

Genome Scan Meta-Analysis of Schizophrenia and Bipolar Disorder, Part III: Bipolar Disorder

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Genome scans of bipolar disorder (BPD) have not produced consistent evidence for linkage. The rank-based genome scan meta-analysis (GSMA) method was applied to 18 BPD genome scan data sets in an effort to identify regions with significant support for linkage in the combined data. The two primary analyses considered available linkage

data for “very narrow” (i.e., BP-I and schizoaffective disorder–BP) and “narrow” (i.e., adding BP-II disorder) disease models, with the ranks weighted for sample size. A “broad” model (i.e., adding recurrent major depression) and unweighted analyses were also performed. No region achieved genomewide statistical significance by several simulation-based criteria. The most significant P values ($<.01$) were observed on chromosomes 9p22.3–21.1 (very narrow), 10q11.21–22.1 (very narrow), and 14q24.1–32.12 (narrow). Nominally significant P values were observed in adjacent bins on chromosomes 9p and 18p–q, across all three disease models on chromosomes 14q and 18p–q, and across two models on chromosome 8q. Relatively few BPD pedigrees have been studied under narrow disease models relative to the schizophrenia GSMA data set, which produced more significant results. There was no overlap of the highest-ranked regions for the two disorders. The present results for the very narrow model are promising but suggest that more and larger data sets are needed. Alternatively, linkage might be detected in certain populations or subsets of pedigrees. The narrow and broad data sets had considerable power, according to simulation studies, but did not produce more highly significant evidence for linkage. We note that meta-analysis can sometimes provide support for linkage but cannot disprove linkage in any candidate region.

Introduction

Bipolar disorder (BPD; loci MAFD1 [MIM 125480] and MAFD2 [MIM 309200]) is a chronic psychiatric disorder with a worldwide lifetime prevalence of 0.5%–1.5% and a predominantly genetic etiology, based on twin-study data (Craddock and Jones 1999; Baron 2002). The disorder is characterized by episodes of mania, with elated or irritable-angry mood and symptoms like pressured speech, racing thoughts, grandiose ideas, increased energy, and reckless behavior, alternating with more normal periods and, in most cases, with episodes of depression. Numerous studies have investigated linkage to BPD over the past 2 decades. Early reports suggestive of linkage led to a focus on regions of chromosome 11 (Egeland et al. 1987), the X chromosome (Baron et al. 1987), and chromosome 18 (Berrettini et al. 1994). Many whole-genome scans have been published, with the most highly positive results receiving support in some but not most other studies.

This lack of agreement among studies could be a false-negative result due to inadequate power. Even the larger available BPD genome scan data sets would not reliably detect a locus associated with a relative risk to siblings (λ_{sibs}) much less than 1.5 (Craddock et al. 1995; Hauser et al. 1996), so that loci of modest effect could produce inconsistent and weak evidence for linkage with variable peak locations (Roberts et al. 1999). Alternatively, many reported results could be false positives. Lander and Kruglyak (1995) noted that, for any large set of genome scans, several studies can produce positive re-

sults in the same regions by chance, particularly when multiple models are tested in most studies. Finally, some of the BPD findings could be true positives that cannot easily be replicated, because of substantial heterogeneity in the loci underlying BPD susceptibility across samples and across families within samples, a point to which we return below.

Meta-analysis represents one strategy for determining the significance of findings from a set of related studies. Meta-analysis of genome scans presents numerous methodological difficulties, because of the use of diverse phenotypic and transmission models, linkage analysis methods, marker maps and map densities, sample sizes, pedigree structures, and ethnic backgrounds. Here we apply the genome scan meta-analysis (GSMA) approach (Wise et al. 1999) to all known genome scans for BPD with ≥ 20 affected cases, to determine whether statistical support might be achieved for any chromosomal regions. The first article in this series (Levinson et al. 2003 [in this issue]) described the GSMA method in greater detail, including a simulation study of the method's power to detect linkage in data sets resembling the available BPD and schizophrenia scans.

Previous attempts at meta-analysis have included a multiple scan probability (MSP) analysis (Badner and Gershon 2002), which combines P values across scans in regions with clusters of positive scores after adjusting for the size of the region, and a preliminary GSMA (Segurado and Gill 2001). Both of these analyses were limited to published data. Differences between GSMA and MSP were discussed in the first article in this series (Levinson et al. 2003 [in this issue]). The GSMA presented here includes studies that were not available to Badner and Gershon (2002) and excludes some smaller studies that they included (see the “Discussion” section for further details); our analysis also includes data provided by the investigators for every marker in each scan, whereas the MSP used only published data (from studies that presented data for all nominally significant regions) and substituted P values of .5 or 1.0 for missing data

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points. By including only complete whole-genome data from each scan, the present analysis may be expected to avoid two problems inherent in publication bias: investigators tend to present their most positive results, as well as weakly positive results that seem to confirm others' findings, which could inflate meta-analysis results in those regions; and, conversely, GSMA can detect significant cross-study results for regions that are weakly positive in many studies but not sufficiently positive to have been presented as "one of the best results" in any study.

A number of decisions were required to perform this GSMA. One is related to diagnoses. Family study data demonstrate that a number of major mood disorders coaggregate in families of probands with BPD, including BP-I disorder (severely dysfunctional manic episodes with or without depressive episodes), schizoaffective-bipolar type (SAB; BP-I with periods of persistent delusions or hallucinations after remission of mood episodes), BP-II (recurrent depression with milder manias), recurrent major depression, single-episode depression, and milder mood swings (cyclothymia). Because it is not known which phenotypic definition best reflects the underlying genetics of the disorder, many investigators have performed linkage analyses designating different combinations of diagnoses as "affected." To preserve statistical power, we selected two primary phenotypic models for the GSMA, but we analyzed two additional broader models that are of interest to many investigators in the field. We did not divide the analyses by any other sample characteristic such as ethnicity.

A second decision was related to sample size. The number of genotyped affected cases in the available studies ranged from 424 to 11. As discussed in the first article in this series (Levinson et al. 2003 [in this issue]), GSMA is best suited to detect loci that influence disease susceptibility in many or all samples. It was not expected to be appropriate for revealing susceptibility loci under a classical locus heterogeneity model, in which a single extended pedigree might have the greatest power to detect linkage. Therefore, we excluded from the primary analyses those scans with <20 affected cases; these were not considered to contribute any additional power to detect linkage by GSMA and represented the extreme of the observed distribution of sample sizes.

