American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 119B:69–76 (2003)

Genome Scan of a Second Wave of NIMH Genetics Initiative Bipolar Pedigrees: Chromosomes 2, 11, 13, 14, and X

Peter P. Zandi,[1]* Virginia L. Willour,[1] Yuqing Huo,[1] Jennifer Chellis,[1] James B. Potash,[1] Dean F. MacKinnon,[1] Sylvia G. Simpson,[1] Francis J. McMahon,[2] Elliot Gershon,[2] Theodore Reich,[3] Tatiana Foroud,[4] John Nurnberger Jr.,[4] J. Raymond DePaulo Jr.,[1] and Melvin G. McInnis[1]

[1]*The Johns Hopkins University, Baltimore, Maryland*
[2]*University of Chicago, Chicago, Illinois*
[3]*Washington University, St. Louis, Missouri*
[4]*Indiana University School of Medicine, Indiana*

As part of the on-going NIMH Genetics Initiative on Bipolar Disorder, we have ascertained 153 multiplex bipolar pedigrees and genotyped them in two waves. We report here the genome scan results for chromosomes 2, 11, 13, 14, and X in the second wave of 56 families. A total of 354 individuals were genotyped and included in the current analyses, including 5 with schizoaffective/bipolar (SA/BP), 139 with bipolar I disorder (BPI), 41 with bipolar II disorder (BPII), and 43 with recurrent unipolar depression (RUP). Linkage analyses were carried out with multi-point parametric and non-parametric affected relative pair methods using three different definitions of the affected phenotype: (model 1) SA/BP and BPI; (model 2) SA/BP, BPI, and BPII; and (model 3) SA/BP, BPI, BPII, and RUP. The best findings were on 11p15.5 (NPL = 2.96, $P = 0.002$) and Xp11.3 (NPL = 2.19, $P = 0.01$). These findings did not reach conventional criteria for significance, but they were located near regions that have been identified in previous genetic studies of bipolar disorder. The relatively modest but consistent findings across studies may suggest that these loci harbor susceptibility genes of modest effect in a subset of families. Large samples such as that being collected by the NIMH Initiative will be necessary to examine the heterogeneity and identify these susceptibility genes.

KEY WORDS: bipolar disorder; linkage; genome scan; heterogeneity

INTRODUCTION

Bipolar disorder is a serious mental illness that affects nearly 1% of the population. The causes of bipolar disorder are unknown. However, several lines of evidence suggest that genetic factors play an important role. Given the pattern of segregation in families, it is likely that the inheritance of bipolar disorder is complex and probably involves multiple genes acting independently and interactively [Craddock and Jones, 1999]. A growing number of studies have tried to map bipolar susceptibility genes with limited success. Although several interesting loci have been identified across the genome [Nurnberger and Foroud, 2000; Baron, 2002], the findings remain inconclusive, and no genes have yet been cloned.

In 1988, the NIMH began an initiative to establish an archival resource for genetic studies of bipolar disorder [NIMH Genetics Initiative Bipolar Group, 1997]. The goal was to collect a large sample of families with multiple first-degree relatives affected with bipolar disorder and/or other affective illnesses ascertained using similar procedures. The four original sites collaborating in the initiative were Indiana University; Johns Hopkins University; Washington University, St. Louis; and the NIMH Intramural Research Program. In 1997, these sites collectively reported findings from

Grant sponsor: National Institute of Mental Health; Grant sponsor: Charles A. Dana Foundation Consortium on the Genetic Basis of Manic Depressive Illness; Grant sponsor: National Alliance for Research on Schizophrenia and Depression; Grant sponsor: Ted and Vada Stanley Foundation.

*Correspondence to: Peter P. Zandi, Department of Mental Hygiene, Bloomberg School of Public Health, The Johns Hopkins University, 8th Floor, Hampton House, 624 N. Broadway, Baltimore, MD 21204. E-mail: pzandi@jhsph.edu

Received 16 July 2002; Accepted 21 October 2002

DOI 10.1002/ajmg.b.10063

a genome scan of a first wave of data collection on 97 bipolar families [Detera-Wadleigh et al., 1997; Edenberg et al., 1997; Rice et al., 1997; Stine et al., 1997].

A second wave of data collection on 56 new families has since been completed. As in the first wave, each of the collaborating sites was responsible for studying a portion of the genome. The JHU site studied chromosomes 2, 11, 13, 14, and X and we now report the findings from a scan of these chromosomes in the second wave of families. The results from scans carried out by the other sites on their respective chromosomes can be found elsewhere [Dick et al., 2002].

MATERIALS AND METHODS

Ascertainment and Assessment

The four sites used common ascertainment and clinical assessment procedures that have been described in detail elsewhere [Genomic survey of bipolar illness in the NIMH genetics initiative pedigrees: a preliminary report, 1997; Dick et al., 2002]. Families were ascertained either systematically through one of the participating treatment facilities or non-systematically through advertisements, advocacy groups, or other non-clinical sources. Systematically ascertained families were included if the proband had bipolar I disorder (BPI), and he/she had an available first-degree relative with either BPI or schizoaffective disorder bipolar sub-type (SA/BP). The family of origin of the proband could not be bilineal (both parents with BPI or SA/BP). Non-systematically ascertained families were also accepted into the study if they met more stringent criteria. These families had to have two relatives with BPI or SA/BP who were either first-degree relatives or second-degree relatives connected through another family member with at least bipolar II disorder (BPII), and the families had to have two additional relatives with BPI, SA/BP, BPII or recurrent unipolar depression (RUP). The study was approved by the local Institutional Review Boards at each collaborating site, and informed written consent was obtained from all family members who agreed to participate.

