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ORIGINAL RESEARCH ARTICLE

Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia

JA Badner and ES Gershon

Department of Psychiatry, University of Chicago, Chicago, IL, USA

Badner and Gershon (2001) presented a technique of meta-analysis of linkage data that could be applied to published genome scans. It combines the reported *P*-values of individual studies, after correcting each value for the size of the region containing a minimum *P*-value. Simulations demonstrated that the type I error rate was at least as low as that for a single genome scan and thus genome-wide significance criteria may be applied. Power to detect linkage was at least as high as the power of pooling the data from all the studies. We applied this method to all the published genome scans for bipolar disorder and schizophrenia. We found the strongest evidence for susceptibility loci on 13q ($P < 6 \times 10^{-6}$) and 22q ($P < 1 \times 10^{-5}$) for bipolar disorder, and on 8p ($P < 2 \times 10^{-4}$), 13q ($P < 7 \times 10^{-5}$), and 22q ($P < 9 \times 10^{-5}$) for schizophrenia. *Molecular Psychiatry* (2002) **7,** 405–411. DOI: 10.1038/sj/mp/4001012

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Introduction

Genetic linkage studies of bipolar disorder and schizophrenia have given apparently conflicting results. Few studies have findings that exceed the threshold for genome-wide significance, and such findings are often not replicated in other studies. This is not surprising for complex genetic traits; similar results are seen in linkage studies of other complex genetic disorders. Suarez *et al*[1] demonstrated a curious finding, which since has been widely cited by statistical analysts of common disease genetics as an explanation of inconsistencies in linkage results. They found that, for an oligogenic trait simulated under reasonable parameters, when sampling families sequentially, the first true linkage to be detected will not likely be replicated when a second pedigree series reaches the same size. One can interpret their sequential sampling simulation results into a fixed sample size, and conclude that acceptable power to replicate the first linkage was present only when the sample was several times larger than the initial sample. The reason is self evident—if there are 10 true linkages to be found, the probability of detecting *any* one of the 10 is higher than the probability of detecting one in particular. This situation leads to results that are difficult to interpret. In a given chromosomal region there may be one or two significant or suggestive reports (by the guidelines of Lander and Kruglyak[2]), and other results that do not suggest linkage. There also have been instances where several studies show nominally significant results within a given chromosomal region (that is, a result that would be significant if there were only one location to be tested) but none exceeds the genome-wide thresholds suggested by Lander and Kruglyak.[2]

Badner and Gershon[3] have presented a technique of meta-analysis for published genome scans. This technique, called the Multiple Scan Probability (MSP) modifies a meta-analysis method of Fisher[4] to allow for the fact that only regional *P*-values may be available from published studies. A similar method was first used by Allison and Heo.[5] Simulations demonstrated that a genome-wide significance criterion is appropriate for this statistic (such as the affected-sib-pair criterion where 2.2×10^{-5} is significant and 7×10^{-4} is suggestive[2]). Passing the threshold is interpreted to mean that a significant deviation from the null hypothesis of no linkage is present in at least part of the data. In our simulations, this method is both more conservative and more powerful than applying a statistical criterion to be met by at least one of several individual studies. The MSP is also robust to a considerable amount of study heterogeneity, unlike simple pooling of the data.[3]

We propose to apply this method to published genome scans for bipolar disorder and schizophrenia. We are not including the results of genetic linkage studies that are not genome scans because these studies are more likely to be susceptible to publication bias which can give misleading results in a meta-analysis. While genome scans are not entirely free of publication bias, it is unlikely that a genome scan will be wholly negative and hence not published.

