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Rapid Publication

Genome Scan of the Fifty-Six Bipolar Pedigrees From the NIMH Genetics Initiative Replication Sample: Chromosomes 4, 7, 9, 18, 19, 20, and 21

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The NIMH genetics initiative on bipolar disorder was established to collect uniformly ascertained bipolar pedigrees for genetic studies. In 1997, the four participating sites published a genome scan on the initial set of 97 bipolar pedigrees. Fifty-six additional bipolar pedigrees have now been ascertained and evaluated. This replication pedigree set contains 354 genotyped subjects, including 139 bipolar I (BPI) subjects, five schizoaffective bipolar type SA/BP subjects, 41 bipolar II (BPII) subjects, and 43 recurrent unipolar (RUP) depression subjects. Our site has recently genotyped the replication study bipolar pedigrees using 107 microsatellite markers from chromosomes 4, 7, 9, 18, 19, 20, and 21. We are now reporting parametric and nonparametric linkage results from this effort. Multipoint nonparametric linkage analysis produced three candidate regions with allele sharing LOD scores $\geq$ 1.0. The linkage signal on 4q35 peaked between markers D4S3335 and D4S2390 with an allele sharing LOD score of 2.49. This finding exceeds standard criteria for suggestive linkage. Two additional loci approach suggestive linkage levels: the 4q32 finding had its maximum near marker D4S1629 with an allele sharing LOD score of 2.16, and the 20p12 finding peaked at D20S162 with an allele sharing LOD score of 1.82. Multipoint parametric linkage analysis produced similar findings. When we combined the genotype data from the original and the replication pedigree sets, 20p12 yielded a nonparametric LOD score of 2.38, which exceeds standard criteria for suggestive linkage, and a corresponding parametric HLOD score of 2.98. The combined analysis did not provide further support for linkage to 4q32 and 4q35.

KEY WORDS: 4q; 20p; manic depression; parametric linkage; nonparametric linkage

INTRODUCTION

Bipolar affective disorder, which affects approximately 1% of the population, is a severe psychiatric disorder characterized by recurrent manias and depressions [Goodwin and Jamison, 1990]. While the etiology of bipolar disorder has yet to be determined, results from family, twin, and adoption studies indicate the presence of a strong hereditary component [Bertelsen et al., 1977;

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Mendlewicz and Rainer, 1977; Gershon et al., 1982; Rice et al., 1987]. Although single gene forms of bipolar disorder cannot be ruled out, recurrence risk data indicates that bipolar illness is likely to involve several interacting genes combined with environmental factors [Craddock and Jones, 2001]. Bipolar disorder genome scans have identified several putative bipolar susceptibility loci, including 4p16, 12q23-24, 13q31-32, 18q21-23, 21q22, and 22q11-13 [Baron, 2002]. However, no susceptibility genes have been isolated.

The mission of the NIMH genetics initiative (bipolar disorder) is to collect DNA, cell lines, and clinical information from uniformly ascertained bipolar pedigrees [Nurnberger et al., 1997]. Four sites initially assumed responsibility for this task: Indiana University, Johns Hopkins University, the NIMH Intramural Program, and Washington University. A 10 cM genome scan on the original 97 NIMH Genetics Initiative bipolar pedigrees was published by the participating sites [Detera-Wadleigh et al., 1997; Edenberg et al., 1997; Nurnberger et al., 1997; Rice et al., 1997; Stine et al., 1997]. Genome-wide multipoint nonparametric analysis of these pedigrees identified four loci (8p22, 10p12, 16p12, and 20q13) with allele sharing LOD scores >1.5 [Foroud et al., 2000].

Fifty-six additional bipolar pedigrees have now been ascertained and evaluated. Companion papers report the genome scan results for this replication pedigree set on chromosomes 2, 3, 5, 11, 13, 14, 15, 16, 17, 22, and X [Dick et al., 2002; Zandi et al., 2003]. Our site has recently genotyped these replication pedigrees for 107 microsatellite markers from chromosomes 4, 7, 9, 18, 19, 20, and 21, and we now report nonparametric and parametric linkage results for these seven chromosomes.

