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ORIGINAL RESEARCH ARTICLE

A genome scan and follow-up study identify a bipolar disorder susceptibility locus on chromosome 1q42

S Macgregor[1,4], PM Visscher[1], SA Knott[1], P Thomson[2], DJ Porteous[2], JK Millar[2], RS Devon[2], D Blackwood[3] and WJ Muir[3]

[1]*Institute of Cell, Animal and Population Biology, University of Edinburgh, Kings Buildings, Edinburgh, UK;* [2]*Molecular Medicine Centre, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, UK;* [3]*Division of Molecular and Clinical Medicine, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK*

In this study, we report a genome scan for psychiatric disease susceptibility loci in 13 Scottish families. We follow up one of the linkage peaks on chromosome 1q in a substantially larger sample of 22 families affected by schizophrenia (SCZ) or bipolar affective disorder (BPAD). To minimise the effect of genetic heterogeneity, we collected mainly large extended families (average family size >18). The families collected were Scottish, carried no chromosomal abnormalities and were unrelated to the large family previously reported as segregating a balanced (1 : 11) translocation with major psychiatric disease. In the genome scan, we found linkage peaks with logarithm of odds (LOD) scores >1.5 on chromosomes 1q (BPAD), 3p (SCZ), 8p (SCZ), 8q (BPAD), 9q (BPAD) and 19q (SCZ). In the follow-up sample, we obtained most evidence for linkage to 1q42 in bipolar families, with a maximum (parametric) LOD of 2.63 at D1S103. Multipoint variance components linkage gave a maximum LOD of 2.77 (overall maximum LOD 2.47 after correction for multiple tests), 12 cM from the previously identified SCZ susceptibility locus DISC1. Interestingly, there was negligible evidence for linkage to 1q42 in the SCZ families. These results, together with results from a number of other recent studies, stress the importance of the 1q42 region in susceptibility to both BPAD and SCZ.
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Bipolar disorder (BPAD) and schizophrenia (SCZ) are severe psychiatric illnesses, with each affecting approximately 1% of most human populations. There is strong evidence for a genetic aetiology in such disorders with high heritabilities reported in twin and adoption studies. However, the task of identifying genomic regions conferring susceptibility has yielded inconsistent results, with a large number of candidate regions identified.[1]

In recent years, several studies have identified two regions of chromosome 1q (1q21 and 1q42) as important in the aetiology of SCZ. At 1q21, a study of Canadian families produced a logarithm of odds (LOD) score of 6.5,[2] a study analysing British and Icelandic families generated an LOD of 3.2[3] and a family-based association study considering Spanish origin families reported a *P*-value of 0.003.[4] A meta-analysis of most of the recent SCZ genome scans reported the 1q21 region as being among the most likely to harbour a SCZ susceptibility locus.[5] Interest in 1q42 began when the region was implicated by the apparent effects of a chromosomal abnormality on major psychiatric disease in a large Scottish family.[6] The family segregated a balanced t(1;11)(q42;q14.3) translocation, with the presence of the translocation appearing to be linked with disease status. A linkage analysis considering the translocation as a marker generated an LOD of 3.6[7] when individuals with SCZ were considered affected, an LOD of 4.5 when individuals with recurrent major depression or BPAD were considered affected and an LOD of 7.1 when individuals with SCZ, BPAD and recurrent major depression were treated as affected. The translocation directly disrupts two genes on chromosome 1: these have been named DISC1 (OMIM 605210) and DISC2 (OMIM 606271), respectively.[8] While this result shows a clear relationship between the presence of the translocation and psychiatric disease, it was unclear if this result was of relevance to other families in the general population. In the last 5 years however, a number of studies have reported independent evidence for the role of 1q42 in psychiatric disease susceptibility. Two studies in Finnish families affected by SCZ generated LODs of 3.82 and 3.21[9,10] for markers close to the translocation break-point. A recent study of Taiwanese families reported