Correspondence: JA Badner MD, PhD, Department of Psychiatry, University of Chicago, 5841 South Maryland Ave, MC3077, Chicago, Illinois, 60637, USA. E-mail: jbadner@yoda.bsd.uchicago.edu
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Materials and methods

Methods

Using the method developed by Fisher,[4] if the probabilities at the same point in a genome scan (ie observed pointwise *P*-values at the same marker across studies) are combined from multiple studies, the resulting probability can be calculated using the equation for MSP, ie given k independent studies with *P*-values $p_1, \ldots, p_k$

$$Y^2 = -2\Sigma_{i=1,k}\ln(p_i) \quad (1)$$

$$MSP = P(\chi^2 \text{ with } 2k \text{ degrees of freedom} > Y^2) \quad (2)$$

This would give a nominal probability which would need to be corrected for genome-wide testing. However, evidence for a linkage can occur over a broad region (20–30 cM). Therefore, it would be of interest to combine probabilities across regions rather than at single points. In order to do this, the observed minimum pointwise *P*-value from each study needs to be corrected for the size of the linkage region. Feingold *et al*[6] estimate the probability of a *P*-value being observed in a given sized region:

$$p^* = Cp + 2\lambda GZ(p)\phi(Z(p))v[Z(p)sqrt(4\lambda\Delta)] \quad (3)$$

where p is the observed pointwise *P*-value from scan i, C is the number of chromosomes, λ is the rate of crossovers per Morgan and varies depending on the method of analysis and family structure analyzed, G is the size of the region in Morgans, $Z(p)$ is standard normal inverse of p, $\phi(Z(p))$ is the normal density function, and Δ is average marker spacing in Morgans. The function $v(x)$ is a discreteness correction for the distance Δ between markers and can be approximated as $\exp(-0.583x)$ when $x < 2$. For the case of continuous markers ($\Delta = 0$, $v(x) = 1$) and small p, the above equation is essentially that used in Lander and Kruglyak[2] to derive genome-wide criteria for significance. Values for lambda can be found in Lander and Kruglayk.[2]

For each study, *P*-values were obtained from each linkage region. A region was analyzed if at least one study had a *P*-value less than 0.01 for that region. *P*-values were estimated from lod scores of different analytic methods using the equations from Nyholt.[7] For analytic methods with one-tailed LOD scores, the correction proposed by Province[8] was used. The locations of each *P*-value were estimated using the Marshfield maps.[9] When a marker could not be identified on the Marshfield map, it was identified in the genetic location database (LDB)[10] and the location of the closest Marshfield marker was used. Usually, a linkage region was defined by the location of the most significant result. However, when there was evidence of clustering of nominally significant results in a region that was distant (>30 cM) from the most significant result, the region of the cluster was defined as the linkage region. Equation 3 was used to correct each *P*-value for twice the distance away from the most significant result of the linkage region. If a result was more than 30 cM away from the most significant result, the corrected *P*-value was set equal to the average *P*-value (0.5). The marker density of each scan was incorporated into Equation 3, thereby accounting for the fact that subsequent studies may have had denser genotyping in regions that earlier studies found significant. Different rates of crossovers for each study, based on family structure and analytic method, were also incorporated into Equation 3. For each linkage region, the MSP was calculated. If the MSP was less than 0.001, a replication MSP, excluding the results of the most significant study, was calculated. Simulations by Badner and Gershon[3] demonstrate that the empirical *P*-value of the replication MSP is equivalent to the nominal *P*-value, ie, a *P*-value of 0.05 occurs 1/20 times.

For studies that have multiple analyses based on different affection models and analytic methods, there are two ways of deciding which *P*-value to use for each region. The first method is the 'Single Analysis' MSP which uses the results from only one analysis based on criteria decided prior to performing the MSP but not based on *P*-value. This will not cause increased false positives but may reduce power to detect loci that are significantly more easily detected with a particular affection model or analytic method. It also has the disadvantage that different *a priori* criteria could lead to different results of the MSP analysis. For this analysis, if a single type of analysis was performed for the whole genome and other analyses were performed in significant regions, the results from the genome-wide method were used. If multiple affection models were available, for bipolar disorder, we used models incorporating schizoaffective disorder, bipolar I and bipolar II and narrower models if that was not available. For schizophrenia, we used models incorporating schizophrenia and schizoaffective disorder and narrower models if that was not available. For multiple analytic methods, we used the result of Affected Sib Pair methods if available, if not, then we used non-parametric pedigree analysis results, and if that was also not available, then we used results from parametric methods. The specific ordering of the hierarchy is not as important as the fact that it exists *a priori* and is used consistently.

