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Predisposition Locus for Major Depression at Chromosome 12q22-12q23.2

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Major depression disorder is a common psychiatric disease with a major economic impact on society. In many cases, no effective treatment is available. The etiology of major depression is complex, but it is clear that the disease is, to a large extent, determined genetically, especially among individuals with a familial history of major depression, presumably through the involvement of multiple predisposition genes in addition to an environmental component. As a first step toward identification of chromosomal loci contributing to genetic predisposition to major depression, we have conducted a genomewide scan by using 628 microsatellite markers on 1,890 individuals from 110 Utah pedigrees with a strong family history of major depression. We identified significant linkage to major depression in males at marker D12S1300 (multipoint heterogeneity LOD score 4.6; $P = .00003$ after adjustment for multiple testing). With additional markers, the linkage evidence became highly significant, with the multipoint heterogeneity LOD score at marker D12S1706 increasing to 6.1 ($P = .0000007$ after adjustment for multiple testing). This study confirms the presence of one or more genes involved in psychiatric diseases on the q arm of chromosome 12 and provides strong evidence for the existence of a sex-specific predisposition gene to major depression at 12q22-q23.2.

Introduction

Major depression disorder (MDD) is one of the most common psychiatric diseases, with lifetime prevalence estimates ranging from a minimum of 5% to a maximum of 17% (Weissman et al. 1991; Kessler et al. 1994; Spaner et al. 1994). As many as 15% of patients with severe MDD die by suicide (Angst et al. 1999). The societal costs of MDD, including costs due to treatment, morbidity, and lost productivity, have been estimated at >$43 billion annually in the United States alone (Greenberg et al. 1993; Pincus and Pettit 2001). According to the World Health Organization (Murray and Lopez 1996), MDD is a major source of disability worldwide and is predicted to become second only to ischemic heart disease by the year 2020. Despite this high prevalence and major economic impact on society, little is known about the etiology of the disease. Adding to the problem is the observation that many people with depression who could be treated effectively do not seek or obtain treatment (Hirschfeld et al. 1997; Davidson and Meltzer-Brody 1999).

Although epidemiological studies have demonstrated a clear environmental component in the etiology of MDD, genetic factors are important as well. Twin studies have shown that there is a much higher concordance with respect to depression-related phenotypes in MZ twins than in DZ twins (Bertelsen et al. 1977; Torgersen 1986; Englund and Klein 1990). In addition, many families show clustering of MDD (Sullivan et al. 2000), suggesting a high level of familiality. The results of segregation analyses are usually inconsistent with a Mendelian mode of inheritance (Cox et al. 1989), although other studies have indicated the possibility of a relatively straightforward inheritance pattern (Marazita et al. 1997).

Even though genetic predisposition to MDD is well established, and despite the importance of the disease, few linkage results for MDD have been reported (Tanna et al. 1976, 1989; Craddock et al. 1994; Balciuniene et al. 1998; Jones et al. 2002; Zubenko et al. 2002*b*). This may be due to the multifactorial etiology of MDD, with vulnerability being influenced in a complex way by both environmental and genetic factors. In addition, the genetic factors may include multiple weak- or moderate-effect genes. One approach to overcoming these diffi-

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culties is to narrowly define the phenotype, such that the impact of environmental influences is minimized and the effect of fewer genes is expected. One of the most reliable findings in the epidemiology of MDD is a two- to threefold female-to-male difference in population risk for MDD (Moldin et al. 1991; Robins and Regier 1991; Tsuang et al. 1994). This suggests that either the sporadic rate among females is significantly higher than among males or that the penetrance of some depression-related genes is sex-specific. Although Kendler et al. (2001) did not observe statistically significant differences in heritability of MDD across sexes, in a large twin study it was found that the genetic risk factors for MDD in men and women, although positively correlated, are significantly different. This observation was recently confirmed in an allelic association study of recurrent, early-onset MDD (Zubenko et al. 2002*a*), in which a strong sex specificity at 16 of 19 candidate susceptibility loci was reported (although caution should be used when applying linkage analysis for the determination of the correct phenotype). Highly significant linkage, using the definition proposed by Lander and Kruglyak (1995), has recently been observed by Zubenko et al. (2002*b*) in chromosomal region 2q33-q34 for women from families with recurrent, early-onset MDD. For these reasons, we also incorporated sex-specific phenotypes in the linkage analysis. Our results provide very strong evidence for the existence of a gene, in the chromosomal region 12q22-q23.2, that predisposes males to MDD.

