and 10 seconds at 72°C), with a final incubation for 10 minutes at 72°C. After the polymerase chain reactions, products from individual and multiplex reactions were pooled in empirically determined ratios into size-specific marker sets prior to gel electrophoresis. This permitted up to 20 discrete marker loci to be analyzed in a single gel lane, with allele peak fluorescence intensities remaining within optimal limits (typically of approximately 200–4000 units). All of the markers were genotyped on either ABI 377 XL DNA sequencers or ABI 3100 sequencers (Applied Biosystems) using the software programs Genescan and Genotyper (Applied Biosystems).

STATISTICAL ANALYSES

Genetic relationships between family members were confirmed using marker data from across the genome and a suite of software packages: Relative,³⁷ RELCHECK,^{38,39} and PREST.⁴⁰ In-house and GRR⁴¹ software were used to detect monozygotic twins and to ensure that no individual was typed in 2 different families. The presence of non-Mendelian errors was detected using the software PedCheck.⁴²

Multipoint analyses were performed using the MAPMAKER/SIBS software package,⁴³ which calculates the maximum likelihood LOD score at each point in the genome by estimating the maximum likelihood identity-by-descent allele-sharing probabilities for each sibling pair. Sample-specific marker allele frequencies were estimated from our data set using SPLINK⁴⁴ by maximum likelihood methods. Our method of analysis makes no assumptions about the genetic model. Consistent with the hypothesis underpinning this analysis, the phenotypic model was to define as “affected” all of the individuals with a diagnosis of DSM-IV schizophrenia, bipolar I disorder, or schizoaffective disorder, bipolar type. All of the other individuals were considered unknown phenotypes.

To assess the statistical significance of our study and to take account of multiple testing, we obtained empirical significance levels and the expected number of given LOD scores per genome screen by simulating 1000 replicates of the entire data set under the null hypothesis of no linkage, then analyzing them with MAPMAKER/SIBS. These simulations maintained the same

Table 1. Family Structure and Composition of Sample

	Bipolar, No.	Schizophrenia, No.	Total, No.
Families and ASPs			
Families	13	11	24
Sibling pair families	11	9	20
Sibling trio families	1	2	3
Sibling quartets	1	0	1
Affected sibling pairs*	20	15	35
Male-male pairs	4	5	9
Male-female pairs	8	8	16
Female-female pairs	8	2	10
Families with 1 parent genotyped	2	4	6
Families with both parents genotyped	2	0	2
Individuals Comprising Affected and Unaffected Siblings in Linkage Analysis			
Affected siblings genotyped	29	24	53
Male	15	14	29
Female	14	10	24
Unaffected siblings genotyped	8	5	13
Diagnoses of Probands†			
DSM-IV schizoaffective, bipolar	13	11	24
Diagnoses of Individuals Comprising Affected Siblings in Linkage Analysis†			
DSM-IV schizoaffective, bipolar	11	12	23
DSM-IV schizophrenia	0	12	12
DSM-IV bipolar I disorder, psychotic	13	0	13
DSM-IV bipolar I disorder, nonpsychotic	5	0	5

Abbreviation: ASP, affected sibling pair.

*The ASPs were counted by the all-possible-pairs method.

†In 2 bipolar pedigrees, the family member with DSM-IV schizoaffective disorder, bipolar type (designated as the “proband”) was not a member of a sibblingship contributing to the linkage analysis. (In 1 case, the proband with schizoaffective disorder was a parent of the sibblingship; in the other case, the proband with schizoaffective disorder was the offspring of 1 of the affected individuals in the sibblingship.)

marker allele frequencies, marker locations, family structures, and individuals typed at each locus as in the observed data set.