Participants were assessed by trained interviewers using the Diagnostic Instrument for Genetic Studies (DIGS) [Nurnberger et al., 1994] and the Family Interview for Genetic Studies (FIGS). At Johns Hopkins the interviewers were psychiatrists, while at the other sites the interviewers were specially trained nurses, social workers, or experienced research interviewers. Medical records were requested for all inpatient and outpatient psychiatric treatment. The interviewer and an editor separately provided working diagnoses based on the DIGS. Final diagnoses were assigned using a best estimate procedure. Two clinician reviewers made separate assessments using all available data. They then discussed the case and agreed on a diagnosis. If the two reviewers were unable to reach an agreement, then a third clinician was referred to for making a final decision. Diagnoses of BPI and SA/BP were made using Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) criteria, while diagnoses of BPII and RUP were made using Research Diagnostic Criteria (RDC). BPII was diagnosed with RDC because DSM-III-R does not provide such a diagnosis. A diagnosis of BPII required RUP, therefore to be consistent across the two diagnostic categories RUP was diagnosed with RDC as well.

A total of 56 families with at least two available siblings diagnosed with one of the core illnesses were included into the second wave of the study. Affected relatives from these families were selected for genotyping. Parents, unaffected siblings, and other intervening biological relatives were also selected for genotyping in order to improve the ability to estimate allele sharing identical-by-descent. A total of 354 individuals were genotyped and included in the current analyses.

Genotyping

The fluorescently labeled tandem repeat microsatellite markers were amplified using polymerase chain reaction (PCR) following a modified standard protocol [Stine et al., 1995]. Electrophoresis and signal recording were performed on ABI PRISM 377 DNA Sequencers (Applied Biosystems, Foster City, CA). Genotype scoring was done automatically with ABI PRISM Genotyper software and then checked by a technician. The recorded genotypes were binned and examined for inheritance using the Genetic Analysis System (GAS v2.0) [Young, 1995] and UNKNOWN v5.2. Alleles that did not segregate were re-examined. In those cases where it was not possible to correct the errors, the data for that marker from that portion of the pedigree were deleted.

Marker Maps

We genotyped a total of 105 polymorphic markers; approximately 73% of the markers genotyped in the wave one families were genotyped here. There were 27 markers on chromosome 2, with an average spacing of 9.66 cM; 18 markers on chromosome 11, with an average spacing of 8.6 cM; 18 markers on chromosome 13, with an average spacing of 6.89 cM; 15 markers on chromosome 14, with an average spacing of 6.69 cM; and 27 markers on the X chromosome, with an average spacing of 3.02 cM. There were approximately 10 alleles per marker for an average heterozygosity of 0.76. The average information content across all the chromosomes as calculated from Genehunter-Plus was 0.60. The order of the markers was taken from Marshfield when available [Broman et al., 1998]. Those markers not included in the Marshfield map were placed using the BUILD option of CRIMAP [Lander and Green, 1987], and the final order was then tested using the FLIPS option. The distances (in Kosambi cM) between markers on the autosomes were estimated by CRIMAP using the FIXED option with the final marker order. The distances for the X-chromosome markers were taken from the Marshfield map.

Statistical Analyses

All genotype and phenotype data were imported into Discovery Manager (Visualize, Inc., Phoenix, AZ). This

software package was used to prepare all data and parameter files for subsequent analyses. It also provided estimates of allele frequencies based on the entire data set.

Multipoint non-parametric and parametric linkage analyses were carried out with Genehunter-Plus for the autosomes and X-Genehunter v1.3 for the X-chromosome. In the non-parametric analyses, non-parametric linkage (NPL) scores for affected relative pairs were calculated using the S(all) option. In the parametric analyses, LOD scores were calculated using only affected family members (all other family members were coded with a phenotype of unknown) under dominant and recessive models. The models were determined based on prevalence estimates for bipolar disorder and allowed for age-dependent phenocopy rates of 0.014 (<30-years old), 0.016 (<30- and ≥40-years old), and 0.040 (>40-years old). The dominant model assumed a disease allele frequency of 0.02, while the recessive model assumed a frequency of 0.2. Both the non-parametric and parametric analyses were performed using three different definitions of the affected phenotype: (model 1) SA/BP and BPI; (model 2) SA/BP, BPI, and BPII; and (model 3) SA/BP, BPI, BPII, and RUP.

For the best finding on chromosome 11 (see below), an additional analysis was carried out using Genefinder [Liang et al., 2001]. Genefinder uses general estimating equation (GEE) methods to estimate the location of an unobserved susceptibility gene within a chromosomal region framed by multiple markers based on IBD sharing among affected sib pairs. The method has been shown to be robust in that no assumption about the genetic mechanism is required other than that the region contains no more than one susceptibility gene.

RESULTS

Table I describes the breakdown of the 56 pedigrees by the three diagnostic categories. A total of 144 individuals were diagnosed with BPI or SA/BP. These individuals comprised 101 affected relative pairs under model 1. An additional 41 individuals were diagnosed with BPII, providing 193 affected relative pairs under model 2. Another 43 individuals were diagnosed with RUP, yielding 206 affected relative pairs under model 3.

TABLE I. Breakdown of the 56 Families by the Three Diagnostic Models

	Diagnostic model		
	1	2	3
Total	144	185	228
No. of families with n affecteds			
0	0	0	0
1	3	1	0
2	29	15	7
3	16	19	18
4	6	11	13
5	1	7	7
6	1	3	5
>7	0	0	6
No. of sib pairs	59	119	182
No. of relative pairs	101	193	306

Only two loci on chromosomes 11 and X had NPL scores that exceeded 2.0 (Fig. 1). On chromosome 11, NPL scores greater than 2.0 spanned approximately 20 cM from markers D11S1984 to D11S2362 under model 2. The peak NPL score was 2.96 ($P = 0.002$) at marker D11S1923. Parametric analyses yielded similar results in this region with a peak HLOD of 2.00 near the same marker under model 2 and dominant inheritance, with an estimated 40% of the families (α) linked to the locus (Fig. 2). Further analysis with Genefinder suggested that the location of a bipolar disorder susceptibility gene on this chromosome was 15.5 cM from the p-terminal marker (and approximately 1 cM away from marker D11S1923) with a 95% confidence interval for the true location ranging from 6.82 to 23.48 cM. Addition of families from the first wave of the NIMH Bipolar Genetics Initiative and analysis of data on all wave one and two markers genotyped in the region of interest yielded somewhat diminished results. The peak NPL score dropped to 2.26 ($P = 0.012$) and the HLOD was 0.90 with an estimated 18% of the families linked.