Correspondence: Dr S Macgregor, Institute of Cell, Animal and Population Biology, University of Edinburgh, Kings Buildings, Edinburgh, UK. E-mail: MacgregorS@cf.ac.uk
[4]Current address: Biostatistics and Bioinformatics Unit, University of Wales College of Medicine, Heath Hospital, Cardiff, UK
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nominally significant evidence for linkage to 1q42 for SCZ.[11] Since the translocation family also showed linkage between the translocation and recurrent major depression and BPAD, the results of BPAD linkage studies are also of interest. A study of 22 families affected by bipolar disorder reported an LOD of 2.3 to chromosome 1q32, with allele sharing in affected individuals reported to extend across the 30 cM region spanning 1q25–q42.[12] Interestingly, 15 of these 22 families included at least one individual affected by SCZ or schizoaffective disorder. A genome scan of 65 North American bipolar families resulted in an LOD of 1.4 for linkage to a marker on chromosome 1q41.[13] Other positive reports of linkage between markers on chromosome 1q42 and bipolar disorder include a recent study of British and Icelandic families (maximum HLOD 2.0 at D1S251[14]), a study of North American families (maximum HLOD 1.98 at D1S103[15]) and a study of Old Order Amish families ($P<0.0001$ under one nonparametric weighting function at D1S103[16]). Together, these results lend support to the hypothesis that bipolar disorder, recurrent depression and SCZ may share causal elements despite clear diagnostic differences.[7,17,18]

The population wide significance of these loci on 1q has been the subject of recent lively debate.[19–22] The results reported in a meta-analysis of affected sibling pairs (ASP)[19] are in striking contrast to the strong linkages reported in analyses of extended family samples.[2,3,7] It has been previously suggested[20] that, in the presence of locus heterogeneity, the power of data sets comprising small family structures such as sib pairs will be poor. Large extended families (which are likely to be more genetically homogeneous) have proved more useful in identifying susceptibility loci on 1q thus far. For this reason, the families ascertained for this study were primarily extended (average family size 18, average number of affected individuals per family 7).

An initial genome scan for susceptibility genes was performed on 13 families affected by SCZ or bipolar disorder. These families were part of the European Science Foundation (ESF) project on the molecular neurobiology of mental illness (full results unpublished). Secondary analyses were then performed on an extended superset of the ESF families and on nine additional families on chromosome 1. All families were Scottish, carried no known chromosomal abnormalities and were unrelated to the previously described translocation family.[7] Multipoint variance components techniques were used to ensure maximal use of the available genotypic information. Additional parametric linkage analyses were also performed.

Materials and methods

Study sample

Sample collection A total of 13 Scottish families (six BPAD, seven SCZ) were originally recruited to take part in the ESF project. In all, 132 individuals (64 BPAD, 68 SCZ) were typed for 372 microsatellite markers across the genome to identify regions contributing to psychiatric illness. Family members were interviewed by experienced psychiatrists (DB and WM, University of Edinburgh) using the schedule for affective disorders and SCZ (SADS-L). Diagnoses, based on interviews, case note reviews and information from carers and relatives, were based on DSMIIIR criteria. Families were categorised as either BPAD or SCZ. In the ESF project, families were included where relatives of schizophrenic probands were diagnosed as SCZ, schizoaffective disorder or recurrent major depression. Bipolar families included affected individuals with bipolar I, bipolar II, schizoaffective manic or recurrent depressive disorder. Families in which both SCZ and bipolar disorder were diagnosed in relatives were not included in the ESF study.

Subsequent to the ESF study, nine additional families were recruited and some families extended. Since the family in which the t(1;11) translocation segregated with major mental illness included relatives with SCZ, recurrent major depression and a case of bipolar disorder, the secondary analysis (of the extended sample) included those families classified as 'mixed'. These 'mixed' families had both SCZ and bipolar disorder diagnosed in relatives. In all cases, the vast majority of individuals in each family were either schizophrenic or bipolar. The families are described in the results as 'bipolar' or 'schizophrenic' depending upon the predominant diagnosis. In the case of the largest family, a small nuclear subbranch included a number of schizophrenic sib pairs, but the remainder of the family included mainly affective disorder individuals. In this case, further follow up of family members identified cases of SCZ in close relatives of the married in spouse. The small schizophrenic subbranch was considered a separate SCZ family with the rest of the large family considered a bipolar family.

Including the ESF families, 22 families (10 bipolar, 12 SCZ) comprising 398 (229 BPAD, 169 SCZ) individuals were considered for analysis. While some families were nuclear (five families), most were extended (17 families). Tables 1 and 2 indicate the number of individuals affected under the narrow and broad definitions (see below for these definitions) of affection for the SCZ and the bipolar families.