Finally, we analyzed each phenotypic model with and without a weighting factor for sample size ($\sqrt{N[\text{affected cases}]}$, the square root of the number of genotyped affected cases), which simulation studies demonstrated will increase power when the genetic effect of a locus is similar across samples. Thus, we considered our primary analyses to be the weighted analyses of models 1 and 2 (defined below).

Material and Methods

Data Collection

Genome scans in BPD, either published or unpublished, were identified via literature databases, conference presentations, and personal contact with researchers in the field. Each group was contacted to secure their collaboration and to obtain the full list of markers used and genomewide linkage scores, if these had not been published. Six genome scan reports that included pedigrees from the Old Order Amish (OOA) sample (Detera-Wadleigh et al. 1994; Gerhard et al. 1994; Ginns et al. 1996; LaBuda et al. 1996; Polymeropoulos and Schaffer 1996; Berrettini et al. 1997) were excluded, because of sample overlap, in favor of the study that included OOA data and had the largest overall number of affected individuals (Detera-Wadleigh et al. 1999). An additional four scans (Blackwood et al. 1996; Adams et al. 1998; Radhakrishna et al. 2001; Ewald et al. 2002) had <20 genotyped affected cases and were excluded from primary analyses; a secondary analysis including these four scans, without weighting for sample size, did not reveal any additional findings (details available upon request). Table 1 shows the list of 18 included scans and diagnostic details. These 18 genome scans are from 16 research groups, and 12 of the scan analyses used here have been published or are in press.

After examining the diagnostic schemes used in these 18 studies, we selected two primary models for GSMA: model 1 ("very narrow"), including as affected either BP-I cases or BP-I and SAB cases; and model 2 ("narrow"), including BP-I, SAB, and cases judged by the original investigators to meet current Diagnostic and Statistical Manual (DSM)-IV criteria for BP-II. We felt that the primary analyses should focus on BPDs, and there were too few scans with analyses of the very narrow model for us to be comfortable limiting the primary analyses to those data; therefore, we focused on these two models. Nine studies included linkage analyses consistent with our model 1, with a total of 347 pedigrees and 948 genotyped cases. Fourteen studies included linkage analyses consistent with model 2 (512 pedigrees, 1,733 cases). Among these 14 were 6 studies that had analyzed both models 1 and 2; 3 studies with only a model 1 analysis, which was therefore also included in our model 2; and 5 studies with an analysis under model 2 but not model 1.

Secondary analyses were also performed under a "broad" disease model (model 3, adding recurrent major depressive disorder [MDD]; 593 pedigrees, 2,437 cases), which has been of interest to a majority of investigators because MDD is the most common disorder in families with BPD. Note that we included in the model 3 analysis several studies that included a small proportion of cases

Table 1

Characteristics of Bipolar Genome Scans

STUDY SITE	FIRST AUTHOR ^a	DIAGNOSTIC CRITERIA ^b	TOTAL NO. OF										NO. OF EMPTY BINS ^c	GENETIC MODEL(S) ^d	TYPE OF ANALYSIS	OUTPUT USED ^e	ETHNICITY ^h
			NO. WITH DIAGNOSIS ^d			NO. OF MARKERS			NO. OF OTHER								
			Peds	Aff	Model	1	2	3	BP-I	SAB	BP-II	RUP					
Very narrow analysis:																	
NIMH	Detera-Wadleigh ¹	R+D3R	97	424	264	336	424	232	32	72	88	355	3	NP	Multipoint	NPL	NAm
U.K./Irish	Bennett ²	D4	151	367	288	325	367	288	12	25	34	8	0	NP	Multipoint	MLS	Ir+Br
Columbia	Liu ³	R	39	297	115	208	297	101	14	93	89	333	0	D+R	Two-point	LOD	NAm
Finland	Ekholm ⁴	D4	41	132	107	107	132	95	12	2	16	7	0	D+R	Two-point	LOD	Finnish
Sydney 1	Badenhop ⁵	R	13	69	40	44	69	33	7	4	25	298	0	(4)	Two-point	LOD	Eur (Aust)
Sydney 2	Schofield ⁶	R	15	63	41	46	63	31	10	5	17	382	0	(4)	Two-point	LOD	Eur (Aust)
Quebec	Morissette ⁷	D3R	5	56	42	42	56	39	3	5	9	314	0	D+R	Two-point	LOD	Quebec isol
Edinburgh	Blackwood ⁸	D3R	7	41	27	36	41	27	8	1	5	372	0	D+R	Two-point	LOD	British
Costa Rica	McMinnis ⁹	D3R	2	24	24	24	24	22	2	2	473	1	D	Two-point	LOD	CR isol	
Total (Model 1)					948			868	80								
Added for narrow analysis:																	
Hopkins/Dana	McMinnis ¹⁰	R	65	301	232	301	129	6	97	69	823	0	NP	Multipoint	NPL	NAm	
Bonn	Cichon ^{11,12}	R+D3R	75	245	128	128	104	24	24	(23)	359	0	NP	Multipoint	NPL	G+Is+It	
NIMH-IM	Detera-Wadleigh ¹²	R	22	160	118	160	64	18	36	42	584	0	NP	Multipoint	MLS	NAm+OOA	
UCSD	Kelsoe ¹³	D3R	20	76	48	76	33	15	28	15	428	1	(3)	Two-point	LOD	NAm	
UC London	Curtis ^{14,15}	R	7	74	39	39	24	15	15	(35)	365	0	Max	Two-point/three-point	LOD	Br+Icelandic	
Total (models 1+2)					1,733			1,222	124	394							
Added for broad analysis:																	
Ottawa	Turecki ¹⁵	R	31	106	106	106	33	3	25	45	363	1	(5)	Two-point	LOD	Eur (Can)	
Antwerp 1	Van Broeckhoven ¹⁶	R	10	56	56	56	14	1	15	21	5	372	0	D+R	Two-point	LOD	Belgian
Utah	Coon ¹⁷	R	8	51	51	51	20	12	19	19	328	19	D	Two-point	LOD	Eur	
Antwerp 2	Van Broeckhoven ¹⁶	R	9	47	47	47	22	2	6	17	361	0	NP	Multipoint	NPL	Swedish	
Total (models 1+2+3)					2,437			1,311	130	452	524	20					