To investigate whether the identity-by-descent allele-sharing probabilities differed depending on the sex of the pair, sex covariate linkage analysis was performed using a logistic regression framework according to the method described by Rice^{45,46} and extended by Holmans.⁴⁷ The dichotomous sex information was reduced to male-male, male-female, and female-female pairs of affected individuals. To assess the significance of the LOD score increase, a permutation test was performed. For each permutation, the sex information (male or female) was randomized between all of the affected offspring. The qualitative covariate pairings were reconstructed, and a new test statistic was derived. The number of times a permuted test statistic exceeded the observed test statistic out of the number of permutation tests performed gave the significance level.⁴⁸

RESULTS

A total of 398 and 372 markers were typed in the bipolar and schizophrenia families, respectively, of which 426 markers were unique. The unique markers comprise 344 markers that were typed in both samples, 54 typed only in the bipolar sample, and 28 typed only in the schizophrenia sample. A total of 76 genotyped individuals were

Table 2. Location and Magnitude of the Maximum Linkage Signal for Each Chromosome*

Chromosome Band	Observed Maximum LOD Score	Peak Location, cM	Nearest Marker	Physical Location of Nearest Marker(s), Mb	Estimated IBD Sharing
1q42.2	3.54†	257	D1S2800	231	0.78
2q32.1	0.42	186	D2S364	183	0.58
3p23-3p14.3	1.04	67	D3S1277-D3S1289	35-54	0.66
4q12	1.08	65	D4S1592	58	0.64
5q31.1	0.63	140	D5S2115	135	0.62
6p12.1	0.80	80	D6S257	56	0.63
7q36.3	0.76	180	D7S2465	156	0.63
8q12.1	0.08	71	D8S285	57	0.54
9p13.3	0.08	59	D9S1817	34	0.54
10p12.1	0.51	52	D10S197	27	0.60
11q22.1	0.20	99	D11S898	101	0.57
12q24.21	0.70	125	D12S79	115	0.63
13q12.3	0.06	17	D13S217	28	0.53
14q11.2	0.41	0	D14S261	20	0.60
15q26.2	0.28	81	D15S207	94	0.57
16p12.3	1.03	40	D16S3046	21	0.64
17q21.32	0.91	65	D17S1868	45	0.65
18q21.32-18q21.33	0.89	91	D18S64-D18S68	56-60	0.65
19p13.2	1.85‡	36	D19S221	13	0.69
20q13.12	0.51	69	D20S119	43	0.60
21q11.2	0.52	0	D21S1911	15	0.65
22q11.1	1.96‡	4	D22S420	16	0.75
Xp21.2	1.84	45	DXS1214	31	0.63

Abbreviations: cM, centimorgan; IBD, identity by descent; Mb, megabase.

*Linkage signal was determined by MAPMAKER/SIBS.⁴³ Marker maps for linkage analysis were obtained from the Marshfield genetic map.³⁴ Physical locations for the peak markers were obtained from the Golden Path, Human, May 2004 Assembly.⁴⁹

†The LOD score is significant for genomewide linkage according to the criteria of Lander and Kruglyak.⁵⁰

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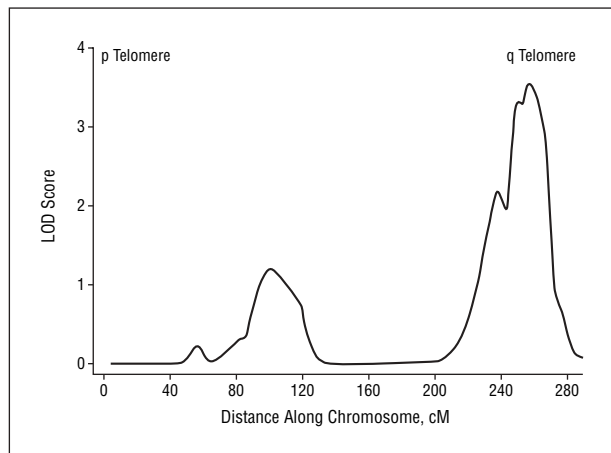


Figure 1. Multipoint LOD scores across chromosome 1, obtained from MAPMAKER/SIBS⁴³ for the schizoaffective disorder, bipolar type, pedigrees. The map distances were obtained from the Marshfield genetic map.³⁴ cM indicates centimorgans.