Genotyping methods The ESF families were typed at the Human Genome Research Centre, Genethon. The 372 microsatellite markers were taken from the Genethon reference map and were evenly spaced across the genome. Genomic DNA was obtained from peripheral blood samples and/or immortalised lymphoblastoid cell lines according to standard procedures. Automated genotyping was carried out with Applied Biosystems (ABI) 373 or 377 sequencer (Perkin–Elmer), and alleles were scored with the Genscan and Genotyper programs. Mendelian inconsistencies were resolved before further analysis.

Table 1 Schizophrenia families summary: number of affected individuals

	Disease definition	
Family number	*Narrow*	*Broad*
1	5	5
2	6	6
6	5	5
9	4	4
10	4	6
11	4	6
20	5	6
19	4	8
29	3	3
33	4	5
36	5	8
500	4	4
Total	53	66

Table 2 Bipolar families summary: number of affected individuals

	Disease definition	
Family number	*Narrow*	*Broad*
4	8	9
5	6	12
12	5	7
15	6	7
18	3	6
24	8	12
26	5	7
28	4	7
32	5	7
54	5	5
Total	55	79

The 13 ESF families were typed for 34 markers across chromosome 1. All nine of the additional families were typed for one of the markers in the initial ESF families, D1S103. All of the bipolar families and all but four of the SCZ families (10 bipolar families and eight SCZ families in all) were also typed for marker D1S459. After data cleaning, 266 (D1S103) and 221 (D1S459) individuals had genotypes at these markers. Since we were particularly interested in the area around 1q42, some of the additional families were also typed for 10 additional markers around the 1q42 region; these markers were six microsatellites (D1S419, D1S439, D1S1621, D1S2709, D1S2850 and a microsatellite in the 5′ region of DISC1) and six SNPs (genotyped in house[23]). Note that some of these 10 additional markers were only typed in families showing evidence for linkage to the 1q42 region. Other than the markers D1S103 and D1S459, the other 44 markers on chromosome 1 were typed in an average of 75 individuals per marker. The markers in the 1q42 region are displayed in Figure 1. The uneven distribution of marker information is dealt with effectively by the multipoint procedures described below. The data were scanned to remove unlikely double recombinants (in addition to Mendelian transmission errors, criteria for removal $P<0.05$ in MERLIN), using the program MERLIN.[24] Since several of the families were too large for exact analysis using MERLIN, some of the pedigrees had to be split up to perform error checking. The families were analysed whole in the single-point parametric and multipoint variance component (VC) linkage analyses however. Marker allele frequencies for the genome scan families were estimated from the full set of 137 families included in the (unpublished) multicentre ESF study. For the extended sample, the allele frequencies were estimated from the Scottish data using the allele frequency estimation routines implemented in SOLAR.[25] Since linkage results can be sensitive to mis-specification of allele frequencies when there are untyped parental genotypes, we repeated the analysis with the frequencies at the D1S103 marker (the only marker typed in all families) set to be equal. The results were very similar (maximum LOD scores changed by 0.01 and 0.04 in the parametric and variance components analysis, respectively).

Statistical methods

The same methods were applied to the BPAD sample and the SCZ sample, and the methods described below apply in both cases. Two-point parametric linkage analysis using FASTLINK[26] was performed across the genome. Two models were fitted to the data; one 'dominant' (labelled model b) and one 'recessive' (labelled model r). Further, under the dominant model, a narrow definition phenotype (labelled model a) was used in addition to the broad definition phenotype. For the SCZ families, the narrow definition considered schizophrenic and schizoaffective individuals as affected: the broad definition also considered recurrent major depression individuals as affected. For the bipolar families, individuals with bipolar I, bipolar II and schizoaffective (manic) disorders were regarded as affected: the broad definition also considered recurrent major depression individuals as affected. For the extended sample, families with both bipolar and SCZ were included (mixed families). In the mixed families, the narrow definition included the diagnoses SCZ, schizoaffective, bipolar I and bipolar II. The broad definition added recurrent major depression. Recurrent major depression individuals were regarded as disease status unknown for all narrow definition analyses.