On the X chromosome there was a broad region of approximately 60 cM showing excess sharing (Fig. 1), with a peak NPL score of 2.19 ($P = 0.01$) at marker GATA144D04 under model 1. Parametric analyses yielded similar but more focused results. The peak HLOD was 2.25 again at marker GATA144D04 under model 1 and recessive inheritance, with an estimated 81% of the families (α) linked to the locus (Fig. 2). The 1-lod support interval spanned approximately 13 cM. As on chromosome 11, the addition of families from wave one of the NIMH Bipolar Genetics Initiative did not improve the findings. The NPL score in the combined sample was 1.26 ($P = 0.10$) and the HLOD was 1.25 with an estimated 38% of the families linked.

DISCUSSION

We studied chromosomes 2, 11, 13, 14, and X in 56 families collected as part of the NIMH Genetics Initiative on Bipolar Disorder. The best findings from both the parametric and non-parametric analyses were on chromosomes 11p15.5 and Xp11.3. These findings did not meet conventional criteria for significance [Lander and Kruglyak, 1995]. However, they are located near regions that have received considerable attention in previous genetic studies of bipolar disorder.

The first report of linkage on 11p15 came from a study of a large Old Order Amish family [Egeland et al., 1987]. This finding received a great deal of attention, but several subsequent studies of independent samples were unable to replicate it [Detera-Wadleigh et al., 1987; Hodgkinson et al., 1987], and a follow-up of the original pedigree yielded reduced evidence for linkage [Kelsoe et al., 1989]. A systematic genome scan in the first wave of the Bipolart Genetics Initiative [Stine et al., 1997] failed to implicate 11p15, and addition of

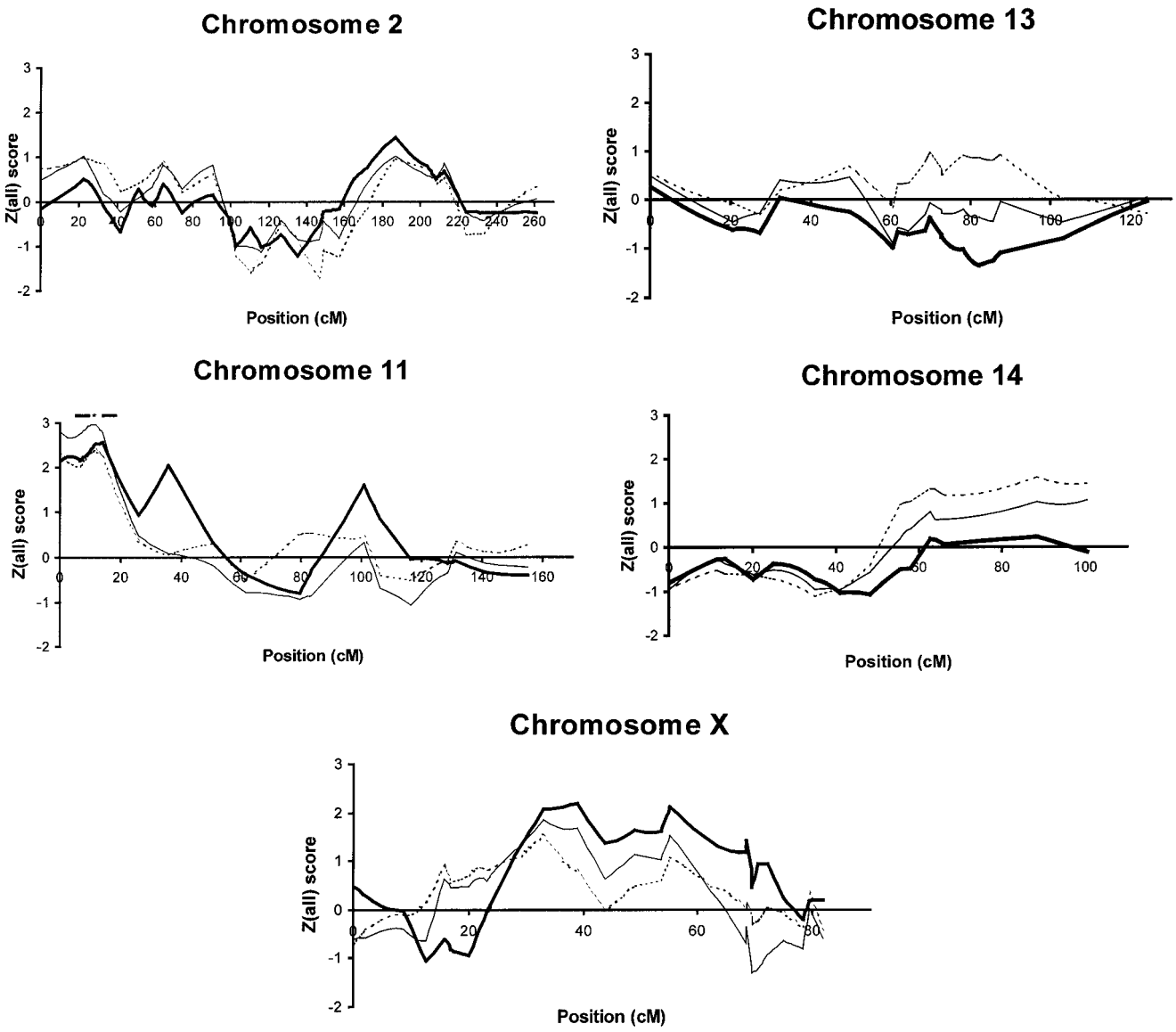

Fig. 1. Results from non-parametric analyses of chromosomes 2, 11, 13, 14, and X. The Genefinder results are shown by an * with 95% confidence bars above the figure on chromosome 11. Legend for figures: (—) Model 1; (—) Model 2; (—) Model 3.