NOTE.—Total number of pedigrees collected is shown here; the numbers included in the model 1 and 2 analyses are shown in figures 1 and 2. ^a Superscripts indicate references as follows: 1 = Detera-Wadleigh et al. (1997), Edenberg et al. (1997), Rice et al. (1997), and Stine et al. (1997); 2 = Bennett et al. (2002); 3 = Liu et al. (2003); 4 = Ekholm et al. (2002) and J.E., L.P., and J.L.O. (unpublished data); 5 = Badenhop et al. (2002); 6 = R.F.B., P.B.M., J.A.D., L.J.A., and P.R.S. (unpublished data) and Badenhop et al. (2002); 7 = Morissette et al. (1999); 8 = Blackwood et al. (1996) and D. Blackwood, W. Muir, D. Porteus, and S. Macgregor (unpublished data); 9 = McMinnis et al. (1996); 10 = McMinnis et al. (2003); 11 = Cichon et al. (2001); 12 = Detera-Wadleigh et al. (1999); 13 = Kelsoe et al. (2001); 14 = Curtis et al. (2003); 15 = Turecki et al. (2001); 16 = C.V., S.C.H., J.M., and R.A. (unpublished data); 17 = Coon et al. (1993).

^b R = RDC; D3R = DSM-III-R; D4 = DSM-IV. ^c Peds = informative pedigrees; Aff = affected genotyped cases. ^d SAB = schizoaffective bipolar; RUP = recurrent major depressive (unipolar) disorder; Other = other mood disorder. Columns for Models 1 (BP-I+SAB), 2 (+BP-II) and 3 (+RUP) show the number of genotyped affected cases; additional columns show numbers for each diagnosis. Data from narrower models were carried over if the broader model was not available. For Bennett and Blackwood, SAB cases (highlighted in boldface italic type) were included in model 2 but not model 1 analyses. For Cichon, BP—not otherwise specified cases were judged equivalent to DSM-IV BP-II by the investigators and are listed as such here. “Other” diagnoses were distributed and handled as follows (included in model 3 analyses, because these cases were a small proportion of the study’s broadest analysis): from Bennett, eight BP—not otherwise specified; from Ekholm, three BP—not otherwise specified, two single-episode unipolar, and two cyclothymia; from Van Broeckhoven (Antwerp 1), five cyclothymia. Excluded from model 1 (included in model 4); from Cichon, 23 single-episode unipolar; from Curtis, 28 single-episode unipolar and RUP, and seven other mood disorders. ^e Number of bins with 0 markers. ^f NP = nonparametric, no model; D = dominant; R = recessive; max = maximized over parameters. Numbers in parentheses indicate the number of models tested. ^g LOD = parametric LOD score; MLS = maximum LOD score, ASP analysis. ^h Br = British; Eur = predominantly European descent; Ir = Irish; It = Italian; NAm = North American (predominantly European); Aust = Australian; CR = Costa Rican; G = German; Is = Israeli; Can = Canadian; OOA = Old Order Amish isolate; isol = genetic isolate.

¹ For Cichon, included in models 2 and 3 was an analysis of 104 BP-I and 24 BP-II cases; the only other analysis included 128 BP-I, 14 SAB, 40 BP-II, 40 RUP, and 23 Other cases and was used here only for model 4. ² For Curtis, an analysis of 24 BP-I and 15 BP-II cases was included in models 2 and 3; an additional 35 Other cases were included only in model 4.

with additional, broader diagnoses (see table 1), but we excluded studies whose broad model included a large proportion of cases with other diagnoses. We also applied a “very broad” model (model 4, adding single-episode major depression and cyclothymic disorder; 617 pedigrees, 2,589 cases); results did not reveal any additional significant findings and are not presented here but are available upon request. Table 1 lists the sample sizes under each disease model; those for models 1 and 2 were small compared with the schizophrenia analysis (1,208 pedigrees, 2,945 cases) reported in the previous article in this series (Lewis et al. 2003 [in this issue]).

The linkage statistics used by each study are detailed in table 1. Research groups were asked to indicate their primary linkage statistic if several were applied, and this was preferentially used for ranking. In most cases, parametric single-point LOD scores had been computed under two to five transmission models, and we selected the most significant of these scores (i.e., maximized across models) as the score for each marker. Other linkage scores included were multipoint nonparametric tests, including the maximum LOD score (MLS), for likelihood-based affected-sibling-pair (ASP) analysis, or nonparametric linkage (NPL) analysis.

The selected studies were consistent in that they achieved reasonably even marker coverage of the genome, used well-established linkage statistical methods, diagnosed mood disorders on the basis of modern diagnostic instruments and criteria, and included predominantly European-ancestry subjects; however, the studies did vary in sample size, evenness of marker spacing, the number of linkage analyses that were applied, community-based versus more ethnically homogeneous samples, and the typical size of pedigrees.

GSMA

Meta-analysis was performed as described by Wise et al. (1999) and in the first two articles of this series (Levinson et al. 2003 [in this issue]; Lewis et al. 2003 [in this issue]). Terminology is summarized in appendix A. In brief, the genome was divided into 120 30-cM bins defined by markers from the Généthon map (CEPH-Généthon Integrated Map Web site). The average bin width on the Marshfield map (Center for Medical Genetics Web site) was 29.1 cM. These boundary markers and their Marshfield locations are shown in figures 1 and 2. Each marker from each study was placed within one of these bins, on the basis of its location on the Généthon, Marshfield, or Southampton (Genetic Location Database Web site) maps or the human genome map (NCBI Home Page). For each study in a given analysis, the maximum linkage score (or minimum P value) was selected within each bin, and the bins were assigned a rank (R_{study}) in ascending order (“1” designates the bin

with the most significant result). Negative or zero scores were treated as a set of ties and given the average rank for the set (e.g., if there were 20 such scores, all were ranked 110.5). The average rank (R_{avg}) across studies was then computed for each bin. For the weighted analysis, each R_{study} value was then multiplied by its study’s weight ($\sqrt{N[\text{affected cases}]}$, divided by the mean of this value over all studies), as discussed in the first article in this series (Levinson et al. 2003 [in this issue]). Two pointwise P values were determined by permutation (5,000 permutations per analysis): P_{AvgRnk} and P_{ord} , as defined in appendix A.

Results

Data for 22 genome scans were collected, and 18 were selected for analysis under models 1–3, as discussed above (table 1). For these 18 studies, an average of 404.2 (SD 122.9) markers were tested per scan, or 3.37 (SD 1.02) per 30-cM bin. Of the 18 scans, 13 had markers in all bins, 4 had no markers in 1–3 bins, and 1 older scan (Utah) had no markers in 19 bins. Linkage results for missing bins were extrapolated as the average of surrounding bins. Bins on chromosomes 5, 18, 21, and 22 were covered by >4.6 markers per study, a potential confounding factor that could not be eliminated, because, for some studies, the available analyses included both “screening” markers and those included to test these candidate regions.