Age-structured penetrance classes were used since unaffected older persons represent more reliable indicators of affection status. While multipoint

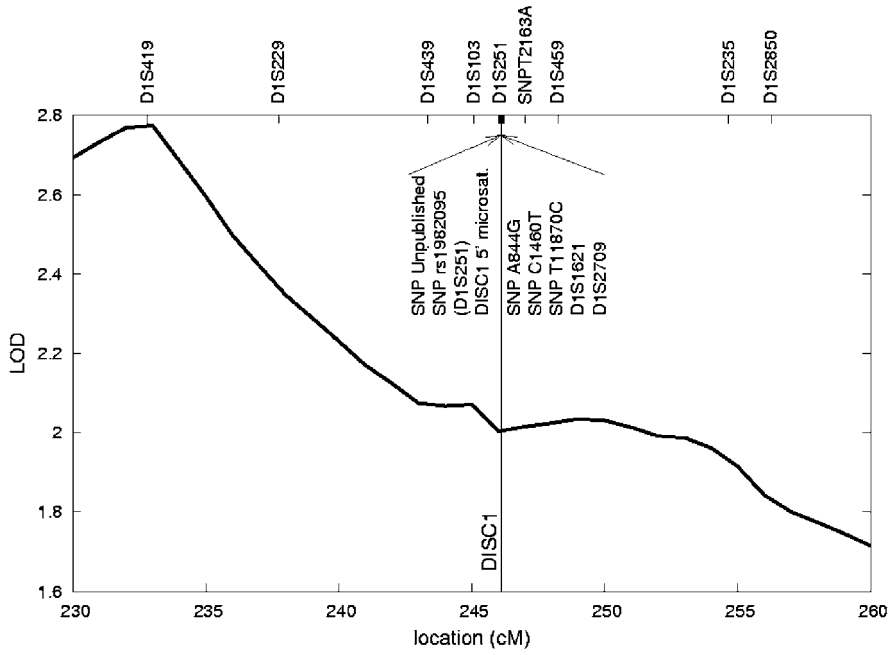

Figure 1 Multipoint VC linkage: bipolar families.

parametric linkage analysis has greater power to detect loci when the putative locus is not near a fully informative marker, it is not robust to mis-specification of the parameters in the model.[27] Explicit modelling of such mis-specification errors within the multipoint parametric framework is possible[28] but not attempted here. A convenient alternative to multipoint parametric linkage analysis is multipoint variance component linkage analysis. For the extended samples (229 individuals for the BPAD analysis, 169 for the SCZ analysis), two-point parametric linkage analysis was performed for the marker typed in all families, D1S103. Multipoint VC linkage analysis was performed with the chromosome 1 markers. A random polygenic effect and a random effect for family were fitted as a basic model. Variance components attributable to quantitative trait loci (QTL) effects were calculated by utilising multipoint identity-by-descent (IBD) coefficients estimated from the marker data. The significance of including a component attributable to one or more such effects is tested via likelihood ratio tests. Standard VC analysis assumes that the phenotypic data are multivariate normal. Although this is clearly untrue for the binary data analysed here, fitting a generalised linear model to account for the non-normal distribution of the data proved computationally difficult (see Discussion). Allison *et al*[29] performed simulations to assess the effects of non-normality of the phenotypic values on the type I error of the likelihood ratio test statistics (or LOD scores). They concluded that although the type I error could be inflated for some non-normal distributions, when the data are half affected and half unaffected, the type I error remains near the nominal level, for a range of plausible values of the residual sibling correlation. In the data presented here, the proportion of affected individuals is near 0.5 for both BPAD (79 of 158 phenotyped) and SCZ (66 of 142 phenotyped) families. This means that the LOD scores reported here should be broadly comparable with the LOD from the parametric analyses (ie by Lander and Kruglyak[30] criteria, an LOD of 3.6 is required for genome-wide significance).

The variance components technique was attempted for the ESF data set but, since the sample size was small, the variance components could not be reliably estimated. With the additional families, the VC technique had greater utility, giving estimates of disease heritability in addition to measures of QTL significance (LOD scores). To minimise multiple testing, only the broad definition phenotype was used for the chromosome 1 analysis. SOLAR[25] was used for the likelihood maximisations and IBD computation.