these families to the current sample did not improve our findings in the region. However, only one of the six markers in the region of interest was genotyped in both sets of families. Moreover, several other studies of the region have found that there might be linkage only in a subset of families [Byerley et al., 1992; Lim et al., 1993; Smyth et al., 1996, 1997b; Malafosse et al., 1997], suggesting the possibility of genetic heterogeneity. These latter findings in particular could help explain the differences observed across samples.

Interestingly, in their study Smyth et al. [1997b] reported evidence that linkage to 11p15 was strongest in those families that were not linked to another locus on chromosome 21q22. We tested for such heterogeneity by stratifying the families based on linkage to 21q22. We found no evidence for increased linkage at 11p15 in those families that were not linked to 21q22 (results not shown), and therefore were not able to provide further support for the finding of Smyth et al. [1997b].

We estimated from our sample of families that the most likely location of a gene on 11p15 is approximately 1 cM telomeric from marker D11S1923. This marker is approximately 1.5 Mb from the tyrosine hydroxylase (*TH*) gene. Because TH is the rate-limiting enzyme in the synthesis of catecholamines, which are thought to play a role in the pathophysiology of bipolar disorder, it is a plausible candidate gene. Several studies reported that bipolar disorder was associated with polymorphisms at *TH* [Leboyer et al., 1990; Meloni et al., 1995], but a later meta-analysis was unable to substantiate these claims [Turecki et al., 1997].

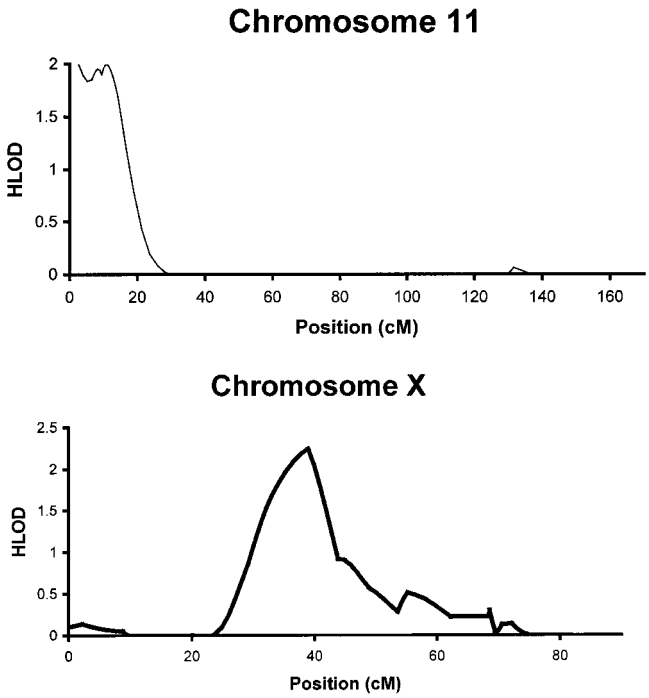

Fig. 2. Results from parametric analyses of chromosomes 11 (phenotype model–2, genetic model–dominant) and X (phenotype model–1, genetic model–recessive).

Another plausible candidate gene in this region is the dopamine D4 receptor (*DRD4*) gene. DRD4 is a G-protein coupled receptor that inhibits adenylyl cyclase and has a high affinity for the anti-psychotic clozapine [Van Tol et al., 1991]. Studies of an association between *DRD4* and bipolar disorder have been mixed. Several smaller studies showed little evidence of such an association [Lim et al., 1994; Perez dC et al., 1994; Weiss et al., 1996; Oruc et al., 1997; Li et al., 1999; Serretti et al., 1999]. However, one relatively large study [Serretti et al., 2001] suggested that polymorphisms at *DRD4* might be associated specifically with delusional symptoms in bipolar patients, while another more recent study [Muglia et al., 2002] reported evidence of a parent-of-origin effect at this locus with bipolar disorder. Given the difficulties in demonstrating an association between a gene of modest effect and a complex disease with a heterogeneous etiology such as bipolar disorder [Bellivier et al., 1998], inconsistent findings may not be unexpected. Thus, further study of the region, and *TH* or *DRD4* specifically, may be warranted.

There have also been notable but inconsistent findings for bipolar disorder susceptibility genes on the X chromosome. Several earlier studies found that bipolar disorder co-segregated in some families with X-linked traits such as color blindness and glucose-6-phosphate dehydrogenase deficiency [Smyth et al., 1997a; Mendlewicz et al., 1979, 1980]. A later study reported that bipolar disorder was linked to DNA markers on Xq26-28 in three Israeli pedigrees [Baron et al., 1987]. However, a follow-up examination of the same pedigrees was unable to confirm the initial findings [Baron et al., 1993]. Other studies of the region have since reported mixed results, with some providing evidence in support of linkage [Mendlewicz et al., 1987; Lucotte et al., 1992; Pekkarinen et al., 1995] and others not [Berrettini et al., 1990; Gejman et al., 1990; Smyth et al., 1997a; Vallada et al., 1998]. The previous scan of families collected in the first wave of the NIMH Bipolar Genetics Initiative reported evidence for linkage on Xq26-28 and Xp22. Only one other study has reported linkage to Xp22 [Mendlewicz and Fleiss, 1974].