The power of these data sets to detect linkage at various thresholds was studied as described in detail in the first article in this series (Levinson et al. 2003 [in this issue]). Empirical significance thresholds are summarized in appendix A. When there were 10 linked bins in the genome with a populationwide λ_{sibs} of 1.3 for each locus, the mean number of bins achieving $P < .000417$ was 0.4 for model 1 and 2.34 for model 2. The power to detect any one locus associated with a λ_{sibs} of 1.15 at $P < .05$ was 0.49 for model 1 and 0.77 for model 2, averaged across simulated conditions. The most powerful empirical index of linkage was the observation of both P_{AvgRnk} and $P_{\text{ord}} < .05$ —for example, with 10 linked bins in the genome, for $\lambda_{\text{sibs}} = 1.3$, a mean of 4.54 linked bins would achieve this for model 1, and a mean of 8.43 would achieve this for model 2; or, for $\lambda_{\text{sibs}} = 1.15$, 1.53 and 4.68 bins, respectively.

Figures 1 and 2 summarize the ranked data for each study for models 1 and 2 and show the average ranks for each bin for the weighted analysis and its place in the order of average ranks. The markers that define the bin boundaries are shown, along with their locations on the Marshfield map. For clarity, the R_{study} values have been divided into eight ranges, with “1” representing ranks 1–5, “2” representing ranks 6–10, etc., as shown in the legend at the bottom of each figure.

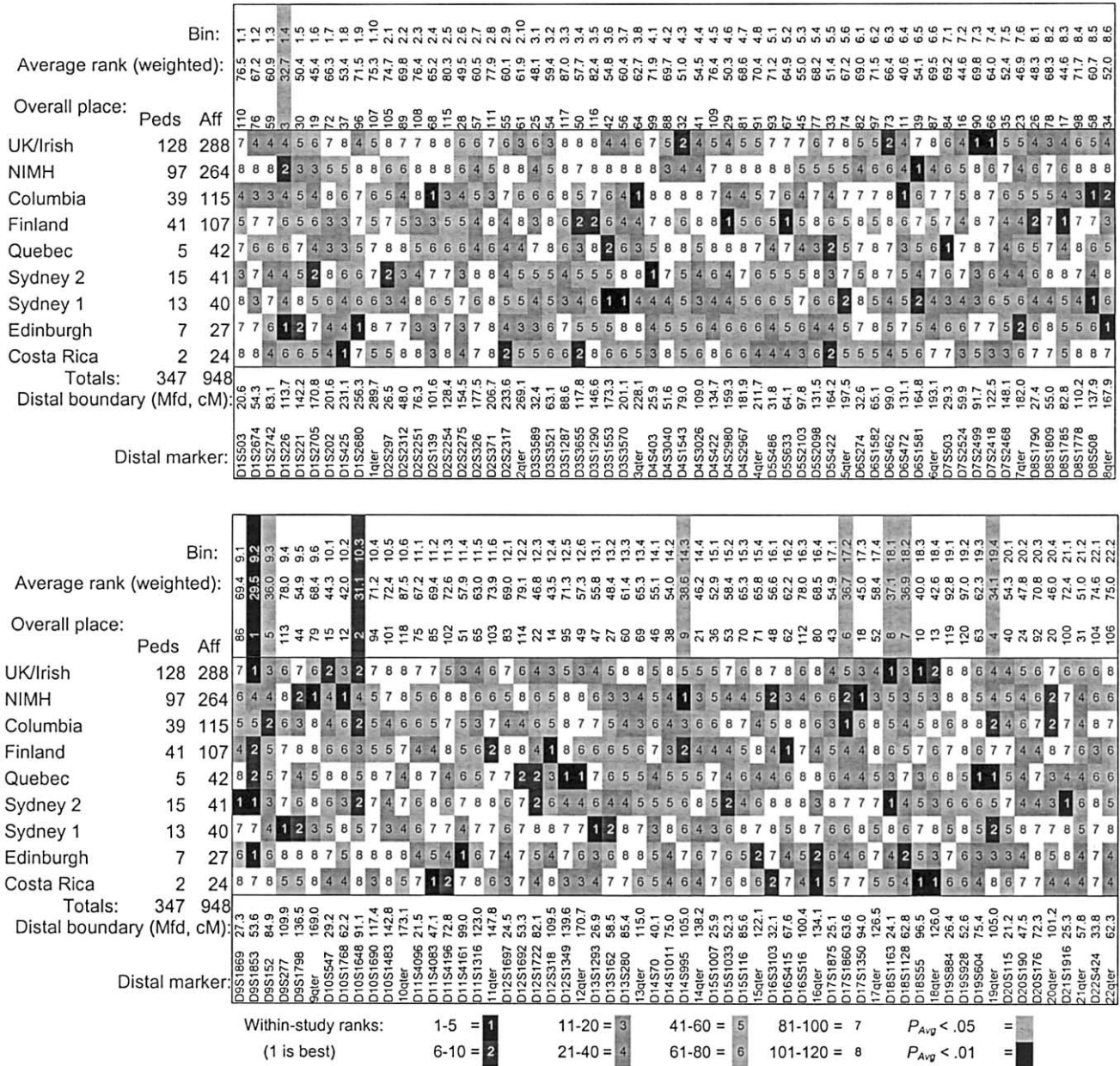


Figure 1 Individual study and weighted average ranks by bin (model 1). The following are shown: within-study ranks (R_{study}) grouped as shown in the legend; the average rank (R_{avg}) for each bin across studies (low values are best), weighted proportional to \sqrt{N} (affected cases) for each study; and the overall place of each bin in ascending order of average ranks (the lowest/best average rank is first-place). Average ranks with significant P_{AvgRnk} values are highlighted above the columns (black for $P_{AvgRnk} < .01$, gray for $P_{AvgRnk} < .05$). Tied ranks sometimes resulted in uneven numbers of bins in some groupings, particularly for lower ranks when there were many zero or negative scores. Marshfield (“Mfd”) locations are shown for the marker at the distal boundary of each bin. Bin boundaries were selected at ~30-cM spacing on the Génethon map; mean bin width is 29.1 cM on the Marshfield map. Peds = number of pedigrees; Aff = number of genotyped affected cases. See table 1 for the references associated with each study.