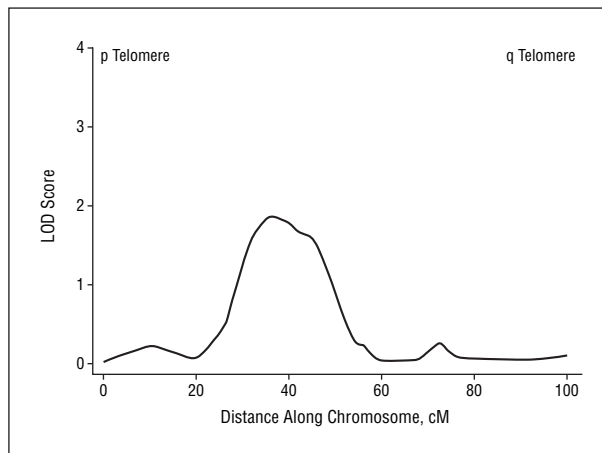


Figure 2. Multipoint LOD scores across chromosome 19, obtained from MAPMAKER/SIBS⁴³ for the schizoaffective disorder, bipolar type, pedigrees. The map distances were obtained from the Marshfield genetic map.³⁴ cM indicates centimorgans.

included within the current analysis. Their characteristics are shown in Table 1.

A summary of the highest LOD scores observed on each chromosome is shown in **Table 2**. More detailed results for the 3 chromosomes of greatest interest are shown in **Figure 1** (chromosome 1), **Figure 2** (chromosome 19), and **Figure 3** (chromosome 22). Simulation studies demonstrated that a maximum LOD score of 3.40 was required for genomewide significance. The maximum LOD score of 3.54 observed on chromosome 1q42 was,

thus, significant genomewide according to the criteria of Lander and Kruglyak⁵⁰ ($P = .04$). A LOD score of 1.54 was expected to occur by chance once per genome scan—ie, genomewide suggestive linkage according to the criteria of Lander and Kruglyak.⁵⁰ We had 3 such LOD scores (1.85, 1.96, and 3.54 on chromosomes 19p13, 22q11, and 1q42, respectively). Thus, in addition to the genomewide significant region on chromosome 1, there were also genomewide suggestive regions on chromosomes 19p13 and 22q11. (Interpretation of the LOD scores for the X

chromosome must be treated separately from those for the autosomes because higher LOD scores can arise by chance⁵¹; our simulation studies demonstrated that the LOD score of 1.84 on the X chromosome had an associated genomewide significance level of 0.17 and should not be considered suggestive according to the criteria of Lander and Kruglyak.⁵⁰ It should be noted that simulation studies and genomewide significance levels are used routinely in genetic linkage scans, and they effectively correct for multiple testing.

The highest LOD score was observed on chromosome 1q, close to marker *DIS2800*. The LOD-1 interval, which approximates the 95% confidence interval assuming that the linkage reflects the presence of a single susceptibility locus,⁵² spans approximately 24 cM. Inspection of the LOD scores by family showed that increased sharing was observed in 17 families with an equal contribution from schizophrenia and bipolar disorder families. The estimated probability of allele sharing between affected siblings in this region was 0.78 (compared with the null expectation of 0.50). Including sex as a covariate on chromosome 1 increased the maximum LOD score by 1.63, an increase that was statistically significant ($P = .04$). The estimated probabilities of allele sharing were 0.93, 0.60, and 0.94 in the male-male, male-female, and female-female pairs, respectively. The effect of sex as a covariate was tested because of a prior finding at this location in a Finnish study.⁵³ No other chromosomes were tested for a sex effect, so no adjustment for multiple testing was made.

The second highest LOD score was on 22q11 (LOD=1.96), with 14 families contributing positive LOD scores equally distributed between bipolar and schizophrenia pedigrees. The third region meeting statistical criteria for suggestive linkage was 19p13 (LOD=1.85), with 16 families contributing positive LOD scores, again equally distributed between bipolar and schizophrenia pedigrees.

COMMENT

The current analysis is the first linkage study to our knowledge that has used families selected through a member with schizoaffective disorder with the aim of identifying loci that influence susceptibility to illness across the schizophrenia-bipolar disorder spectrum. Most previous studies have focused on either schizophrenia or bipolar disorder. The preconception that bipolar and schizophrenic disorders are genetically unrelated, and the subsequent exclusion from studies of relative pairs comprising 1 subject with schizophrenia and 1 subject with bipolar disorder, would be expected to bias against the inclusion of families segregating alleles that simultaneously increase the risk of both disorders in favor of families segregating alleles specific to either of the dichotomous phenotypes separately. Such studies are, therefore, unlikely to identify linkage signals representing genes whose influence spans the enforced dichotomy. Consistent with this notion, the most recent and comprehensive meta-analyses of genome scans of schizophrenia⁸ and bipolar disorder,⁷ each based on identical methodologies, failed to find regions of overlap in linkage signals in the 2 disorders, although the smaller meta-analysis by