In the current study, we found increased evidence for linkage in Xp11.3, which is approximately 15–20 cM away from Xp22 and 35–40 cM from Xq26-28. It has been shown through simulation studies that the localization of findings in replicated samples may vary across considerable distances [Roberts et al., 1999], therefore it difficult to assess whether our finding corresponds to one of those from the previous scan of NIMH Bipolar families. The addition of the two waves of families did not help resolve the finding, but the best marker in our current sample was not genotyped in both samples. Nevertheless, the finding on Xp11.3 is interesting and has received considerable attention because it harbors the monoamine oxidase A (*MAOA*) gene. MAOA catalyzes the oxidative degradation of biogenic amines, including neurotransmitters such as norepinephrine, epinephrine, dopamine, and serotonin. It is a plausible candidate gene for bipolar disorder since inhibitors of the enzyme can successfully treat depression, and a mutation in the gene has been associated with a syndrome of mental retardation that exhibits a behavioral phenotype similar to mania [Brunner et al., 1993]. Studies of the association between polymorphisms in *MAOA* and bipolar disorder have reported both positive [Lim et al., 1995; Rubinsztein et al., 1996; Ho et al., 2000; Lin et al., 2000; Preisig et al., 2000] and negative [Craddock et al., 1995; Parsian and Todd, 1997; Sasaki et al., 1998; Furlong et al., 1999; Kunugi et al., 1999; Turecki et al., 1999] findings, but two recent meta-analyses [Furlong et al., 1999; Preisig et al., 2000] provided overall support for such an association. Although we were unable to formally localize our linkage finding on the X chromosome as we were for chromosome 11, the peak NPL score occurred at a marker that is less than 1 Mb from *MAOA*. This finding is consistent with the hypothesis that *MAOA*, or a gene nearby, has a modest effect on bipolar disorder susceptibility.

Finally, the previous scan of families from the first wave of the NIMH Bipolar Genetics Initiative identified a locus of interest on chromosome 13q14-32. Two previous studies of bipolar disorder have reported similar findings at this locus [Detera-Wadleigh et al., 1999; Kelsoe et al., 2001]. Interestingly, two studies of schizophrenia also found significant evidence for linkage on 13q32 [Blouin et al., 1998; Brzustowicz et al., 1999], leading some to hypothesize that the locus harbors a susceptibility gene shared in common by the two disorders [Berrettini, 2000]. We were unable to provide further support for this hypothesis. We genotyped two of the markers that showed the greatest evidence of linkage in the wave one families, plus seven additional markers in between these, but could not replicate a finding of linkage in the region.

In summary, the current survey of chromosomes 2, 11, 13, 14, and X in the 56 families collected during the second wave of the NIMH Bipolar Genetics Initiative provided relatively modest evidence for linkage on 11p15.5 and Xp11.3. Intriguingly, these findings occurred in regions implicated in previous linkage and association studies. Because bipolar disorder is a complex disorder with a heterogeneous etiology, it may not be surprising that the previous findings are not entirely consistent.

The NIMH Bipolar Genetics Initiative has recently collected a third wave of families for study. Combining families from all waves of the initiative will lead to one of the largest samples ascertained under common criteria for study of the genetics of bipolar disorder. Although the addition of families from the first two waves did not help clarify the findings reported here, large samples like the one being collected by the NIMH Bipolar Genetics Initiative will be necessary to examine the genetic heterogeneity that underlies bipolar disorder. Only by taking this heterogeneity into consideration will we be able to more definitively map the regions on 11p15.5 and Xp11.3 identified in this report. Given the poor overlap in markers, the successful mapping of these regions will require the genotyping of additional markers at a greater density than currently exists across all families in order to maximally derive the information available from this growing and important sample.

ACKNOWLEDGMENTS

Data and biomaterials were collected in four projects that participated in the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. From 1991–1998, the Principal Investigators and Co-Investigators were: Indiana University, Indianapolis, IN, U01 MH46282, John Nurnberger, M.D., Ph.D., Marvin Miller, M.D., and Elizabeth Bowman, M.D.; Washington University, St. Louis, MO, U01 MH46280, Theodore Reich, M.D., Allison Goate, Ph.D., and John Rice, Ph.D; Johns Hopkins University, Baltimore, MD, U01 MH46274, J. Raymond DePaulo Jr, M.D., Sylvia Simpson, M.D., MPH, and O. Colin Stine, Ph.D.; NIMH. Intramural Research Program, Clinical Neurogenetics Branch, Bethesda, MD, Elliot Gershon, M.D., Diane Kazuba, B.A., and Elizabeth Maxwell, M.S.W.

REFERENCES

Baron M. 2002. Manic-depression genes and the new millennium: poised for discovery. Mol Psychiatry 7(4):342–358.

Baron M, Risch N, Hamburger R, Mandel B, Kushner S, Newman M, Drumer D, Belmaker RH. 1987. Genetic linkage between X-chromosome markers and bipolar affective illness. Nature 326(6110):289–292.

Baron M, Freimer NF, Risch N, Lerer B, Alexander JR, Straub RE, Asokan S, Das K, Peterson A, Amos J. 1993. Diminished support for linkage between manic depressive illness and X-chromosome markers in three Israeli pedigrees. Nat Genet 3(1):49–55.

Bellivier F, Schurhoff F, Nosten-Bertrand M, Mallet J, Feingold J, Leboyer M. 1998. Methodological problems in meta-analysis of association studies between bipolar affective disorders and the tyrosine hydroxylase gene. Am J Med Genet 81(4):349–352.

Berrettini WH. 2000. Are schizophrenic and bipolar disorders related? A review of family and molecular studies. Biol Psychiatry 48(6):531–538.