The second method is the 'Best Analysis' MSP. For studies with multiple analyses, we used the analysis with the most significant *P*-value but we corrected the *P*-value for the number of analyses performed. This will be conservative since the results from different analyses on the same data are correlated but it may have more power to detect particular loci than the 'Single Analysis' MSP.

Data

A literature search on Entrez PubMed (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?db=PubMed) was performed to identify all published genome scans for bipolar disorder and schizophrenia ever performed. Studies were included if all regions and/or markers with *P*-values < 0.05 were reported and the specific location (ie, cM along a marker) was given. When a region was presented as not having a *P*-value < 0.05 but a specific linkage statistic was not given, the *P*-value was set to the average *P*-value (0.5). When there

Table 1 Genome scans for bipolar disorder included in the meta-analysis

Study	*Diagnosis*[a]	*Population*	*No. of families*	*No. of affecteds*
Coon[19]	BPI/BPII/UP	Mixed US	8	51
Blackwood[20]	BPI/BPII	Scottish	1	13
Ginns[21]	BPI	Amish	1	31
NIMH[22–25]	SA/BPI/BPII	Mixed US	97	336
Detera-Wadleigh[26]	SA/BPI/BPII	Mixed US	22	117
Morissette[27]	SA/BPI	French Canadian	1	47
Friddle[28]	SA/BPI/BPII	Mixed US	50	183
Garner[29]	BPI	Costa Rica	1	81
Kelsoe[30]	SA/BPI/BPII/UP	US, Canada	20	48
Radhakrishna[31]	BPI/UP	Turkish	1	13
Bennet[32]	BPI	Irish	151	308

[a]SA = schizoaffective disorder; BPI = bipolar I; BPII = bipolar II; UP = unipolar depression.

were multiple distinct peaks in a region, the peak closest to the most significant result was used. The marker density at the most dense point was used to correct for distance. For multistage studies, the results from increased genotyping of markers and/or people were used if they were reported within the same paper as the initial genome scans. Follow-up papers were not included in the analysis as these would be more subject to publication bias (ie, less likely to be published if negative). When two or more publications had shared authors, an attempt was made to make sure the samples did not significantly overlap. However, it is possible there may have been some unintentional overlap of samples included in this analysis. Tables 1 and 2 describe the studies that were included in this analysis.

Results

The results of the meta-analysis for bipolar disorder are presented in Table 3. The Replication MSP was calculated when the MSP was equal or less than 0.001 (which would be similar to criteria for 'suggestive linkage'). The most significant results were for 13q (Single Analysis: MSP = 9×10^{-6}, Replication MSP = 0.003; Best Analysis: MSP = 6×10^{-6}, Replication MSP = 0.0007) and 22q (Single Analysis: MSP = 3×10^{-5}, Replication MSP = 0.006; Best Analysis: MSP = 1×10^{-5}, Replication MSP = 0.003). No other regions had an MSP less than or equal to 0.001.

For schizophrenia (Table 4), three regions had a significant MSP and a significant Replication MSP: 8p

Table 2 Genome scans for schizophrenia included in the meta-analysis

Study	*Diagnosis*[a]	*Population*	*No. of families*	*No. of affecteds*
Barr[13]	Schiz	Sweden	1	31
Coon[33]	Schiz, SA	US	9	36
Moises[34]	Schiz, SA	Iceland	5	37
Blouin[35]	Schiz, SA	Mixed US	54	276
Levinson[36]	Non-affective psychosis	Mixture	43	126
NIMH-EA[37,b]	Schiz, SA-D	US–EA	43	96
NIMH-AA[38,b]	Schiz, SA-D	US–AA	30	79
Shaw[39]	Schiz, SA	European	70	153
Hovatta[40]	Schiz	Finland	1	17
Rees[15]	Non-affective psychosis	UK/Japan	13	63
Williams[16]	Schiz, SA	UK	154	327
Bailer[41]	Non-affective psychosis + Schizotypal	Austria	5	17
Brzustowicz[42]	Schiz, SA	Celtic–Canadian	22	79
Ekelund[43]	Psychosis + affective disorder	Finland	134	308
Schwab[44]	Schiz, SA	German	71	>142
Stober[45]	Periodic catatonia	German	12	57
Gurling[46]	Schiz, SA	British, Iceland	13	56
Lindholm[14]	Schiz, SA	Sweden	1	29