MATERIALS AND METHODS

For bipolar pedigrees obtained through the systematic screening of local treatment centers, the ascertainment scheme required a proband with a bipolar I (BPI) diagnosis and an available first-degree relative with either a BPI diagnosis or a schizoaffective bipolar type (SA/BP) diagnosis [Nurnberger et al., 1997]. Potential probands with bilineal (BPI or SA/BP) parentage were rejected from the study. Bipolar pedigrees were also ascertained through the use of opportunistic methods, such as advocacy groups and advertisements. In these nonsystematic cases, BPI–BPI or BPI–SA/BP first-degree or second-degree relatives formed the core of the pedigree. The nonsystematic ascertainment criteria also required that two additional pedigree members be affected with BPI, SA/BP, bipolar II with recurrent depression (BPII), or recurrent unipolar (RUP) depression. Subjects with bilineal parentage (BPI or SA/BP) were excluded. All subjects signed IRB-approved written informed consent forms prior to enrolling in the study.

Psychiatrists and trained interviewers conducted the diagnostic interviews using the Diagnostic Instrument for Genetic Studies (DIGS) semi-structured interview [Nurnberger et al., 1994]. Following the interview, two independent psychiatrists determined the best-estimate final diagnosis for each subject using information from the DIGS interview and all available family and medical records [Nurnberger et al., 1997]. If the two clinicians failed to reach an agreement, then a third clinician served as the arbiter. In the best estimate process, DSM-III-R standards were used to diagnose BPI and SA/BP; RDC standards were used to diagnose BPII and RUP. The 56 pedigrees under study contained 354 individuals: 139 were diagnosed as BPI, five were diagnosed as SA/BP, 41 were diagnosed as BPII, and 43 were diagnosed as RUP.

A total of 107 di-, tri-, and tetra-nucleotide microsatellite markers were used in this study. Specifically, we genotyped 21 microsatellite markers on chromosome 4, 19 microsatellite markers on chromosome 7, 16 microsatellite markers on chromosome 9, 19 microsatellite markers on chromosome 18, 12 microsatellite markers on chromosome 19, 11 microsatellite markers on chromosome 20, and nine microsatellite markers on chromosome 21. This corresponds to an 8.9 cM (average) microsatellite marker map. The microsatellite markers were PCR amplified, and the resulting fluorescently labeled PCR products were pooled and sent to the Johns Hopkins University DNA Analysis Facility for electrophoresis on an ABI PRISM 377 DNA Sequencer (Applied Biosystems, Foster City, CA). Alleles were scored using the ABI PRISM Genotyper software and binned using the Genetic Analysis System (GAS) v 2.0 [Young, 1995]. Genotyping errors and other non-Mendelian inheritances were identified using GAS and UNKNOWN v 5.20 [Lathrop and Lalouel, 1984]. Inconsistent genotypes were rescored and deleted when irreconcilable.

The multipoint parametric and nonparametric analyses were conducted under affecteds-only linkage conditions with GENEHUNTER-PLUS using S_{all}, and the results from GENEHUNTER-PLUS were used to calculate allele sharing LOD scores with ASM [Kong and Cox, 1997]. The linkage parameter files contained the following age-dependent penetrance values: 0.630 for an age of onset ≤ 30; 0.760 for an age of onset >30 and ≤ 40; and 0.850 for an age of onset >40. The disease allele frequencies were set at 0.02 for the dominant analyses and 0.20 for the recessive analyses, and the marker allele frequencies were based on the genotypes from the 56 bipolar pedigrees in this study. The Marshfield chromosome-specific maps [Broman et al., 1998] served as the basis for the marker order. CRI-MAP's BUILD and FLIPS options [Lander and Green, 1987] allowed for the incorporation of additional markers, for the identification of our data's best-fit marker map, and for the generation of the final map distances (in Kosambi cM). The cytogenetic map locations cited in this report were taken from the June 2002 build of the UCSC database [Kent et al., 2002].

For the combined analysis, the genotype data from the 97 original pedigrees [Detera-Wadleigh et al., 1997] was added to the data from the 56 replication pedigrees. Two of the original 97 pedigrees were removed from the analysis due to recently identified inheritance inconsistencies. Parametric and nonparametric linkage analyses were conducted using the same conditions as in the replication study. Marker allele frequencies were based on the genotypes from both the original and the replication pedigree sets. The combined genetic map

was generated by CRIMAP [Lander and Green, 1987] using the data from both the original and replication pedigree sets (M.G. McInnis and colleagues, manuscript in review). Genotype data for both pedigree sets are publicly available at http://zork.wustl.edu/nimh/.