Table 2 shows P_{AvgRnk} and P_{ord} values, for all bins that achieved $P_{AvgRnk} < 0.1$ in each of these analyses, in ascending overall order. Table 3 shows the same data in a different format, to illustrate patterns across models: all bins are listed that achieved $P_{AvgRnk} < .05$ under any

of models 1–3 (weighted or unweighted). P_{AvgRnk} values $< .1$ are shown, to illustrate whether a bin tended to achieve lower ranks even under those models in which a nominal level of significance was not observed. Note that these analyses are nonindependent—that is, the

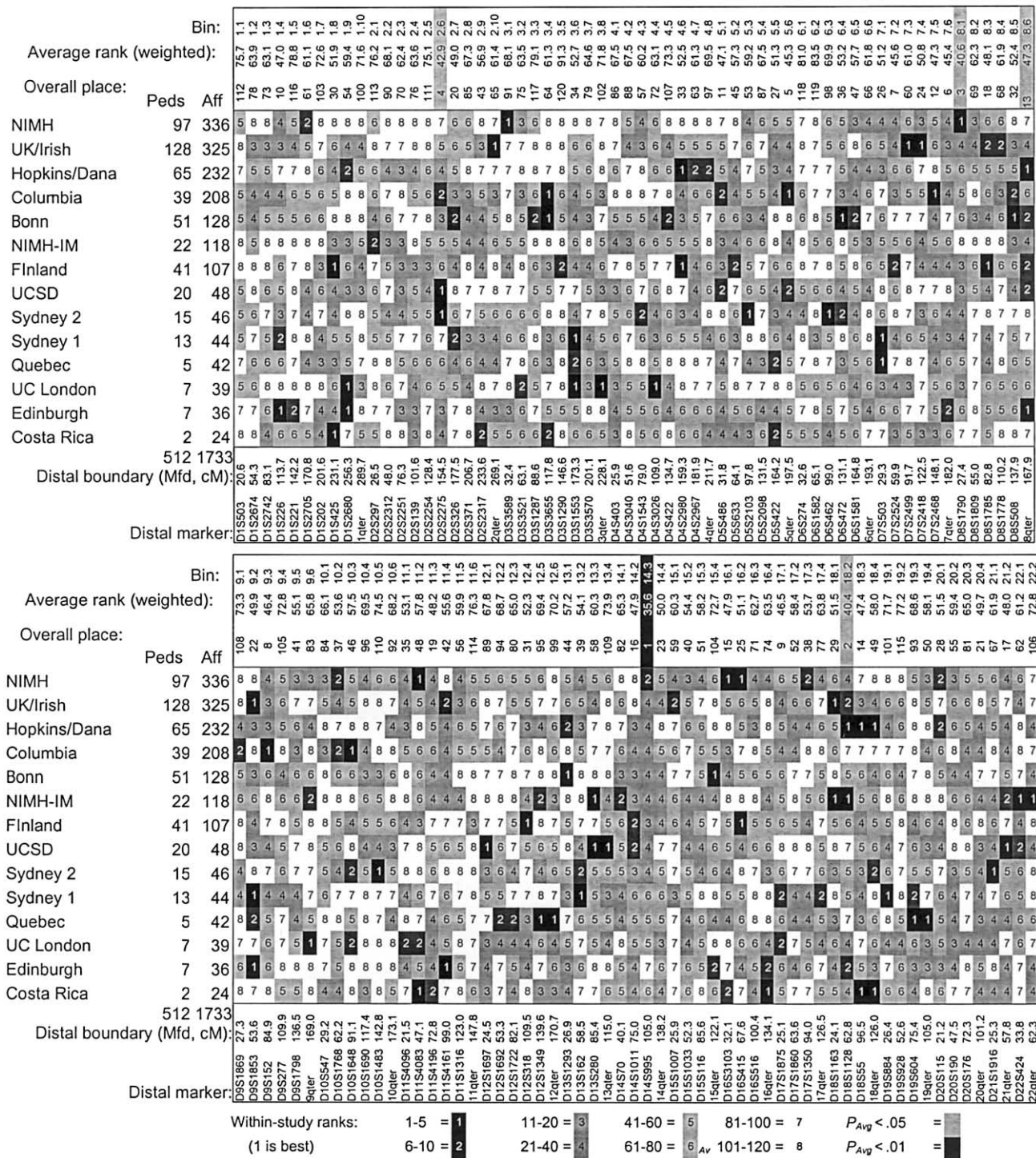


Figure 2 Individual study and weighted average ranks by bin (model 2) (see fig. 1 for explanation)

broader models include the pedigrees from the narrower models.

No bin reached a genomewide level of significance (P_{AvgRnk}) in any analysis, and none of the aggregate criteria for linkage, established in the simulation studies

described in the first article in this series (Levinson et al. 2003 [in this issue]), were met here: in simulated data, <5% of unlinked GSMA replicates had ≥ 11 bins that achieved by-bin P values <.05; here, the maximum number of such values was 9 for model 1-weighted and