Since some of the families were preferentially selected for typing at additional markers on chromosome 1q (three of the families which showed no linkage signal to D1S103 were not typed for further markers), the single point LOD score calculated at markers other than D1S103 may be biased upwards. However, if the markers are analysed within a multipoint framework, the region around D1S103 should yield unbiased LOD scores. Since the heterozygosity of the microsatellite D1S103 was 0.8, marker information was high for the majority of individuals around this region. We would expect the information content in all families to remain high enough for multipoint statistics to remain unbiased for at least 10 cM either side of D1S103. For this reason, multipoint LOD scores are only displayed in the region around 1q42.

Although having more markers available in all families would have enabled more efficient detection of genotyping errors, the small number of families (three) only typed at D1S103 did not contribute to the linkage signal. Genotyping errors in such families would have little impact on results since genotyping errors invariably decrease evidence for linkage (in families segregating the mutation of interest). The large number of markers around 1q42 in the majority of families allowed efficient checks of genotyping errors to be performed in these families.

'Nonparametric' procedures were not utilised since (1) they are no more powerful than VC methods[31] and (2) they can be shown to be equivalent to parametric methods given particular penetrance values.[32] Goring and Terwilliger[32] detail why the distinction between the two is somewhat arbitrary and explain that one should not select a method simply because it is of a particular type.

In addition to the linkage results, we estimated the overall (polygenic) heritability of the traits on the binary (observed) scale. Robertson's equation from Dempster and Lerner[33] was used to convert this binary scale measure to a continuous underlying scale heritability;

$$h^2_{\text{continuous}} = h^2_{\text{binary}} \Phi_p (1 - \Phi_p)/[p(x_p)]^2$$

Where

$$p(x_p) = (2\pi) - 0.5 \exp(-x_p^2/2)$$

and Φ_p is the incidence.

To ensure there was no upward bias in this estimate due to environmental effects, a random effect for familial environment (household) was fitted.

Results

ESF data: genome scan

Parametric linkage LOD scores exceeding 1.5 are given in Table 3. The highest LOD score achieved (on chromosome 9) was not at a region previously identified as contributing to psychiatric disease. However, the genomic region identified on chromosome 1 is in close proximity to the DISC1 gene, a candidate gene for SCZ identified via a chromosomal translocation[6] and recently replicated in independent samples.[9–11]

Table 3 Maximum two-point LOD scores for ESF families

Disease	*Chromosome*	*Model*	*Marker*	*LOD*
Bipolar	1q	b	D1S229	1.55
Schizophrenia	3p	a	D3S3721	2.00
Schizophrenia	8p	b	D8S1989	1.71
Bipolar	8q	b	D8S1741	1.53
Bipolar	9q	b	D9S175	2.35
Schizophrenia	19q	a	D19S220	1.59

Chromosome 1 analyses

The above result prompted our group to type further markers around this region in the ESF families. Furthermore, nine more families from a similar geographic location were also available for analysis and some of the ESF families were extended.

Bipolar results Analysing all bipolar families (229 individuals) together at marker D1S103 with the single-point variance components procedure yielded an LOD score of 2.31. The maximum two-point parametric LOD (broad definition, recessive model, $\theta = 0.1$) was 2.63 at D1S103. The highest single family parametric LOD was 2.28 at marker D1S419. The next highest single family LOD, 2.00, was at D1S103 but this family was only typed at D1S103 and D1S459. Individual family LODs at D1S103 ($\theta = 0.1$) are given in Table 4. Note that the LOD scores shown in Table 4 are not strongly negative in the families displaying evidence against linkage because the LOD is evaluated at $\theta = 0.1$ rather than at $\theta = 0$. That is to say, these families are *not* simply uninformative for linkage. At $\theta = 0$, the LODs are higher in the families showing linkage but summed over all families the LOD maximum occurs when $\theta = 0.1$. The evidence for linkage under the narrow definition model was less than under the broad definition, with a maximum parametric LOD of 0.77.

Multipoint VC LODs are displayed in Figure 1. The maximum LOD was 2.77 at position 233 cM (near marker D1S419, 12 cM from D1S103). The estimate of polygenic heritability was 0.24 (P for difference from 0, 0.25). Without a familial environment term, this produced an (upwardly biased) estimate of 0.69 (P for difference from 0, 0.0006).