Subjects and Methods

Subjects and Pedigrees

A study of the familial nature of disease in Utah benefits from the population, which consists primarily of members of the Church of Jesus Christ of Latter Day Saints (LDS, or Mormons). Many Mormons abstain from coffee, alcohol, and tobacco consumption, affecting the incidence of some related diseases (e.g., Spak et al. 2000). Family size in Utah is larger than the U.S. average. There is also a keen interest in genealogy and the documentation of family histories. Both family size and genealogical records contribute to the success of genetic studies in Utah. It has been demonstrated that the Mormon population of Utah has northern European gene frequencies (McLellan et al. 1984) and normal levels of inbreeding (Jorde and Skolnick 1981). These characteristics make this population appropriate for inferences about common diseases in populations of northern European descent.

A total of 407 pedigrees were ascertained for a family history of MDD for this study. Among these pedigrees, 110 that contain a minimum of four affected individuals were selected for genotyping. A Brief Screen for Psychopathology (BSP) was developed by our team of clinicians and was administered by clinician-trained clinic coordinators. This tool was an adaptation of the Composite International Diagnostic Interview (CIDI) (World Health Organization 1990), modified to particularly screen for MDD and bipolar disorder (BPD) rather than the full spectrum of psychiatric disorders. All affected individuals in our study met the Diagnostic and Statistical Manual of Mental Disorders criteria for MDD or BPD (American Psychiatric Association 1994). We tested the tool for reliability against the CIDI and also performed a test-retest for the BSP. We phenotyped 37 individuals with both tools, and 41 individuals were screened twice with the BSP. For the CIDI-BSP reliability test, we found that 95% were concordant for the phenotype definition we were analyzing (only two individuals changed phenotype classification). In one of the two discrepant cases, the individual responded differently to identical questions on both tools and was called "unaffected" by BSP and "affected" by CIDI; the difference was thus due to intraindividual variability. The other person had never reported any symptoms to a physician (required in CIDI) but gave the same answers for all questions in BSP and CIDI. He was called "affected" by BSP and "unaffected" by CIDI. For the BSP test-retest, 95% were concordant (two individuals changed phenotype classification). One individual was called "unaffected" at the first interview but 56 d later was in an MDD episode and answered the BSP questions differently. The second individual was called "affected" by MDD, but 2 mo later the diagnosis was changed to generalized anxiety disorder. All phenotypes were independently assigned by at least two clinicians, after reviewing the results from the BSP and available medical records. If there was disagreement in phenotype assignments or evidence for an alternative phenotype not screened for comprehensively in the BSP, then the CIDI was administered.

This study was approved by the institutional review boards of Intermountain Health Care and Valley Mental Health. Informed consent was obtained from each participant.

MDD and BPD are clearly differentiated by the absence or presence of episodes of mania. However, it has been shown that relatives of probands with BPD have increased risk of MDD (Kelsoe 2003), and, in multiple linkage studies, MDD and BPD have been included in a broader phenotype of affective disorders. We included individuals with BPD as "affected" in the phenotype definition, which we will refer to throughout as "DEP." However, it must be pointed out that, in contrast to other studies, the majority of affected individuals in all our pedigrees have MDD, and the minority have type I and type II BPD, since pedigrees in our study were ascertained for MDD. Our sample set included 1,890 indi-