[a]Schiz = schizophrenia; SA = schizoaffective disorder; SA-D = schizoaffective disorder, depressed.
[b]EA = European–American; AA = African–American.

Table 3 Meta-analysis results for bipolar disorder. The Single Analysis MSP (Multiple Scan Probability) involves using *a priori* criteria to determine which *P*-value to choose from a study which has multiple analyses for each region. The Best Analysis MSP uses the most significant probability for each study and region and makes a Bonferonni correction for the number of analyses performed by a given study. The Replication MSP omits the probability from the most significant study

Chromosome	*Location*[a]	*Single Analysis MSP*	*Replication MSP*	*Best Analysis MSP*	*Replication MSP*
1	238	0.01		0.06	
2	133	0.04		0.06	
3	209	0.02		0.05	
4	16	0.007		0.006	
5	200	0.2		0.1	
6	1 (138)	0.09		0.01	
7	17 (116)	0.01		0.01	
8	153	0.05		0.04	
9	123	0.2		0.08	
10	156	0.1		0.1	
11	66	0.01		0.03	
12	14 (112)	0.2		0.08	
13	**79**	$\mathbf{9 \times 10^{-6}}$	**0.003**	$\mathbf{6 \times 10^{-6}}$	**0.0007**
15	122	0.2		0.2	
17	126	0.3		0.3	
18p	41	0.003		0.003	
18q	126	0.004		0.007	
20	40	0.003		0.003	
21	31	0.006		0.01	
22	**36**	$\mathbf{3 \times 10^{-5}}$	**0.006**	$\mathbf{1 \times 10^{-5}}$	**0.003**

[a]Number in parenthesis refers to location for the Best Analysis MSP if different from the Single Analysis MSP.
Results in bold in Tables 3–5 are those that exceed significance criteria for MSP and replication MSP in at least one analysis.

Table 4 Meta-analysis results for schizophrenia. See legend for Table 3 for description of the methods

Chromosome	*Location*[a]	*Single Analysis MSP*	*Replication MSP*	*Best Analysis MSP*	*Replication MSP*
1	171	0.0002	0.09	0.007	
2	116	0.0008	0.2	0.0005	0.1
3	124	0.04		0.2	
4	61	0.03		0.05	
5	164	0.1		0.1	
6p	44	0.03		0.04	
6q	179	0.02		0.0001	0.3
7	114	0.004		0.002	
8	**50**	$\mathbf{2 \times 10^{-4}}$	**0.009**	**0.0005**	**0.02**
10	46	0.03		0.04	
11	76 (126)	0.04		0.03	
12	109	0.04		0.2	
13	**85**	**0.0004**	**0.04**	$\mathbf{7 \times 10^{-5}}$	**0.01**
14	44	0.02		0.02	
15	35	0.005		0.001	0.09
18	72	0.4		0.4	
22	**32**	**0.0002**	**0.002**	$\mathbf{9 \times 10^{-5}}$	**0.0009**
X	40	0.3		0.1	

[a]Number in parenthesis refers to location for the Best Analysis MSP if different from the Single Analysis MSP.