RESULTS

We genotyped the 56 NIMH genetics initiative replication pedigrees at 107 microsatellite markers from chromosomes 4, 7, 9, 18, 19, 20, and 21, and we performed parametric and nonparametric linkage analysis on the resulting data. Three hierarchical phenotypic models were used in the analysis: model I considered BPI and SA/BP affected and contained 59 affected sib pairs and 101 affected relative pairs; model II considered BPI, BPII, and SA/BP affected and contained 119 affected sib pairs and 193 affected relative pairs; and model III considered BPI, BPII, SA/BP, and RUP affected and contained 182 affected sib pairs and 306 affected relative pairs.

Nonparametric allele sharing LOD score plots for all studied chromosomes are shown in Figure 1. The average information content value was 0.54. On

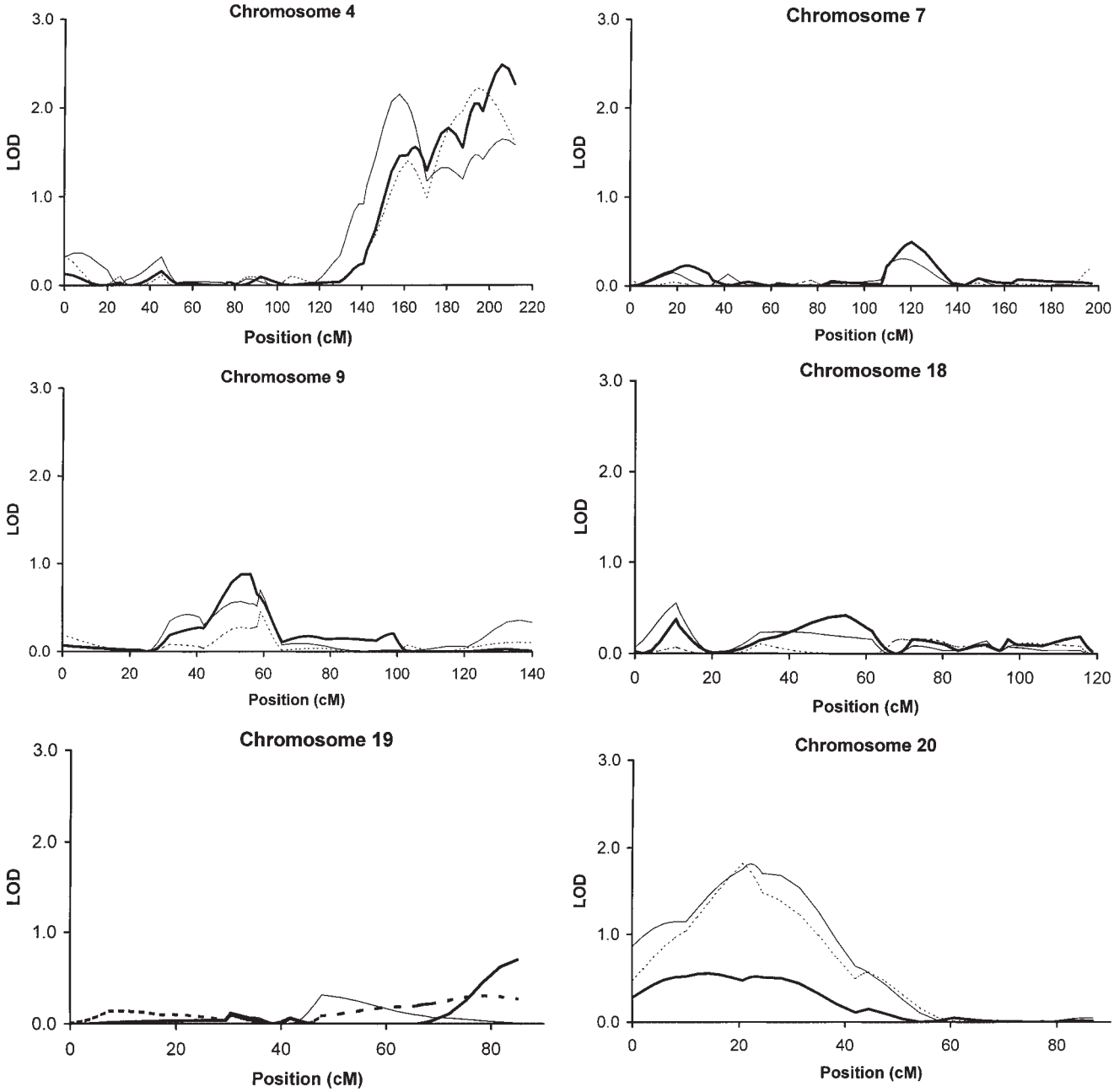

Fig. 1. Multipoint nonparametric linkage results for chromosomes 4, 7, 9, 18, 19, 20, and 21. Chromosomal positions are listed in Kosambi cM. Allele sharing LOD score values exceed 1.0 on chromosomes 4 and 20. ▬▬, Model 1; ——, Model 2; ·····, Model 3.

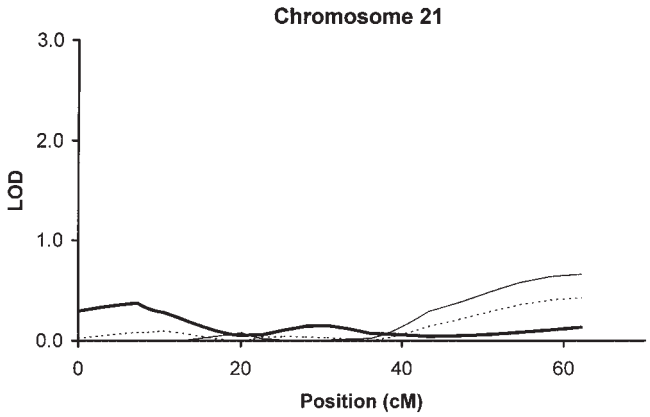

Fig. 1. (*Continued*)

chromosome 4, the strongest nonparametric finding was a LOD score of 2.49 between D4S3335 and D4S2390 using model I. The one LOD confidence interval for this peak spanned 38 cM. A second chromosome 4 nonparametric linkage finding peaked near D4S1629 with a LOD score of 2.16 using model II. The one LOD confidence interval for this peak spanned 66 cM. On chromosome 20, the nonparametric analyses peaked at D20S162 with a LOD score of 1.82 using model III. The one LOD confidence interval for this peak spanned 29 cM.