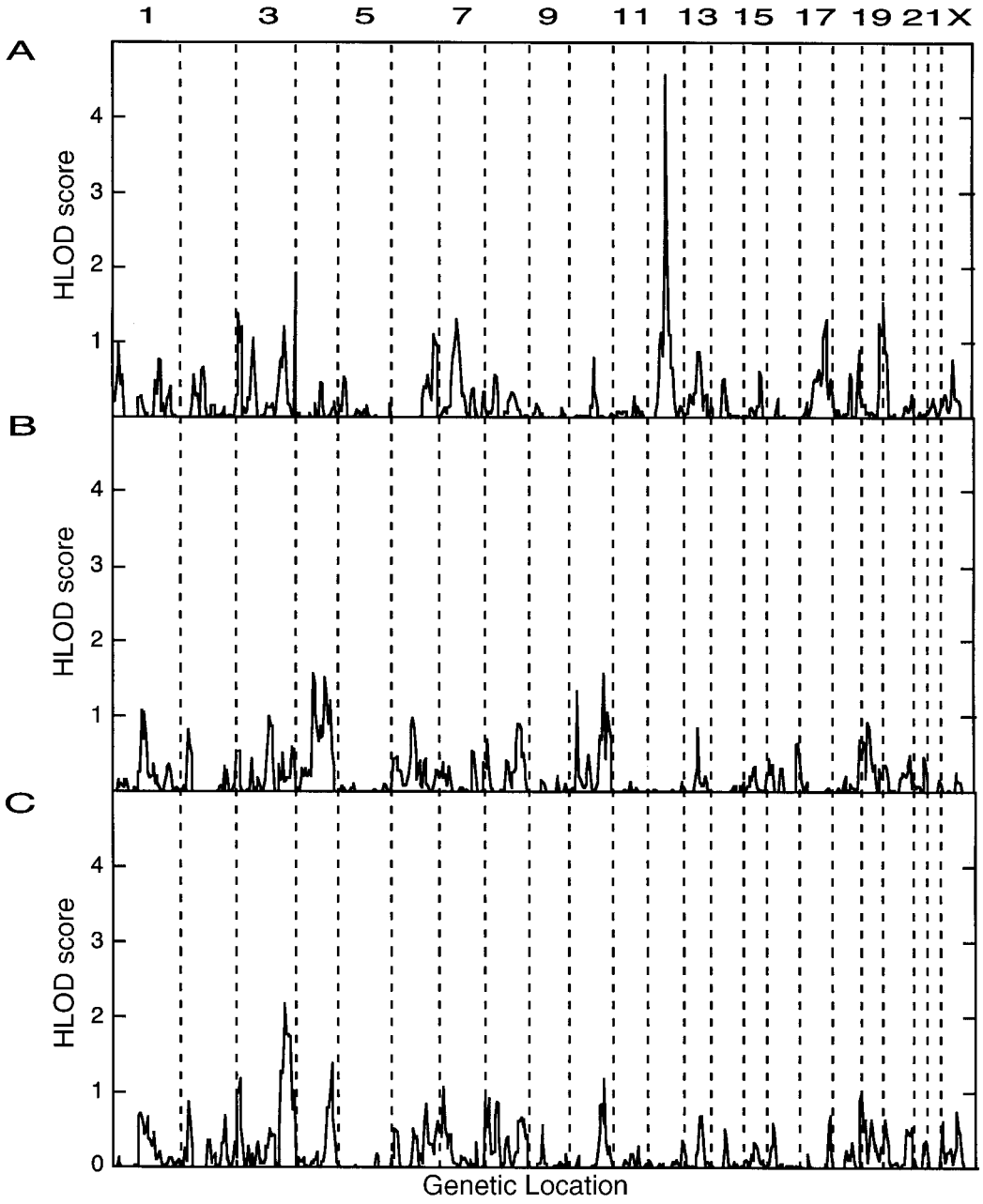

Figure 1 Results of genomic search for loci linked to MDD. Multipoint HLOD scores for the dominant model are plotted on the *Y*-axis, and marker positions (in cM) are plotted on the *X*-axis. Vertical dashed lines delimit the chromosomes, and chromosome numbers (odd numbers only) are indicated at the top of the figure. *A*, HLOD for DEPM phenotype. *B*, HLOD for DEPF phenotype. *C*, HLOD for DEP phenotype.

viduals, 784 of whom are affected with recurrent MDD (238 males and 546 females), 161 with a single episode of MDD (48 males and 113 females), and 162 with BPD (62 males and 100 females). The average pedigree contains 17 studied individuals, 10 of whom are affected; the pedigree size varies from 6 to 55 individuals, with 4–31 of them being affected. In total, 69% of all affected individuals are females, and 31% are males. The average size of pedigrees, as well as the number of affected individuals used in this study, is substantially higher than in most other studies of psychiatric diseases.

Genotyping

DNA was extracted from blood buffy coats through use of PUREGENE DNA isolation kits (Gentra Systems).