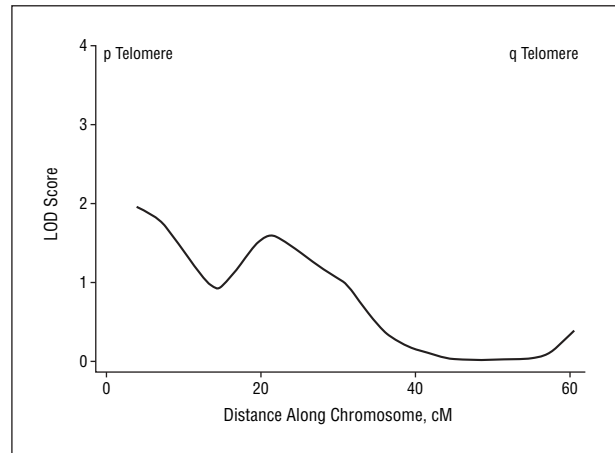


Figure 3. Multipoint LOD scores across chromosome 22, obtained from MAPMAKER/SIBS⁴³ for the schizoaffective disorder, bipolar type, pedigrees. The map distances were obtained from the Marshfield genetic map.³⁴ cM indicates centimorgans.

Badner and Gershon⁹ found areas of overlap at chromosomes 13q and 22q.

There has been increasing interest in exploration using linkage approaches of the overlap between bipolar disorder and schizophrenia. One approach has been to use the occurrence of psychosis in individuals with bipolar disorder to identify a subset of families with bipolar disorder for analysis.^{54,55} There is a small number of linkage studies⁵⁶⁻⁵⁸ that have included families with both bipolar and schizophrenia diagnoses within the same analysis, but they have also included some families with only schizophrenia, some families with only bipolar disorder, and some families with both of the disorders. This is unlikely to be the optimal approach for identifying loci that influence risk across the schizophrenia-bipolar diagnostic spectrum because such sample sets will include some pedigrees enriched for bipolar-specific genes, some enriched for schizophrenia-specific genes, and only a subset enriched for genes conferring risk across the spectrum. In contrast, our design, being based only on families in which at least 1 proband had a diagnosis spanning the diagnostic divide (that is, schizoaffective disorder, bipolar type), would be expected to highly enrich for alleles conferring risk across the spectrum of schizophrenia, schizoaffective disorder, and bipolar disorder.

We recognize that current diagnostic classifications are blunt tools for biological research. Our choice of affection status for our analysis (ie, affected defined as *DSM-IV* schizoaffective disorder of bipolar type, bipolar I disorder, or schizophrenia) is based directly on the twin analysis by Cardno et al.²² From the phenotypic viewpoint, in addition to the proband with schizoaffective disorder, the other affected family members that contributed to the analysis (ie, those with *DSM-IV* diagnoses of schizophrenia or bipolar I disorder) frequently had both prominent mood and psychotic features. Of the 18 individuals with *DSM-IV* bipolar I disorder, 13 had experienced psychotic episodes of mood disturbance. Of the 12 individuals with *DSM-IV* schizophrenia, 2 met Research Diagnostic Criteria⁵⁹ for schizoaffective disorder, bipolar type, and 4 met Research Diagnostic Criteria for

schizoaffective disorder, depressed type. Thus, our sample is highly enriched for cases with prominent mood and psychotic features, although it should be noted that there were also family members included in our analysis that did not have this mix of symptoms.

We found 3 chromosome regions (1q42, 19p13, and 22q11) with suggestive evidence for linkage according to the criteria of Lander and Kruglyak,⁵⁰ of which the LOD score of 3.54 at chromosome 1q42 achieved genome-wide significance ($P=.04$).