(Single Analysis: MSP = 2×10^{-4}, Replication MSP = 0.009; Best Analysis: MSP = 0.0005, Replication MSP = 0.02), 13q (Single Analysis: MSP = 0.0004, Replication MSP = 0.04; Best Analysis: MSP = 7×10^{-5}, Replication MSP = 0.01), 22q (Single Analysis: MSP = 0.0002, Replication MSP = 0.002; Best Analysis: MSP = 9×10^{-5}, Replication MSP = 0.0009). 1q, 2q, 6q, and 15q each had an MSP $\leq$ 0.001 in at least one of the analyses but did not have a significant Replication MSP. This suggests that the results were predominantly due to a single study.

It has been suggested that bipolar disorder and schizophrenia share some susceptibility genes due to the overlap in regions found to be linked to each dis-

order.[11,12] To examine this, a meta-analysis combining the results of genome scans for bipolar disorder and schizophrenia was performed (Table 5) for the chromosomes that were examined for both bipolar disorder and schizophrenia individually. Because these regions were selected on the basis of having a nominally significant result ($P < 0.01$) for bipolar disorder and schizophrenia, the Replication MSP was calculated excluding the most significant result for bipolar disorder and the most significant result for schizophrenia. In this analysis, 13q (Single Analysis: MSP = 4×10^{-7}, Replication MSP = 0.002; Best Analysis: MSP = 2×10^{-7}, Replication MSP = 0.0004) and 22q (Single Analysis: MSP = 8×10^{-8}, Replication MSP = 8×10^{-5}; Best Analysis: MSP = 2×10^{-8}, Replication MSP = 2×10^{-5}). 7q had a significant MSP and Replication MSP in one analysis (Best Analysis: MSP = 0.0003, Replication MSP = 0.02). For 7q, the more significant Best Analysis MSP appears to be due to the inclusion of results for the broad susceptibility models such as those including unipolar depression (results not shown). 1q and 2q had significant results for the MSP in at least one analysis but the replication MSP was not significant.

In these analyses, unknown *P*-values were set to 0.5 which would be the average *P*-value. To determine if this significantly affected the results, the MSPs for 13q and 22q for both bipolar disorder and schizophrenia were recalculated setting the unknown *P*-values to 1.0 which would be expected to be conservative. For 13q, the Best Analysis MSP was 4×10^{-5} for bipolar disorder and 0.0002 for schizophrenia. For 22q, the Best Analysis MSP was 0.0001 for bipolar disorder and 9×10^{-5} for schizophrenia. This suggests that the results are not significantly affected by the unknown *P*-values being set to 0.5.

Discussion

The results of the meta-analysis show strong evidence for 13q and 22q as regions harboring susceptibility loci for both bipolar disorder and schizophrenia. There is also strong evidence for a susceptibility locus for schizophrenia on 8q. 7q was significant for the Best Analysis MSP in the combined bipolar and schizophrenia analysis, which may reflect the inclusion of results from the broad affection models. 1q, 2q, 6q, and 15q showed significant MSPs for schizophrenia and non-significant Replication MSPs, which suggests that the results were due predominantly to a single study. This does not mean that there is not a susceptibility locus in these regions but the evidence for one is not as strong as those regions with significant replication MSPs.

For this analysis, we were very inclusive, not omitting any studies that had enough information to be included in this analysis. This meant including studies that had small sample sizes that might be adequate to detect a Mendelian locus but not likely to detect loci for complex genetic traits. The decision to include these studies was made on the basis of the fact that significant results from these studies are cited as evidence for particular linkage regions particularly when they are consistent with results from other studies. However, it would be possible to perform a meta-analysis on a subset of studies meeting some predefined criteria such as sample size or marker density/informativeness. This would be unbiased as long as the criteria were not based on the results of the studies. We performed a secondary meta-analysis on studies with sample sizes of 100 or more affecteds (Tables 1 and 2). For bipolar disorder, the Best Analysis MSPs were 8×10^{-5} and 0.004 for 13q and 22q respectively. For schizophrenia, the Best Analysis MSPs were 0.004 and 0.007 for 13q and 22q respectively. Although these results are less significant than the all-inclusive MSP, the results suggest that evidence for linkage is not limited to the smaller studies.