Parametric analysis provided supporting evidence for linkage in these regions (Fig. 2). Heterogeneity LOD scores (HLODs) $\geq$2.0 are seen on both chromosomes 4 and 20. The model I dominant parameters yielded a single peak at D4S2390 with an HLOD of 2.37. Under this model, 66% of the families (α) were estimated to be linked to this locus. Interestingly, the model I recessive parameters generated an HLOD of 2.51 ($\alpha = 0.64$) at D4S1629 and an HLOD of 2.53 ($\alpha = 0.87$) between D4S3335 and D4S2390. On chromosome 20, model III recessive parameters generated a broad peak with an HLOD of 2.00 ($\alpha = 0.60$) located between D20S604 and D20S477.

We then combined the genotype data from the replication pedigrees with the genotype data from the original NIMH pedigrees for chromosomes 4 and 20. For chromosome 4, this additional data diminished the nonparametric signal at both the proximal and distal peaks (Fig. 3). However, the strength of the chromosome 20 finding rose in the combined sample. Nonparametric linkage analysis yielded a LOD score of 2.38 at D20S162 under model III. The one LOD confidence interval for this peak spanned 31 cM. Parametric linkage analysis provided supporting evidence for linkage in this region. Using model III recessive parameters, the chromosome 20 linkage signal peaked between markers D20S162 and D20S604 with an HLOD of 2.98 ($\alpha = 0.41$).

DISCUSSION

Replication Sample

The nonparametric and the parametric analyses suggest that there may be one and possibly two bipolar susceptibility loci on chromosome 4 in the NIMH genetics initiative replication bipolar pedigrees. In these families, the model II nonparametric 4q32 linkage findings peak near marker D4S1629, and the model I nonparametric 4q35 linkage findings peak between markers D4S3335 and D4S2390. The 4q35 linkage result exceeds the established criteria for suggestive linkage [Lander and Kruglyak, 1995]. The strongest additional evidence for a 4q35 bipolar susceptibility locus comes from a 15 cM genome scan of one large Australian bipolar pedigree, which produced a two-point dominant parametric LOD score of 2.39 at 4q35 [Adams et al., 1998]. When the