Table 2

 P_{AvgRnk} and P_{ord} Values for Models 1–3

PLACE	WEIGHTED ANALYSES									UNWEIGHTED ANALYSES								
	Model 1			Model 2			Model 3			Model 1			Model 2			Model 3		
	Bin	P_{AvgRnk}	P_{ord}	Bin	P_{AvgRnk}	P_{ord}	Bin	P_{AvgRnk}	P_{ord}	Bin	P_{AvgRnk}	P_{ord}	Bin	P_{AvgRnk}	P_{ord}	Bin	P_{AvgRnk}	P_{ord}
1	9.2	.006	.497	14.3	.003	.309	14.3	.006	.544	9.2	.009	.685	2.6	.014	.829	14.2	.011	.751
2	10.3	.008	.267	18.2	.013	.478	18.2	.015	.557	1.4	.016	.583	14.2	.016	.605	18.2	.018	.647
3	1.4	.013	.191	2.6	.036	.841	8.6	.037	.850	19.4	.021	.465	14.3	.017	.334	18.3	.019	.406
4	19.4	.017	.144	8.1	.044	.809	7.6	.043	.803	18.1	.038	.698	18.3	.023	.294	11.3	.025	.355
5	9.3	.026	.195	8.6	.045	.672	18.3	.048	.727	10.3	.046	.685	18.2	.027	.209	14.3	.040	.552
6	17.2	.031	.143	5.6	.051	.588	11.3	.054	.658	18.2	.057	.719	5.1	.038	.293	20.1	.045	.456
7	18.2	.031	.057	18.3	.061	.631	20.1	.058	.572	18.3	.059	.595	1.8	.041	.203	21.2	.052	.454
8	18.1	.033	.026	5.1	.065	.547	14.2	.059	.420	5.5	.062	.468	21.2	.042	.107	7.5	.056	.357
9	14.3	.043	.049	21.2	.075	.582	12.4	.064	.354	17.2	.070	.469	3.6	.047	.088	2.6	.056	.214
10	18.3	.055	.091	7.6	.079	.483	21.2	.071	.333	1.8	.070	.325	8.1	.049	.047	1.8	.057	.124
11	6.4	.060	.070	9.3	.080	.342	5.6	.073	.230	9.3	.073	.236	7.5	.059	.065	12.4	.059	.074
12	10.2	.075	.153	14.2	.100	.572	11.1	.079	.212	20.4	.083	.269	8.6	.069	.081	7.6	.059	.036
13	18.4	.082	.138				2.6	.082	.151	12.3	.091	.259	20.4	.074	.067	8.6	.064	.024
14	12.4	.094	.200				9.3	.085	.102	3.4	.092	.170	5.6	.080	.060	20.4	.093	.194
15							5.1	.097	.140	7.5	.095	.117	11.3	.085	.051			
16										18.4	.097	.070	9.2	.087	.029			
17													2.9	.091	.021			

NOTE.—Shown are P_{AvgRnk} and P_{ord} values for all bins with P_{AvgRnk} values $<.1$ in each analysis, sorted by their overall place in the order of average ranks for that analysis. P values $<.05$ and the associated bin labels are shown in boldface italic type.

10 for model 2—unweighted. Also, $<5\%$ of unlinked GSMA replicates had five or more bins that achieved both P_{AvgRnk} and $P_{\text{ord}} <.05$; this was not observed in any of the BPD analyses. Finally, $<5\%$ of unlinked GSMA replicates had four or more bins with $P_{\text{ord}} <.05$ among the bins with the 10 best average ranks; no BPD analysis had more than two such bins.

The simulation studies also suggest that, among those bins with nominally significant P_{AvgRnk} values, those that also achieve nominally significant P_{ord} values are the most likely to be linked. In the model 1—weighted analysis, this was observed for bins 18.1 ($P_{\text{AvgRnk}} = .033$; $P_{\text{ord}} = .026$) and 14.3 ($P_{\text{AvgRnk}} = .043$; $P_{\text{ord}} = .049$). However, these P values do not meet genomewide levels of significance.

We also performed an exploratory GSMA (not shown in tables 2 and 3) under model 3 for the nine studies that had no model 1 analysis, since these represented an independent model 3 data set. P_{AvgRnk} values $<.01$ were observed for bins 14.2 ($P_{\text{AvgRnk}} = .0025$) and 8.6 ($P_{\text{AvgRnk}} = .0046$), and $P_{\text{AvgRnk}} <.05$ was observed for bins 12.4, 11.3, 18.2, 8.5, 20.1, and 9.6 (for which P_{ord} was also $<.05$). Thus, no new striking evidence for linkage was observed, and the regions of interest were similar to other analyses, with the addition of chromosomes 9q and 12q.

Finally, to determine whether the placement of bin boundaries was having a critical effect on results, adjacent bins were combined into 60-cM bins, for the two possible combinations (e.g., for chromosome 1, bins 1+2, 3+4, etc.; and then 2+3, etc.), for models 1 and 2 (weighted and unweighted). More highly significant P values were not observed. Regions of interest were

the same, with two exceptions. For model 2 (weighted and unweighted), bins 7.5 and 7.6 (7q31.1-qter) and bins 9.2 and 9.3 now achieved $P_{\text{AvgRnk}} <.05$, suggesting that a different placement of bins might have produced nominally significant average ranks in 30-cM bins surrounding the boundaries between these two pairs of markers (148.1 cM on chromosome 7 and 53.6 cM on chromosome 9).

Additional data are available at the University of Pennsylvania Web site listed in the “Electronic-Database Information” section, including tables of summed ranks (weighted and unweighted) for each sample and scatterplots of average ranks, for models 1–4.

Discussion

We have conducted a rank-based meta-analysis of genome scans for BPD, incorporating data from all known nonoverlapping studies with >20 affected cases, to investigate the combined evidence for linkage across studies. The rank-based nature of the analysis and the stringency in selection of studies should ensure that the meta-analysis is not biased by statistical methodology or by the nature of the individual samples, although it remains possible that it was confounded by typing of additional markers in well-known candidate regions.

Previous meta-analyses (Segurado and Gill 2001; Badner and Gershon 2002) have used only published data. Badner and Gershon (2002) used the MSP method, based on P values, which identified regions of chromosomes 13q (at 79 cM; bin 13.3 here) and 22q (at 36 cM; bin 22.2 here) as being likely to contain BPD

Table 3
Patterns of Significance across Models

BIN	MARSHFIELD LOCATION (BEGIN-END) (cM)	CYTOGENETIC POSITION	P_{AvgRnk}^a					
			Weighted			Unweighted		
			Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
1.4	83.07–113.69	1p32.1-q31.1	<.05			<.05		
1.8	201.58–231.11	1q31-q32				<.1	<.05	<.1
2.6	128.41–154.48	2q22.1-q23.3		<.05	<.1		<.05	
3.6	146.6–173.34	3q22.1-q25.31					<.05	
5.1	0–31.78	5pter-p15.1		<.1	<.1		<.05	
7.6	122.48–148.11	7q34-qter		<.1	<.05			<.1
8.1	148.11–190.0	8pter-p22		<.05			<.05 ^b	
8.6	137.92–167.9	8q24.21-qter		<.05	<.05		<.1	<.1
9.2	27.32–53.6	9p22.3-p21.1	<.01			<.01	<.1	
9.3	53.6–84.9	9p21.1-q21.32	<.05	<.1	<.1	<.1		
9.6	109.9–136.5	9q33.3-9qter						
10.3	62.23–91.13	10q11.21-q22.1	<.01			<.05		
11.3	47.06–72.82	11p13-q13.3			<.1		<.1	<.05
12.4	82.12–109.47	12q15-q23.2						
14.2	40.11–74.96	14q13.1-q24.1			<.1		<.05	<.05
14.3	74.96–105	14q24.1-q32.12	<.05 ^b	<.01	<.01		<.05	<.05
17.2	25.14–63.62	17p12-q21.33	<.05			<.1		
18.1	0–24.08	18pter-p11	<.05 ^b			<.05		
18.2	24.08–62.84	18p11-q12.3	<.05	<.05	<.05	<.1	<.05	<.05
18.3	62.84–96.48	18q12.3-q22.1	<.1	<.1	<.05	<.1	<.05	<.05
19.4	75.41–105.0	19q13.33-qter	<.05			<.05		
20.1	0–21.15	20pter-p12.3			<.1			<.05
21.2	25.26–57.8	21q21.3-qter			<.1		<.05	<.1

^a Listed are all bins with $P_{\text{AvgRnk}} < .05$ under any disease model. P_{AvgRnk} values $< .1$ are shown only to indicate how consistently a bin achieved lower ranks across models.