SCZ results Analysing all SCZ families (169 individuals) together at marker D1S103 with the single-point variance components procedure yielded an LOD score of 0. The single-point parametric maximum LOD (dominant model, $\theta = 0.3$) was 0.25 at D1S103. Multipoint variance component LODs were less than 0.2 in the 30 cM around D1S103. The estimate of polygenic heritability was 0.79 (P for

Table 4 Bipolar families: by family parametric LOD scores at marker D1S103

Family	*LOD*
4	−0.14
5	1.75
12	−0.32
15	0.11
18	−0.17
24	1.28
26	0.47
28	−0.21
32	0.09
54	−0.24

difference from 0, 0.05). There was no evidence for a family environment term.

Discussion

This paper reports the results of a genome scan for psychiatric disease susceptibility loci in 13 Scottish families. In the genome scan, linkage peaks with LOD scores >1.5 were found on chromosomes 1q (BPAD), 3p (SCZ), 8p (SCZ), 8q (BPAD), 9q (BPAD) and 19q (SCZ). The linkage peak on chromosome 1q was followed up in a substantially larger sample (22 in total, 398 individuals) of families affected by SCZ or BPAD. Adding nine extended families, together with more individuals from the original (ESF) families, increased the evidence for linkage to bipolar disorder (maximum single-marker parametric LOD 2.63), providing further evidence for the importance of the 1q42 region as a risk factor for psychiatric disease. Multipoint VC linkage gave a maximum LOD of 2.77 12 cM from the previously identified SCZ susceptibility locus, DISC1.[8]

To minimise the effect of genetic heterogeneity, large extended families (average family size >18) were ascertained. The families collected were Scottish, carried no chromosomal abnormalities and were unrelated to the large family previously reported as segregating a balanced t(1;11) translocation with major psychiatric disease.

When DISC1 was first identified in a Scottish family, which segregated a balanced translocation with major psychiatric disease,[6] it was not clear how relevant this locus was to other families or populations. Furthermore, while the translocation family that allowed identification of DISC1 had several schizophrenic individuals, the highest LOD score was achieved when a number of recurrent major depression individuals and a bipolar individual were included as affected. This study provides evidence for the effects of a susceptibility locus (or loci) for psychiatric diseases in the 1q42 region in a set of independent Scottish families. Some other studies have reported evidence for linkage of 1q42 to SCZ, with two Finnish studies[9,10] and a Taiwanese study[11] providing evidence for the relevance of the 1q42 region in different populations. The 1q42 region has also been implicated in bipolar disorder susceptibility, with a number of studies, considering a number of different populations reporting evidence for linkage to 1q.[12–16] The possibility of distinct psychiatric disorders such as bipolar and SCZ sharing susceptibility loci has received attention in the literature[7,10,18] and, given the main reports of linkage to 1q have been in SCZ, the results presented here add weight to this assertion. There is evidence for an increase in familial risk for one disorder in the presence of the other[18] and the data presented here suggest that susceptibility loci such as DISC1 may be acting to increase the genetic risk of both. Interestingly, there was negligible evidence for linkage to 1q42 in the SCZ families considered here. However, the sample analysed had limited power to detect loci of small effect and, in the event of there being substantial locus heterogeneity, the sample may include families which by chance are affected by psychiatric disease as a result of loci unlinked to 1q42. It is therefore possible that the failure to detect linkage to SCZ in these families was a false negative result.

The bipolar multipoint peak was 12 cM from the marker D1S103, mainly as a result of two of the families showing linkage to D1S419. It should be stressed that a 95% confidence interval on the peak is likely to be in the tens of centimorgans, and that the marker information was only complete across all families at D1S103. The DISC1 gene (MIM 615210[8]), less than 1 cM from D1S103 on 1q42.1, represents the strongest candidate gene and it seems likely that random variation (and/or possible bias due to selective typing of families for markers around D1S103) has moved the linkage peak from this point.