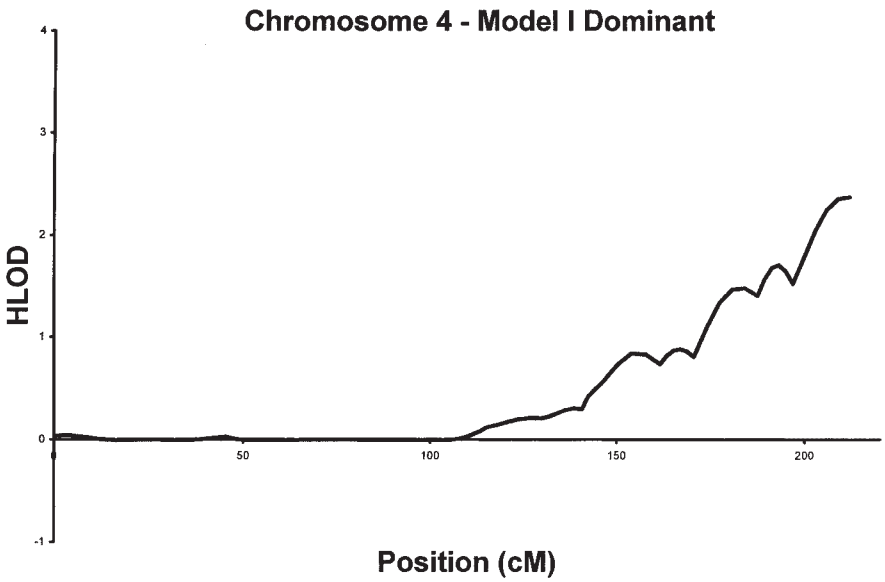

Fig. 2. Multipoint parametric linkage results for chromosomes 4 (model I dominant and model I recessive parameters) and 20 (model III recessive parameters). Chromosomal positions are listed in Kosambi cM. ——, Model 1; ——, Model 2; ·····, Model 3.