Berrettini WH, Goldin LR, Gelernter J, Gejman PV, Gershon ES, Detera-Wadleigh S. 1990. X-chromosome markers and manic-depressive illness. Rejection of linkage to Xq28 in nine bipolar pedigrees. Arch Gen Psychiatry 47(4):366–373.

Blouin JL, Dombroski BA, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G, Thornquist M, Ullrich G, McGrath J, Kasch L, Lamacz M, Thomas MG, Gehrig C, Radhakrishna U, Snyder SE, Balk KG, Neufeld K, Swartz KL, DeMarchi N, Papadimitriou GN, Dikeos DG, Stefanis CN, Chakravarti A, Childs B, Pulver AE. 1998. Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. Nat Genet 20(1):70–73.

Broman KW, Murray JC, Sheffield VC, White RL, Weber JL. 1998. Comprehensive human genetic maps: Individual and sex-specific variation in recombination. Am J Hum Genet 63(3):861–869.

Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. 1993. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science 262(5133):578–580.

Brzustowicz LM, Honer WG, Chow EW, Little D, Hogan J, Hodgkinson K, Bassett AS. 1999. Linkage of familial schizophrenia to chromosome 13q32. Am J Hum Genet 65(4):1096–1103.

Byerley W, Plaetke R, Hoff M, Jensen S, Holik J, Reimherr F, Mellon C, Wender P, O'Connell P, Leppert M. 1992. Tyrosine hydroxylase gene not linked to manic-depression in seven of eight pedigrees. Hum Hered 42(4):259–263.

Craddock N, Jones I. 1999. Genetics of bipolar disorder. J Med Genet 36(8):585–594.

Craddock N, Daniels J, Roberts E, Rees M, McGuffin P, Owen MJ. 1995. No evidence for allelic association between bipolar disorder and monoamine oxidase A gene polymorphisms. Am J Med Genet 60(4):322–324.

Detera-Wadleigh SD, Berrettini WH, Goldin LR, Boorman D, Anderson S, Gershon ES. 1987. Close linkage of c-Harvey-ras-1 and the insulin gene to affective disorder is ruled out in three North American pedigrees. Nature 325(6107):806–808.

Detera-Wadleigh SD, Badner JA, Yoshikawa T, Sanders AR, Goldin LR, Turner G, Rollins DY, Moses T, Guroff JJ, Kazuba D, Maxwell ME, Edenberg HJ, Foroud T, Lahiri D, Nurnberger JI Jr, Stine OC, McMahon F, Meyers DA, MacKinnon D, Simpson S, McInnis M, DePaulo JR, Rice J, Goate A, Gershon ES. 1997. Initial genome scan of the NIMH genetics initiative bipolar pedigrees: Chromosomes 4, 7, 9, 18, 19, 20, and 21q. Am J Med Genet 74(3):254–262.

Detera-Wadleigh SD, Badner JA, Berrettini WH, Yoshikawa T, Goldin LR, Turner G, Rollins DY, Moses T, Sanders AR, Karkera JD, Esterling LE, Zeng J, Ferraro TN, Guroff JJ, Kazuba D, Maxwell ME, Numberger JI Jr, Gershon ES. 1999. A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. Proc Natl Acad Sci USA 96(10):5604–5609.

Dick DM, Foroud T, Edenberg HJ, Miller M, Bowman E, Rau NL, DePaulo JR, McInnis M, Gershon E, McMahon F, Rice JP, Bierut LJ, Reich T, Nurnberger J Jr. 2002. Apparent replication of suggestive linkage on chromosome 16 in the NIMH genetics initiative bipolar pedigrees. Am J Med Genet 114(4):407–412.

Edenberg HJ, Foroud T, Conneally PM, Sorbel JJ, Carr K, Crose C, Willig C, Zhao J, Miller M, Bowman E, Mayeda A, Rau NL, Smiley C, Rice JP, Goate A, Reich T, Stine OC, McMahon F, DePaulo JR, Meyers D, Detera-Wadleigh SD, Goldin LR, Gershon ES, Blehar MC, Nurnberger JI Jr. 1997. Initial genomic scan of the NIMH genetics initiative bipolar pedigrees: Chromosomes 3, 5, 15, 16, 17, and 22. Am J Med Genet 74(3):238–246.

Egeland JA, Gerhard DS, Pauls DL, Sussex JN, Kidd KK, Allen CR, Hostetter AM, Housman DE. 1987. Bipolar affective disorders linked to DNA markers on chromosome 11. Nature 325(6107):783–787.

Furlong RA, Ho L, Rubinsztein JS, Walsh C, Paykel ES, Rubinsztein DC. 1999. Analysis of the monoamine oxidase A (MAOA) gene in bipolar affective disorder by association studies, meta-analyses, and sequencing of the promoter. Am J Med Genet 88(4):398–406.

Gejman PV, Detera-Wadleigh S, Martinez MM, Berrettini WH, Goldin LR, Gelernter J, Hsieh WT, Gershon ES. 1990. Manic depressive illness not linked to factor IX region in an independent series of pedigrees. Genomics 8(4):648–655.

Ho LW, Furlong RA, Rubinsztein JS, Walsh C, Paykel ES, Rubinsztein DC. 2000. Genetic associations with clinical characteristics in bipolar affective disorder and recurrent unipolar depressive disorder. Am J Med Genet 96(1):36–42.

Hodgkinson S, Sherrington R, Gurling H, Marchbanks R, Reeders S, Mallet J, McInnis M, Petursson H, Brynjolfsson J. 1987. Molecular genetic evidence for heterogeneity in manic depression. Nature 325(6107): 805–806.

Kelsoe JR, Ginns EI, Egeland JA, Gerhard DS, Goldstein AM, Bale SJ, Pauls DL, Long RT, Kidd KK, Conte G. 1989. Re-evaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. Nature 342(6247): 238–243.