Some 80 cM from the DISC1 region, two other groups have reported strong linkage to chromosome 1q21.[2,3] These two studies are likely to have found evidence for linkage to a genomic region distinct from 1q42. The 13 family sample analysed here did not show linkage to 1q21 and there was insufficient marker information to adequately assess linkage to 1q21 in the additional families. The bipolar linkage described in Detera-Wadleigh *et al*[12] is likely to be 1q42, particularly since the linkage they detected exhibited elevated IBD sharing across some 30 cM of 1q, including the DISC1 region. The other linkages on 1q42 described above are clearly to the DISC1 region.

The maximum LOD for the 10 family bipolar data set was obtained when individuals with bipolar I, bipolar II, schizoaffective (manic) disorder or recurrent major depression were regarded as affected (broad definition of affection). The evidence for linkage decreased when individuals with recurrent major depression were regarded as disease status unknown in the analysis (narrow definition of affection).

Studies utilizing only narrow definition individuals may have greater utility if the samples are more genetically homogenous, but the cost of this is usually a loss of power due to a reduction in sample size.

It is worth pointing out that while recurrent depression individuals under study here were included in the broad disease definition for both bipolar and SCZ families, the families were ascertained through narrow definition probands. Furthermore, all families had at least three affected individuals using the narrow definition. The inclusion of recurrent major depression individuals in psychiatric genetic studies is not universally agreed upon and many investigators perform at least two separate analyses under different disease definitions (eg Melnnis *et al*[13], Segurado *et al*[34]). The adoption of multiple disease definitions complicates the multiple testing issue in linkage studies. The narrow and the broad definition of disease yield different results, but are not independent tests. Similarly, the VC and

parametric linkage results are different but are expected to correlate highly. In total, we performed three tests for the full 22 family data set, but a bonferroni correction for three tests would be overconservative. A convenient correction for N tests is to subtract $\log_{10} N$ from the maximum LOD score.[27] Since the three correlated tests may constitute approximately two independent tests, the multiple testing corrected maximum LOD is 2.47 ($2.77-\log_{10}2=2.47$).

A multipoint analysis of the data was performed by applying variance components techniques to the data. Several of the families were too large for exact analysis using several markers simultaneously; the program used, SOLAR,[25] uses an approximation that performs a weighted regression of the single-marker IBD coefficients. Maximisation of the likelihoods assuming the binary data was multivariate normal was carried out both in SOLAR and in another maximisation program ASREML[35] with similar results being obtained in both cases. Ideally, a generalised linear model (glm) would be fitted to the data. A glm would allow the binary trait values to be treated as coming from a binomial distribution (with a probit link function leading to a threshold model mapping the observed trait value to an underlying model[36]). We attempted to fit a glm in ASREML but found inconsistent parameter estimates across different possible models. SOLAR also has a glm (threshold model) procedure but this too gave inconsistent results. Although for some analyses the results from the glm analysis in SOLAR were similar to those obtained in the analysis not using the threshold model (ie assuming the binary data are multivariate normal), the results from the threshold model were liable to large changes when small changes were made to the data. For example, a follow up of one of the bipolar families increased the number of phenotyped individuals from 157 to 158. This led to a change in the calculated single-marker LOD at marker D1S103 (under the threshold model) from 2.00 to 0.82, with the estimated polygenic heritability changing from 0.45 to 0.00. The analyses reported in the results (assuming the binary data are multivariate normal) were considerably more robust to small changes in the data and we hence report these as the main findings. As indicated above, the type I error can be affected by non-normality of the data but Allison *et al*[29] report such effects are likely to be minor for these data (where the proportion of affected individuals is approximately 50%).

The genome scan of the ESF families generated a number of positive results alongside the peak on 1q. Of perhaps most interest among these was the LOD of 1.71 on chromosome 8p. This region has been implicated in a number of independent studies[3,37,38] and may merit further follow up in the nine additional families described here. None of the other regions indicated by the ESF genome scan overlap with any other published reports of strong linkage.

In summary, a genome scan of Scottish families affected by SCZ or bipolar disorder provided evidence for linkage to chromosome 1q in bipolar families. In a further analysis of a larger sample of bipolar families, a maximum parametric LOD of 2.63 was found. This was close to the previously identified psychiatric disease susceptibility locus DISC1. This finding supports the results of previous studies implicating this locus in a small but significant subset of all families affected by psychiatric disease, and suggests that SCZ and bipolar disorder may share a common genetic component in this region.

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