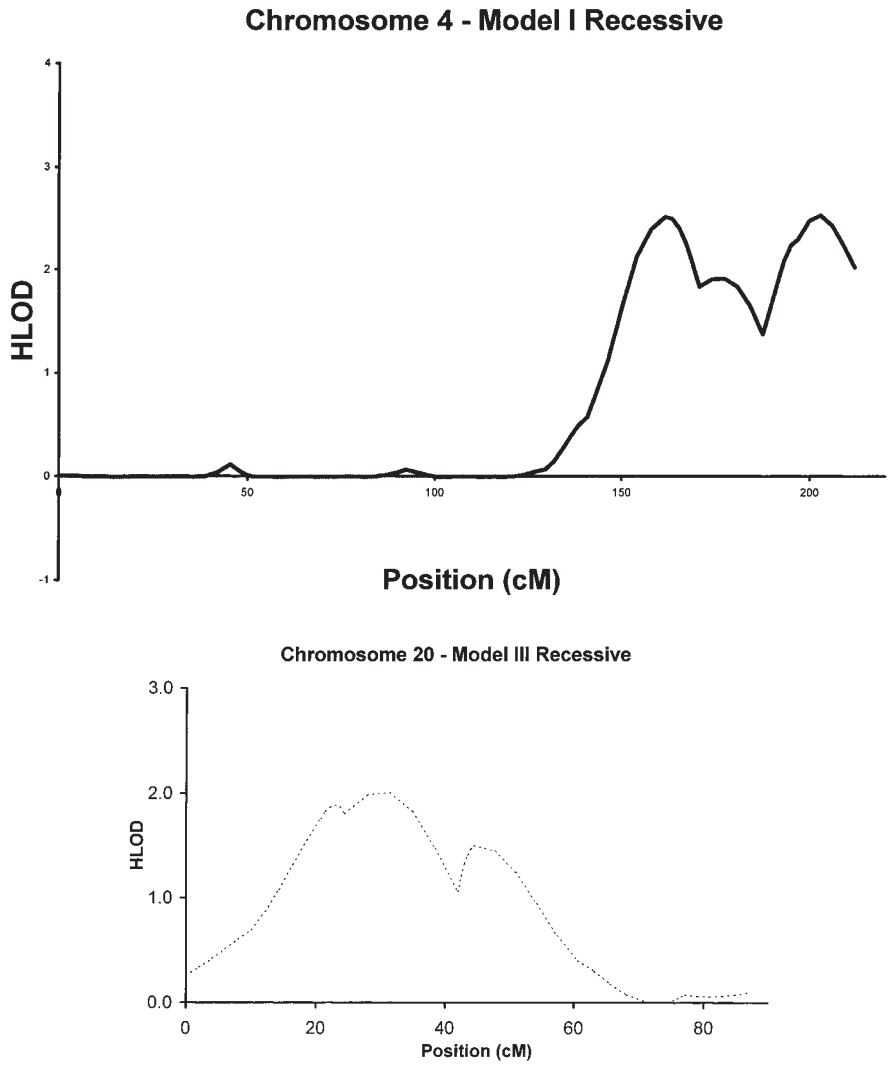

Fig. 2. (*Continued*)

authors included additional microsatellite markers and pedigree members in the analysis, the evidence for linkage to 4q35 increased to a three-point LOD score of 3.19. The strongest evidence for a 4q32 bipolar susceptibility locus comes from a genome scan on 41 Finnish bipolar pedigrees [Ekholm et al., 2001], that yielded a Z_{max} of 3.3 at D4S1629. While the original NIMH genetics initiative bipolar pedigree set showed no evidence supporting linkage in the 4q32-35 region [Detera-Wadleigh et al., 1997; Foroud et al., 2000], supporting evidence for the 4q32-35 region does come from a recent genome scan on 65 multiplex bipolar pedigrees [McInnis et al., 2003], which yielded an NPL of 2.80 ($P = 0.004$) at 4q32 and an NPL of 2.43 ($P = 0.01$) at 4q35. Parametric linkage analysis conducted on 50 of these pedigrees generated a recessive HLOD of 2.11 ($\alpha = 0.41$) at 4q35 [Friddle et al., 2000]. Interestingly, a genome scan conducted on a set of Old Order Amish bipolar pedigrees identified evidence for a protective locus on nearby 4q31 [Ginns et al., 1998].

In the replication sample, the chromosome 20 nonparametric findings peaked at marker D20S162 on 20p12. There was a similar modest finding in the original NIMH genetics initiative bipolar disorder genome scan [Detera-Wadleigh et al., 1997], where affected sib pair analysis of chromosomes 4, 7, 9, 18, 19, 20, and 21 identified 20 polymorphic markers with elevated allele sharing ($P \leq 0.05$), including marker D20S604, which lies ~2.5 Mb from D20S162 on 20p12 [Kent et al., 2002]. Stronger evidence for a chromosome 20 bipolar disorder susceptibility locus comes from a genome scan on a large Turkish pedigree [Radhakrishna et al., 2001]. In that study, two-point dominant parametric linkage analysis identified four chromosome 20 polymorphic markers with strong evidence (LOD score of 4.34 at $\theta = 0$) for linkage to bipolar disorder. Haplotype analysis of this data implicated a 42 cM candidate region spanning 20p11.2-q11.2.

Combined Sample

The genotype data from the original and replication pedigree sets was combined for both chromosomes 4 and