It is of great interest that the location of the peak of our genomewide significant linkage signal on chromosome 1q42 coincides with a locus that has received support in some previous linkage studies of both schizophrenia⁶⁰⁻⁶² and bipolar disorder,^{63,64} although this locus did not emerge in meta-analyses of linkage scans for either disorder⁷⁻⁹ or in our own genome scans of schizophrenia³¹ or bipolar disorder.²⁹ Of particular relevance is the fact that this locus was originally implicated from the study⁶⁵ of a large multigenerational Scottish family in which a balanced translocation, t(1;11), cosegregated with psychiatric disorders. The maximum LOD score (7.1) was obtained when the affected status included both schizophrenia and major mood disorders (bipolar and recurrent major depression) whereas the LOD scores for schizophrenia alone and for major mood disorders alone were 3.6 and 4.5, respectively. Further studies have allowed Millar et al⁶⁶ to localize the translocation breakpoints and identify 2 genes on chromosome 1, the sequences of which were disrupted by the breakpoint, named *disrupted in schizophrenia 1 (DISC1)* and *disrupted in schizophrenia 2 (DISC2)*. Macgregor et al⁶³ have recently described suggestive evidence of linkage to this locus in a set of bipolar pedigrees, although they found no evidence for linkage in their schizophrenia pedigrees. Linkage at this locus has been described in 2 sets of Finnish schizophrenia pedigrees^{61,62} and is supported by evidence for linkage disequilibrium between markers across the *DISC1* gene and susceptibility to schizophrenia.⁵³ In this latter study, evidence for a sex effect at this locus was found with a haplotype of 2 single nucleotide polymorphisms, spanning intron 1 to exon 2 of the *DISC1* gene, that was significantly undertransmitted only to affected females. It is, therefore, of interest that we also found significant evidence for a sex effect when this was considered as a covariate in our linkage data at chromosome 1q42. In our data, however, the finding was that identity-by-descent allele sharing was increased in the female-female and male-male pairs, but not in the male-female pairs. If not a chance finding, this suggests that there could be different variants at this locus that operate to influence susceptibility in males and females. The possibility of a sex effect requires further exploration.

Our linkage findings strongly suggest that the susceptibility locus at chromosome 1q42 confers risk to that subset of the schizophrenia-bipolar disorder spectrum in which there are features of both disorders. This has implications for the choice of samples in which to use association approaches for gene identification. Individuals with schizoaffective disorder, bipolar type (or affected individuals with a family history of schizoaffective disorder, bipolar type), are likely to be more powerful in gene identification than are samples selected for purity of the schizophrenia or bi-

polar phenotypes (or, indeed, simply pooling together sets of bipolar and schizophrenia cases that were selected for purity of phenotype). It is, therefore, of great interest that Hodgkinson et al⁶⁷ have described evidence for association with disease status with polymorphisms and haplotypes at the *DISC1/DISC2* locus in a case-controlled study of North American white individuals, including patients with diagnoses of schizophrenia, bipolar disorder, and schizoaffective disorder. Our findings, together with those of Hodgkinson et al,⁶⁷ highlight the importance of a careful consideration of the clinical phenotypes of samples. In addition to stochastic factors, there may be systematic differences in linkage findings between samples according to the proportion of the schizophrenia cases with bipolar features and vice versa. Genetic researchers need to pay close attention to the phenotypic characteristics of their samples and, where appropriate, need to undertake covariate-based analyses. In publications, it is highly desirable that researchers describe the phenotypic characteristics of their samples in detail (perhaps in an online supplement) and make such data available for future meta-analyses.

It is also of interest that chromosome 22q11 yielded the second largest linkage in our study, as this has been implicated in both published meta-analyses^{8,9} of schizophrenia-genome scans and in 1 of the meta-analyses⁹ of bipolar disorder scans. Subsequent to the meta-analyses, we obtained suggestive evidence for linkage on chromosome 22q11 (maximum LOD score, 2.29 at 4 cM; 16 megabases [Mb]) in our genome scan of schizophrenia that included families from Sweden and the United States in addition to those in the United Kingdom. However, it is important to note that the present sample was drawn from only the United Kingdom families with schizophrenia who yielded a maximum LOD score of only 0.72 in the region of chromosome 22q11. Support for the involvement of chromosome 22q11 has come from the study of other forms of illnesses that span the schizophrenia-bipolar spectrum. Thus, Potash et al⁵⁴ found a linkage signal in this region in a subset of bipolar pedigrees with psychotic features, while from the opposite side of the divide, Pulver et al⁶⁸ found a signal in schizophrenia pedigrees with prominent mood features. Our linkage peak also coincides with the region deleted in velo-cardio-facial syndrome (Online Mendelian Inheritance in Man [OMIM] 192430; also known as DiGeorge or Shprintzen syndrome [OMIM 188400]), in which psychosis occurs at an increased frequency as compared with the general population.¹⁰