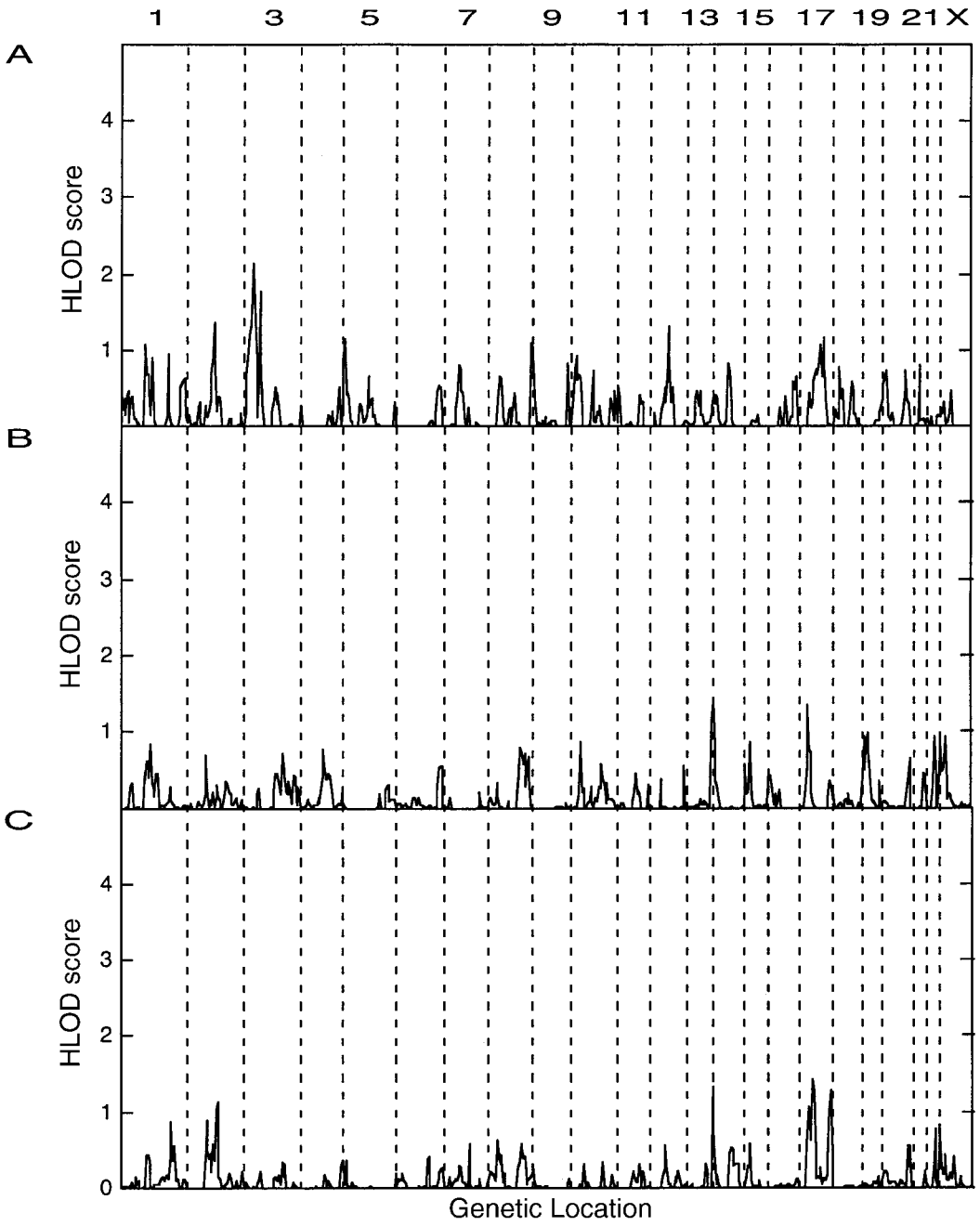

Figure 2 Results of genomic search for loci linked to MDD. Multipoint HLOD scores for the recessive model are plotted on the *Y*-axis, and marker positions (in cM) are plotted on the *X*-axis. Vertical dashed lines delimit the chromosomes, and chromosome numbers (odd numbers only) are indicated at the top of the figure. *A*, HLOD for DEPM phenotype. *B*, HLOD for DEPF phenotype. *C*, HLOD for DEP phenotype.

We were able to obtain blood samples from 1,357 of 1,890 family members from 110 pedigrees (the remainder were either deceased or did not volunteer to participate in the study). All samples were genotyped using 628 fluorescent dye–labeled microsatellite markers (di-, tri-, and tetranucleotide repeats) developed at Myriad Genetics, covering the entire genome, including the X chromosome. The mean heterozygosity index for these genomic search markers was ~75%. All dinucleotide repeat markers contained GTTT extensions at the 5′ ends of the unlabeled PCR primers to reduce the variability of addition of nontemplated nucleotides at the 3′ ends