^b Indicates that a bin with $P_{\text{AvgRnk}} < .05$ also had $P_{\text{ord}} < .05$.

susceptibility loci. The data sets only partially overlap—that is, their analysis included four studies that contributed identical data to the present meta-analyses, three that were not included here, and four for which there were apparently differences in the data used (details available on request). Further, for the present analysis, the investigators provided data for all markers in each scan if these were not listed in the publication. Badner and Gershon (2002) also combined data from different diagnostic models. Thus, it is possible that differences in the data sets account for the differences in results. This interpretation is supported by the fact that a preliminary GSMA of a similar set of published data (Segurado and Gill 2001) also observed its most significant results on chromosomes 13q and 22q. These results are not supported by the present analysis, which was based on a larger number of data sets, complete genome scan data, and separate analyses of each diagnostic model. Linkage might be present in these regions in some samples, or it might be present too weakly to detect consistently.

In the absence of genomewide significant findings, we note here the patterns of results that may be of interest to BPD researchers. The most significant P_{AvgRnk} values in the primary weighted analyses of models 1 and 2

were observed for bin 14.3 ($P_{\text{AvgRnk}} = .003$; model 2), bin 9.2 ($P_{\text{AvgRnk}} = .006$; model 1), and bin 10.3 ($P_{\text{AvgRnk}} = .008$; model 1). Two other trends of possible interest include (1) observing low average ranks for a bin across diagnostic models, which would be consistent with family study data suggesting a BPD spectrum; and (2) observing low average ranks for adjacent bins, which was common in the simulation studies in the presence of linkage. In the primary analyses, bins 9.2 and 9.3 achieved $P_{\text{AvgRnk}} < .01$ and $P_{\text{AvgRnk}} < .05$, respectively, and bins 18.1 and 18.2 achieved $P_{\text{AvgRnk}} < .05$ (all under model 1). Bins 14.3 and 18.2 achieved $P_{\text{AvgRnk}} \leq .05$ across models 1–3 (weighted analyses), bin 8.6 achieved this for models 2 and 3, and bins 9.2 and 9.3 achieved this for models 1 and 2 when they were combined into a single 60-cM bin. Thus, the present analyses provide some support for the hypothesis that regions on chromosomes 14q, 9p-q, 10q, 18p-q, and 8q could contain loci that are weakly linked to BPD in multiple populations. Because none of these findings achieved a genomewide level of significance on the basis of empirical criteria, we do not review in detail the previous data supporting these findings; most of these data are contained in the genome scan studies that had the lowest average ranks in these regions (figs. 1 and 2) and can

be found in the referenced publications for these studies and in other publications by these research groups.

One possible confounding factor here is that bins 18.2, 18.3, and 18.4 were tested with more markers per bin than elsewhere in the genome—an average of 6.56 for bin 18.2 (the largest value in the genome), 4.78 for bin 18.3, and 5.28 for bin 18.4. For model 3, there was a Pearson correlation of -0.46 ($P < .00001$) between the average number of markers for the 120 bins and their average ranks. Uniformly high marker density would be an advantage, but, if some bins have much higher marker density than average, a slightly higher maximum linkage score tends to be observed within them because of increased information content (recall that lower scores are ignored), although the higher densities observed here are not extreme in this regard (L. Wise, unpublished data). GSMA could be further confounded if investigators who observed some evidence for linkage in a candidate region then decided to increase marker density. Low average ranks were not noted for other regions with very high marker density on chromosomes 5, 21, and 22. Marker density might have contributed to our evidence for linkage on chromosome 18 or might simply have been a response to reports of linkage in this region.

There are many possible interpretations of our failure to find genomewide significant evidence for linkage to BPD. A general caveat is that, in complex disorders, negative results do not disprove linkage; therefore, the present study should not be interpreted as an absence of genetic effects that might be detected by other methods—we tested only the hypothesis that GSMA could detect loci that contributed to BPD susceptibility in many of these diverse populations, through use of available samples.

It is possible that methodological factors contributed to the negative results. On the broadest level, one might consider the strengths and limitations of GSMA as a method of meta-analysis. Whereas traditional meta-analysis methods estimate an effect size from studies that used the same methods and statistical tests, GSMA is a nonparametric approach that tolerates a degree of variability in sampling and statistical methods, yielding largely empirically based measures of significance rather than an effect size and localizing signals into relatively broad bins (here, 30 cM in width). This flexibility of GSMA is also a limitation, dictated by the limitations of available genome scan data—it is possible that the variability among BPD studies is impacting negatively on the GSMA in undetected ways, and, indeed, in our simulation studies we did not study the effects of some of the decisions we made here, such as maximizing LOD scores across two or more transmission models, marker by marker, or including samples with diverse pedigree sizes and structures. In most respects, however, there

was similar variability in the schizophrenia GSMA that did produce genomewide significant results.