Kelsoe JR, Spence MA, Loetscher E, Foguet M, Sadovnick AD, Remick RA, Flodman P, Khristich J, Mroczkowski-Parker Z, Brown JL, Masser D, Ungerleider S, Rapaport MH, Wishart WL, Luebbert H. 2001. A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. Proc Natl Acad Sci USA 98(2):585–590.

Kunugi H, Ishida S, Kato T, Tatsumi M, Sakai T, Hattori M, Hirose T, Nanko S. 1999. A functional polymorphism in the promoter region of monoamine oxidase-A gene and mood disorders. Mol Psychiatry 4(4): 393–395.

Lander ES, Green P. 1987. Construction of multilocus genetic linkage maps in humans. Proc Natl Acad Sci USA 84(8):2363–2367.

Lander E, Kruglyak L. 1995. Genetic dissection of complex traits: Guidelines for interpreting and reporting linkage results. Nat Genet 11(3):241–247.

Leboyer M, Malafosse A, Boularand S, Campion D, Gheysen F, Samolyk D, Henriksson B, Denise E, des LA, Lepine JP. 1990. Tyrosine hydroxylase polymorphisms associated with manic-depressive illness. Lancet 335(8699):1219.

Li T, Liu X, Sham PC, Aitchison KJ, Cai G, Arranz MJ, Deng H, Liu J, Kirov G, Murray RM, Collier DA. 1999. Association analysis between dopamine receptor genes and bipolar affective disorder. Psychiatry Res 86(3):193–201.

Liang KY, Chiu YF, Beaty TH. 2001. A robust identity-by-descent procedure using affected sib pairs: Multipoint mapping for complex diseases. Hum Hered 51(1–2):64–78.

Lim LC, Gurling H, Curtis D, Brynjolfsson J, Petursson H, Gill M. 1993. Linkage between tyrosine hydroxylase gene and affective disorder cannot be excluded in two of six pedigrees. Am J Med Genet 48(4):223–228.

Lim LC, Nothen MM, Korner J, Rietschel M, Castle D, Hunt N, Propping P, Murray R, Gill M. 1994. No evidence of association between dopamine D4 receptor variants and bipolar affective disorder. Am J Med Genet 54(3):259–263.

Lim LC, Powell J, Sham P, Castle D, Hunt N, Murray R, Gill M. 1995. Evidence for a genetic association between alleles of monoamine oxidase A gene and bipolar affective disorder. Am J Med Genet 60(4):325–331.

Lin S, Jiang S, Wu X, Qian Y, Wang D, Tang G, Gu N. 2000. Association analysis between mood disorder and monoamine oxidase gene. Am J Med Genet 96(1):12–14.

Lucotte G, Landoulsi A, Berriche S, David F, Babron MC. 1992. Manic depressive illness is linked to factor IX in a French pedigree. Ann Genet 35(2):93–95.

Malafosse A, Leboyer M, d'Amato T, Amadeo S, Abbar M, Campion D, Canseil O, Castelnau D, Gheysen F, Granger B, Henrikson B, Poirier MF, Sabate O, Samolyk D, Feingold J, Mallet J. 1997. Manic depressive illness and tyrosine hydroxylase gene: Linkage heterogeneity and association. Neurobiol Dis 4(5):337–349.

Meloni R, Leboyer M, Bellivier F, Barbe B, Samolyk D, Allilaire JF, Mallet J. 1995. Association of manic-depressive illness with tyrosine hydroxylase microsatellite marker. Lancet 345(8954):932.

Mendlewicz J, Fleiss JL. 1974. Linkage studies with X-chromosome markers in bipolar (manic-depressive) and unipolar (depressive) illnesses. Biol Psychiatry 9(3):261–294.

Mendlewicz J, Linkowski P, Guroff JJ, Van Praag HM. 1979. Color blindness linkage to bipolar manic-depressive illness. New evidence. Arch Gen Psychiatry 36(13):1442–1447.

Mendlewicz J, Linkowski P, Wilmotte J. 1980. Linkage between glucose-6-phosphate dehydrogenase deficiency and manic-depressive psychosis. Br J Psychiatry 137:337–342.

Mendlewicz J, Simon P, Sevy S, Charon F, Brocas H, Legros S, Vassart G. 1987. Polymorphic DNA marker on X chromosome and manic depression. Lancet 1(8544):1230–1232.

Muglia P, Petronis A, Mundo E, Lander S, Cate T, Kennedy JL. 2002. Dopamine D4 receptor and tyrosine hydroxylase genes in bipolar disorder: Evidence for a role of DRD4. Mol Psychiatry 7(8):860–866.

NIMH Genetics Initiative Bipolar Group. 1997. Genomic survey of bipolar illness in the NIMH genetics initiative pedigrees: a preliminary report. Am J Med Genet 74(3):227–237.

Nurnberger JI Jr, Foroud T. 2000. Genetics of bipolar affective disorder. Curr Psychiatry Rep 2(2):147–157.

Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry 51(11):849–859.

Oruc L, Verheyen GR, Furac I, Jakovljevic M, Ivezic S, Raeymaekers P, Van Broeckhoven C. 1997. Analysis of the tyrosine hydroxylase and dopamine D4 receptor genes in a Croatian sample of bipolar I and unipolar patients. Am J Med Genet 74(2):176–178.

Parsian A, Todd RD. 1997. Genetic association between monoamine oxidase and manic-depressive illness: Comparison of relative risk and haplotype relative risk data. Am J Med Genet 74(5):475–479.

Pekkarinen P, Terwilliger J, Bredbacka PE, Lonnqvist J, Peltonen L. 1995. Evidence of a predisposing locus to bipolar disorder on Xq24-q27.1 in an extended Finnish pedigree. Genome Res 5(2):105–115.

Perez dC I, Torres P, Fernandez-Piqueras J, Saiz-Ruiz J, Llinares C. 1994. No association between dopamine D4 receptor polymorphism and manic depressive illness. J Med Genet 31(11):897–898.