The third region meeting statistical criteria for suggestive linkage was chromosome 19p13 at *D19S221* (13 cM; 12.5 Mb from the p telomere). This region has not received support in meta-analyses⁷⁻⁹ of schizophrenia or bipolar disorder and was not identified in our own genome scans of schizophrenia³¹ or bipolar disorder.²⁹ Our findings are consistent with this region harboring a susceptibility locus involved in the pathogenesis of psychotic disorder in the schizophrenia-bipolar spectrum. Replication is required.

In the context of studies of complex disorders, our sample size was modest (24 families). This reduces our statistical power but does not affect the statistical significance of our finding because our methods for obtaining significance levels (using simulation rather than relying on asymptotic distributions) allow for small sample

sizes. It is, of course, desirable that our findings are replicated in independent samples. That such a sample could yield 1 signal that is significant genomewide and 2 other suggestive signals suggests that our study has benefited from increasing the genetic homogeneity by selection of families through an index case of schizoaffective disorder. As already pointed out, molecular genetic studies of major psychiatric disorders in the schizophrenia-mood spectrum to date have proceeded with explicit or implicit adherence to the Kraepelinian dichotomy, starting with sets of bipolar cases and families or sets of schizophrenia cases and families. Schizoaffective cases, while collected, have usually been treated as a potential complicating nuisance. They have usually been accommodated into linkage analyses, but often within a broad phenotype category.²⁹ Schizoaffective cases have not yet been studied systematically in association analyses. Our findings, together with those of Hodgkinson et al,⁶⁷ demonstrate the value of focusing on schizoaffective cases to localize and identify the set of genes that contributes to susceptibility across the dichotomy.

Our findings have implications for the classification of the functional psychoses. Our data provide genetic support for the existence of distinct biological mechanisms that contribute to the expression of schizoaffective phenotypes and those cases of schizophrenia and bipolar disorder that are closely related to schizoaffective phenotypes. Our findings are not consistent with a dichotomous view of the major psychoses. They are fully consistent with the twin finding by Cardno et al²² that suggests there are some susceptibility genes that have specificity to schizophrenia, other susceptibility genes that have specificity to bipolar disorder, and others that confer risk across the spectrum. This may be conceptualized as overlapping sets of susceptibility genes that influence risk on a clinical spectrum from prototypical schizophrenia through schizoaffective disorder to prototypical bipolar disorder.⁶⁹

In summary, we describe, to our knowledge, the first systematic genome scan aimed at localizing genes that simultaneously influence susceptibility to schizophrenia, bipolar disorder, and intermediate phenotypes (schizoaffective disorder). We have identified regions of interest on chromosomes 1q42 (LOD=3.54; significant genomewide), 22q11 (LOD=1.96; suggestive genomewide), and 19p13 (LOD=1.85; suggestive genomewide). Our data support the hypothesis that genetic loci exist that influence risk across the functional psychosis spectrum. Our findings at chromosome 1q42 are particularly interesting and, taken together with previous linkage and association findings, strongly suggest the existence of 1 or more genes in this region that influence susceptibility to psychosis across the schizophrenia-bipolar spectrum. Within this region, the *DISC1* gene is an outstanding positional candidate. Our data provide evidence to support the usefulness of the schizoaffective disorder phenotype for future studies of the 1q42 locus as well as for future studies aimed at the identification of other genes that influence susceptibility across the traditional schizophrenia-bipolar disorder boundary, such as the locus on chromosome 22q11.

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Correspondence: Nick Craddock, PhD, FRCPsych (craddockn@cardiff.ac.uk) or Michael J. Owen, PhD, FRCPsych (owenmj@cardiff.ac.uk), Department of Psychological Medicine, Henry Wellcome Building, Wales School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, United Kingdom.

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