It is possible that there may have been families that were analyzed in two or more of the studies included in this analysis, specifically Barr[13] and Lindholm *et*

Table 5 Meta-analysis for bipolar disorder and schizophrenia combined. See legend for Table 3 for description of the methods

Chromosome	*Location*[a]	*Single Analysis MSP*	*Replication MSP*	*Best Analysis MSP*	*Replication MSP*
1	171	0.001	0.03	0.004	
2	116	0.002	0.4	0.002	0.4
3	209	0.1		0.3	
4	16	0.01		0.007	
5	164 (200)	0.1		0.5	
6	44 (138)	0.02		0.004	
7	114	0.01		**0.0003**	**0.02**
8	50	0.0001	0.07	0.006	
10	46	0.06		0.07	
11	66	0.01		0.08	
12	109	0.1		0.06	
13	**85**	$\mathbf{4 \times 10^{-7}}$	**0.002**	$\mathbf{2 \times 10^{-7}}$	**0.0004**
15	35	0.01		0.003	
18	41	0.05		0.04	
22	**36**	$\mathbf{8 \times 10^{-8}}$	$\mathbf{8 \times 10^{-5}}$	$\mathbf{2 \times 10^{-8}}$	$\mathbf{2 \times 10^{-5}}$

[a]Number in parenthesis refers to location for the Best Analysis MSP if different from the Single Analysis MSP.

al[14] and/or Rees *et al*[15] and Williams *et al*,[16] although it is not evident from the family data section of these studies that the samples do overlap. However, if there was some overlap, this would mean the results from these studies were not independent, which would violate the assumptions of the MSP. This could result in either false positives or false negatives. However, if the overlap was small and affected only a few of the included studies, the effect of this would be minimal.

A significant MSP and replicated MSP does not imply that evidence for linkage is present in all the studies included in the analysis. On the contrary, our simulations show that this method is powerful in the presence of study heterogeneity where linkage is present in some but not all studies.[3] Given the differing ascertainment schemes, ethnic groups, affection models, analytic methods, and markers genotyped, it would be surprising if there was no heterogeneity among the studies. Therefore, using a method that does not require homogeneity to have power to detect linkage is ideal.

Evidence for a linkage region could be due to one or more susceptibility loci in the region. This is particularly true when results for different disorders are combined. Shared linkage regions between bipolar disorder and schizophrenia do not necessarily mean shared genes for the two disorders although that is one possible explanation.

Failure to show evidence of linkage does not rule out loci present on other chromosomal regions. If most analyses have very low power to detect a particular susceptibility locus, it is likely the meta-analysis will too. Also, results may change as other genome scans are completed and included in the analysis. Thus, some regions which have low MSP but are not significant may become significant with the addition of new studies.

Two multicenter studies[17,18] combined samples from several independent centers studying schizophrenia and performed genotyping on the pooled sample and analyzed the combined data as a single set, also allowing for intersample heterogeneity. Chromosomes 3, 5q, 6p, 6q, 8, 10p and 13q were studied. Evidence for linkage was found on 6p, 6q and 8 while inconclusive evidence for linkage was found on 10p. Chromosomes 3 and 13q did not show evidence for linkage. While these results do not completely agree with the meta-analysis, they do not contradict the results either. The data from the multicenter studies were from centers that agreed to share their data. As discussed in Badner and Gershon[3] there may be biases that affect whether or not data are shared, eg, a group with a highly significant result may not want their samples to be investigated by others. And even if there were no systematic biases, the meta-analysis tends to be more inclusive simply because it requires no effort on the original investigators other than publishing their findings, whereas a collaborative study requires much effort on the original investigators. Thus, when the results differ between these two different types of analyses, it is not obvious which result is more accurate.

In conclusion, meta-analysis of genome scans for bipolar disorder and schizophrenia has found strong evidence for loci on 13q and 22q for both bipolar disorder and schizophrenia and 8p for schizophrenia. These results may help to prioritize further efforts in the identification of susceptibility genes for these disorders.

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