Preisig M, Bellivier F, Fenton BT, Baud P, Berney A, Courtet P, Hardy P, Golaz J, Leboyer M, Mallet J, Matthey ML, Mouthon D, Neidhart E, Nosten-Bertrand M, Stadelmann-Dubuis E, Guimon J, Ferrero F, Buresi C, Malafosse A. 2000. Association between bipolar disorder and monoamine oxidase A gene polymorphisms: results of a multicenter study. Am J Psychiatry 157(6):948–955.

Rice JP, Goate A, Williams JT, Bierut L, Dorr D, Wu W, Shears S, Gopalakrishnan G, Edenberg HJ, Foroud T, Nurnberger J Jr, Gershon ES, Detera-Wadleigh SD, Goldin LR, Guroff JJ, McMahon FJ, Simpson S, MacKinnon D, McInnis M, Stine OC, DePaulo JR, Blehar MC, Reich T. 1997. Initial genome scan of the NIMH genetics initiative bipolar pedigrees: Chromosomes 1, 6, 8, 10, and 12. Am J Med Genet 74(3):247–253.

Roberts SB, MacLean CJ, Neale MC, Eaves LJ, Kendler KS. 1999. Replication of linkage studies of complex traits: An examination of variation in location estimates. Am J Hum Genet 65(3):876–884.

Rubinsztein DC, Leggo J, Goodburn S, Walsh C, Jain S, Paykel ES. 1996. Genetic association between monoamine oxidase A microsatellite and RFLP alleles and bipolar affective disorder: analysis and meta-analysis. Hum Mol Genet 5(6):779–782.

Sasaki T, Hattori M, Sakai T, Kato T, Kunugi H, Hirose T, Nanko S. 1998. The monoamine oxidase-A gene and major psychosis in Japanese subjects. Biol Psychiatry 44(9):922–924.

Serretti A, Lilli R, Di Bella D, Bertelli S, Nobile M, Novelli E, Catalano M, Smeraldi E. 1999. Dopamine receptor D4 gene is not associated with major psychoses. Am J Med Genet 88(5):486–491.

Serretti A, Lilli R, Lorenzi C, Lattuada E, Smeraldi E. 2001. DRD4 exon 3 variants associated with delusional symptomatology in major psychoses: A study on 2,011 affected subjects. Am J Med Genet 105(3):283–290.

Smyth C, Kalsi G, Brynjolfsson J, O'Neill J, Curtis D, Rifkin L, Moloney E, Murphy P, Sherrington R, Petursson H, Gurling H. 1996. Further tests for linkage of bipolar affective disorder to the tyrosine hydroxylase gene locus on chromosome 11p15 in a new series of multiplex British affective disorder pedigrees. Am J Psychiatry 153(2):271–274.

Smyth C, Kalsi G, Brynjolfsson J, O'Neill J, Curtis D, Rifkin L, Moloney E, Murphy P, Petursson H, Gurling H. 1997a. Test of Xq26.3-28 linkage in bipolar and unipolar affective disorder in families selected for absence of male to male transmission. Br J Psychiatry 171:578–581.

Smyth C, Kalsi G, Curtis D, Brynjolfsson J, O'Neill J, Rifkin L, Moloney E, Murphy P, Petursson H, Gurling H. 1997b. Two-locus admixture linkage analysis of bipolar and unipolar affective disorder supports the presence of susceptibility loci on chromosomes 11p15 and 21q22. Genomics 39(3):271–278.

Stine OC, Xu J, Koskela R, McMahon FJ, Gschwend M, Friddle C, Clark CD, McInnis MG, Simpson SG, Breschel TS. 1995. Evidence for linkage of bipolar disorder to chromosome 18 with a parent-of-origin effect. Am J Hum Genet 57(6):1384–1394.

Stine OC, McMahon FJ, Chen L, Xu J, Meyers DA, MacKinnon DF, Simpson S, McInnis MG, Rice JP, Goate A, Reich T, Edenberg HJ, Foroud T, Nurnberger JI Jr, Detera-Wadleigh SD, Goldin LR, Guroff J, Gershon ES, Blehar MC, DePaulo JR. 1997. Initial genome screen for bipolar

disorder in the NIMH genetics initiative pedigrees: chromosomes 2, 11, 13, 14, and X. Am J Med Genet 74(3):263–269.

Turecki G, Rouleau GA, Mari J, Joober R, Morgan K. 1997. Lack of association between bipolar disorder and tyrosine hydroxylase: A meta-analysis. Am J Med Genet 74(4):348–352.

Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Ahrens B, Berghofer A, Muller-Oerlinghausen B, Dvorakova M, Libigerova E, Vojtechovsky M, Zvolsky P, Joober R, Nilsson A, Prochazka H, Licht RW, Rasmussen NA, Schou M, Vestergaard P, Holzinger A, Schumann C, Thau K, Rouleau GA, Alda M. 1999. MAOA: Association and linkage studies with lithium responsive bipolar disorder. Psychiatr Genet 9(1):13–16.

Vallada HP, Vasques L, Curtis D, Zatz M, Kirov G, Lauriano V, Gentil V, Murray RM, McGuffin P, Owen M, Gill M, Craddock N, Collier DA. 1998. Linkage analysis between bipolar affective disorder and markers on chromosome X. Psychiatr Genet 8(3):183–186.

Van Tol HH, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB, Civelli O. 1991. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 350(6319): 610–614.

Weiss J, Magert HJ, Cieslak A, Forssmann WG. 1996. Association between different psychotic disorders and the DRD4 polymorphism, but no differences in the main ligand binding region of the DRD4 receptor protein compared to controls. Eur J Med Res 1(9):439–445.

Young A. 1995. Genetic Analysis System, version 1.4. 1995. Internet: (ftp.well.ox.ac.uk).