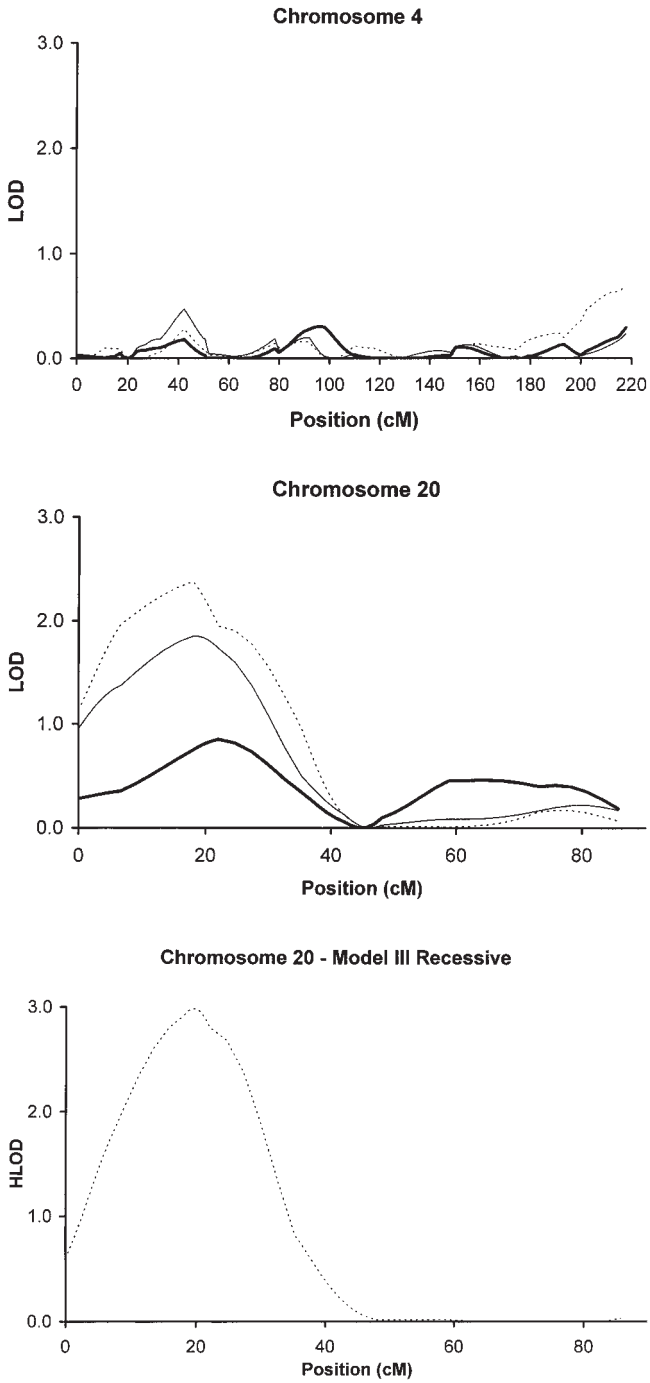

Fig. 3. Multipoint nonparametric linkage results from the combined analysis of chromosomes 4 and 20, and multipoint parametric linkage results from the combined analysis of chromosome 20 (model III recessive parameters). Chromosomal positions are listed in Kosambi cM. ▬▬, Model 1; ——, Model 2; ·····, Model 3.

20. The subsequent parametric and nonparametric linkage analyses on the combined dataset yielded improved evidence for linkage at 20p12, a result that was anticipated given that both the original and the replication datasets independently yielded evidence for linkage at this location. The peak LOD score rose from 1.82 in the replication pedigree set to 2.38 in the combined pedigree set. This finding now exceeds standard criteria for suggestive linkage [Lander and Kruglyak, 1995] and makes 20p12 an attractive candidate for extensive characterization using both microsatellite markers and SNP markers in order to confirm the presence of this bipolar susceptibility locus and to generate a more narrowly defined linkage peak. As for chromosome 4, the combined analysis diminished the findings on 4q32 and 4q35. Given the lack of evidence for linkage at these locations in the original pedigree set, this result is not unexpected. Additional genotyping in the 4q32-35 region in all of the pedigrees may clarify whether these discrepant results are due to type 1 error, type 2 error, or locus heterogeneity.

Summary

The 56 bipolar pedigrees in the replication sample may lack the power to identify bipolar susceptibility loci with small risk ratios [Risch and Merikangas, 1996]. Heterogeneity and power limitations may explain why several previously reported bipolar susceptibility loci (such as 4p16, 18p11, 18q21-23, and 21q22) failed to reach suggestive significance in the replication sample dataset. A new set of ~500 bipolar pedigrees is currently being collected by the expanded NIMH genetics initiative collaboration, and half of these pedigrees have recently undergone a whole genome scan at the Center for Inherited Disease Research (CIDR). Combining this genotype data with the genome scan data from the original and replication pedigree sets may provide a large enough sample to identify additional bipolar susceptibility loci in the population as a whole and to allow for extensive clinical subtyping in an attempt to identify more homogeneous bipolar populations.

We have identified evidence for linkage to 4q32, 4q35, and 20p12 using genome scan data from the replication and/or the combined set of NIMH genetics initiative bipolar pedigrees. All three of these regions have been previously implicated in bipolar disorder and deserve further investigation, including extensive microsatellite marker mapping. A third set of NIMH genetics initiative bipolar pedigrees has now become available. Together, these three bipolar pedigree sets will provide an exemplary genetic resource for chromosome 4 and chromosome 20 candidate region characterization, including extensive polymorphism testing using haplotype analysis and family-based tests of association in positional and functional candidate genes.

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