There are unresolved issues regarding the genetic epidemiology of the spectrum of mood disorders that could have influenced these results. A full review of these issues is beyond the scope of this article, but we will note several of them. The relative risk of BP-I disorder in relatives of probands with BP-I versus the general population has been estimated at 4–10 (Maier et al. 1993; Merikangas et al. 2002; Taylor et al. 2002). Relative risk appears to be elevated for probands with younger age at onset (Todd 2002), but genome scans have not focused on early-onset cases. There are conflicting data about differential risks depending on the sex of the transmitting parent and/or of the proband (McMahon et al. 1995; Gershon et al. 1996; Grigoriou-Serbanescu et al. 1998). There are a number of issues regarding the differentiation between BP-I and BP-II disorders. Although they are often combined in analyses, it is possible that they are partially genetically distinct: BP-II is more common in the relatives of probands with BP-II than it is in the relatives of probands with BP-I (Endicott et al. 1985; Heun and Maier 1993), one study reported a greater relative risk for BP-II than for BP-I (Heun and Maier 1993), and at least one linkage result was observed primarily in families with BP-II–BP-II ASPs (McMahon et al. 2001). Interrater reliability in assessment of BP-II can be quite high (Simpson et al. 2002) but has typically been only fair (Rice et al. 1986; Leboyer et al. 1991). The proportion of BP-I to BP-II cases varies greatly across studies (table 1). Thus, differences in approaches to diagnosing and analyzing these two disorders may be a source of unmeasured variability across linkage studies. Lastly, although major depression is the most common disorder among the relatives of probands with BPD, it is also common in the population, and it has not been possible to distinguish “bipolar” and “unipolar” depression on the basis of clinical features and course (Blacketer et al. 1996); therefore, BPD genome scans might be including genetically heterogeneous cases of depression. Different and more consistent approaches to some of these issues might produce greater consistency in linkage findings across studies.

Our negative results could also be due to the interrelated problems of sample size, ethnic background, and pedigree structure. A parsimonious interpretation would be simply that power was inadequate. Only 347 pedigrees with BPD have been analyzed with a very narrow model (model 1), versus $\sim 1,200$ for schizophrenia, for which the GSMA was more successful. If there are differences in the genetic architecture of BP-I, BP-II, and MDD in these families, then it is possible that only analyses of much larger samples of narrowly diagnosed cases will detect loci that influence BPD sus-

ceptibility in many or most populations. Larger samples are currently being collected or analyzed, so that this hypothesis should be testable in the near future.

Alternatively, it is possible that BPD is characterized by one or several types of substantial genetic heterogeneity—that is, major differences in the loci that underlie susceptibility in different populations, the existence of multiple sets of interacting loci within each population, and/or the existence of many different loci that play major roles in susceptibility in a small proportion of extended pedigrees. In each of these cases, GSMA would be unlikely to have sufficient power. The present analysis included three samples from unique populations (Finland, Quebec, and the Central Valley of Costa Rica), as well as samples comprised of highly selected extended pedigrees (such as Columbia, Edinburgh, National Institute of Mental Health [NIMH]–Intramural Program [IM], and University College [UC] London) and others of smaller nuclear families. Although the large schizophrenia GSMA was apparently successful despite similar variability among samples, it is possible that the genetics of BPD are sufficiently different to make a GSMA of all available scans a less useful strategy. An additional limitation here is that X- and Y-chromosome data are not currently accommodated by the GSMA procedure.

There was little evidence to support an overlap between BPD and schizophrenia susceptibility regions, although it is possible that such evidence will emerge as the BPD data set increases. None of the cluster of 19 bins with $P_{\text{ord}} < .05$ in the schizophrenia analysis achieved even nominal significance in the BPD analysis. It has been suggested that more information about possible BPD/schizophrenia overlap might be obtained with linkage analysis of BPD data limited to subjects with overt psychotic symptoms (hallucinations or delusions), as well as with combined analyses of schizophrenia and psychotic BPD data.

In summary, the GSMA of BPD represents an unbiased exploration of evidence for common susceptibility genes for BPD. No chromosomal region produced statistically significant results at the genomewide level. There were several promising results, including $P_{\text{AvgRnk}} < .01$ for bin 9.2 (with $P_{\text{AvgRnk}} < .05$ in bin 9.3) and bin 10.3 for model 1 and for bin 14.3 for model 2. Nominally significant evidence for linkage was observed for bins 14.3 and 18.2 under three different diagnostic models and for bin 8.6 under two models, as well as for adjacent bins under some models. It would appear that each BPD susceptibility gene might have a small populationwide effect, thus requiring larger or more refined samples to detect, and/or that locus heterogeneity across samples is considerable, and/or that methodological problems in the meta-analysis or the scan analyses themselves have limited the power of this

study. For complex disorders, an analysis of this type is intended only to provide additional support for further study of regions that provide evidence for linkage across multiple scans. The results should not be interpreted as disconfirming findings of individual scans, and there may be linkages that can be identified only in specific pedigrees or populations. Finally, it is not at all clear to what degree future studies using large collaborative samples versus samples of one or more extended pedigrees will prove useful in finding and confirming linkages. It would seem important that both strategies be pursued.

We plan to update this analysis when several new BPD genome scans are completed, and we invite investigators with new genome scan data to contact the present authors.

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Appendix A

Summary of Terminology

Bin: One of 120 30-cM autosomal segments used as units of analysis in GSMA; bin 2.1 is the first 30 cM of chromosome 2.

R_{study} (within-study rank): The rank of each bin within a single study, based on the maximum linkage score (or lowest P value) within it. The bin containing the best score has a rank of 1. All negative and 0 scores are considered to be tied. For weighted analyses, each raw rank is multiplied by the study's weighting factor.

R_{Avg} (average rank): The average of a bin's within-study ranks or weighted ranks across all studies.

P_{AvgRnk} (probability of R_{Avg}): The pointwise probability of observing a given R_{Avg} for a bin in a GSMA of N studies, determined by theoretical distribution (unweighted analysis only) or by permutation test (fig. 2).

P_{ord} (probability of R_{Avg} given the order): The pointwise probability that, for example, a first-place, second-place, third-place, etc., bin would achieve R_{Avg} at least this extreme in a GSMA of N studies.

Genomewide significance: For $\alpha = 0.05$, correction for 120 bins yields a threshold for genomewide significance of .000417 for P_{AvgRnk} or P_{ord} . For suggestive linkage (a result observed once per scan by chance), $\alpha = 1/120 = 0.0083$.

Electronic-Database Information

The URLs for data presented herein are as follows:

Center for Medical Genetics, <http://research.marshfieldclinic.org/genetics> (for the Marshfield genetic map)

CEPH-G n thon Integrated Map, <http://www.cephb.fr/ceph-genethon-map.html>

D. F. Levinson Research, <http://depressiongenetics.med.upenn.edu/meta-analysis.html> (for further details, including weighted and unweighted ranks for each bin for each study)

Genetic Location Database, http://cedar.genetics.soton.ac.uk/public_html/ldb.html (for the Cedar genetic map)

NCBI Home Page, <http://www.ncbi.nlm.nih.gov/> (for cytogenetic locations obtained from the April, 2002 freeze of the Human Genome Project)

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for MAFD1 and MAFD2)

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