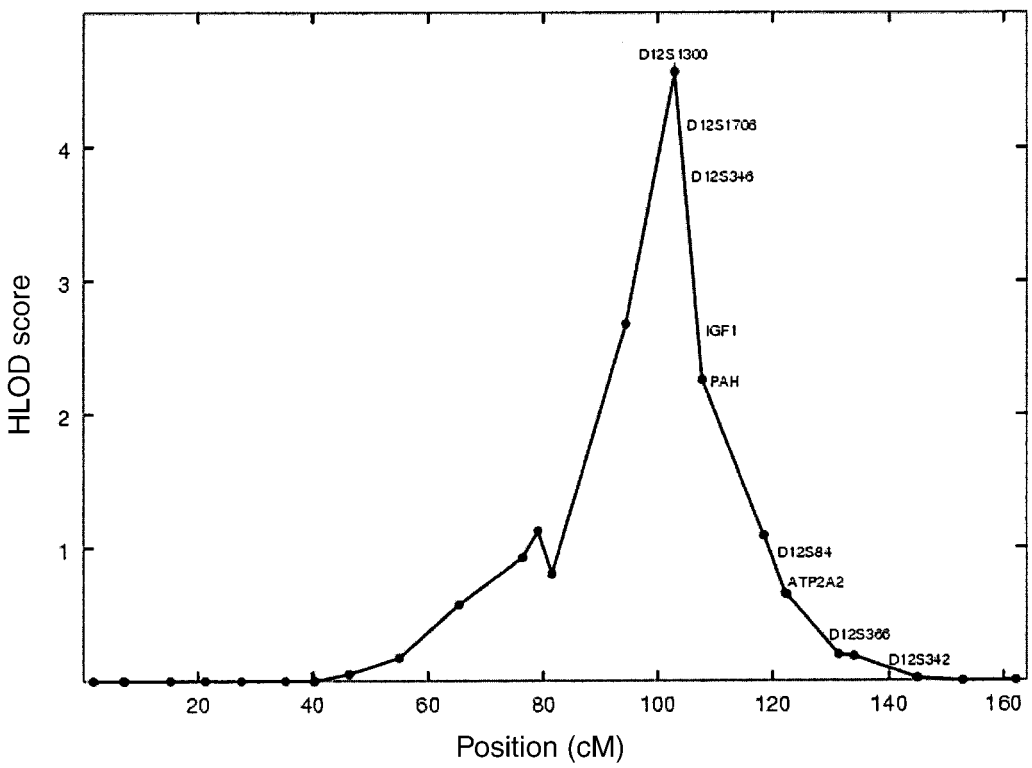

Figure 3 Results of linkage analyses for chromosome 12, from the genomic search for loci linked to MDD. Multipoint HLOD scores for the dominant model and DEPM phenotype are plotted on the *Y*-axis, and marker positions (in cM) are plotted on the *X*-axis. Black dots correspond to the position of markers used in the analysis. Markers at which the strongest linkages were observed for psychiatric disorders (see fig. 6) are indicated.

of the labeled products (Brownstein et al. 1996). PCR products were analyzed on ABI 377 fluorescent sequencers. The average spacing between genomic search markers was 5.8 cM. The genetic map used for all analyses was generated internally, through use of the CRI-MAP program (Lander and Green 1987), on 3,916 meioses, and it closely corresponds to the deCODE map (Kong et al. 2002). After a strong linkage signal was obtained on chromosome 12q23, 33 additional markers were added to a 33-cM region between markers D12S303 and D12S353. This decreased the average marker spacing in the region to 0.9 cM. Inheritance of all alleles was verified using the PEDCHECK program (O'Connell and Weeks 1998). Samples with incompatibilities were generally regenotyped and were set to "missing" if they could not be resolved.

Linkage Analysis

In this study, we employed the robust multipoint linkage statistics proposed by Göring and Terwilliger (2000). Linkage analysis was performed using MCLINK, a program developed by Myriad Genetics, which allows analysis of very large pedigrees with any number of genotyped markers (Thomas et al. 2000). This analysis tool has been successfully employed to map common disease genes (Kort et al. 2000; Camp et al. 2001; Samuels et al. 2001; Stone et al. 2002). Two models (dominant and recessive) were used in the linkage analysis. A gene frequency of 0.003 was chosen for the dominant model, and a gene frequency of 0.0775 was chosen for the recessive model, yielding an approximate disease prevalence due to a single locus of 0.6%. This disease frequency is equivalent (if we assume the existence of 10 major genes with similar effects on MDD) to 6% of the general population having heritable MDD. Only affected individuals were considered informative for linkage. The penetrance was chosen to be nine times higher than the sporadic rate. This penetrance is equivalent to a fivefold increased risk of MDD among first-degree relatives of MDD probands, a value close to the one observed in families ascertained through adult probands with recurrent MDD (Zubenko et al. 2001).

Three phenotypes were defined for our analyses: in the first one (DEP), all affected individuals are equally informative; in the second one (DEPF), only affected

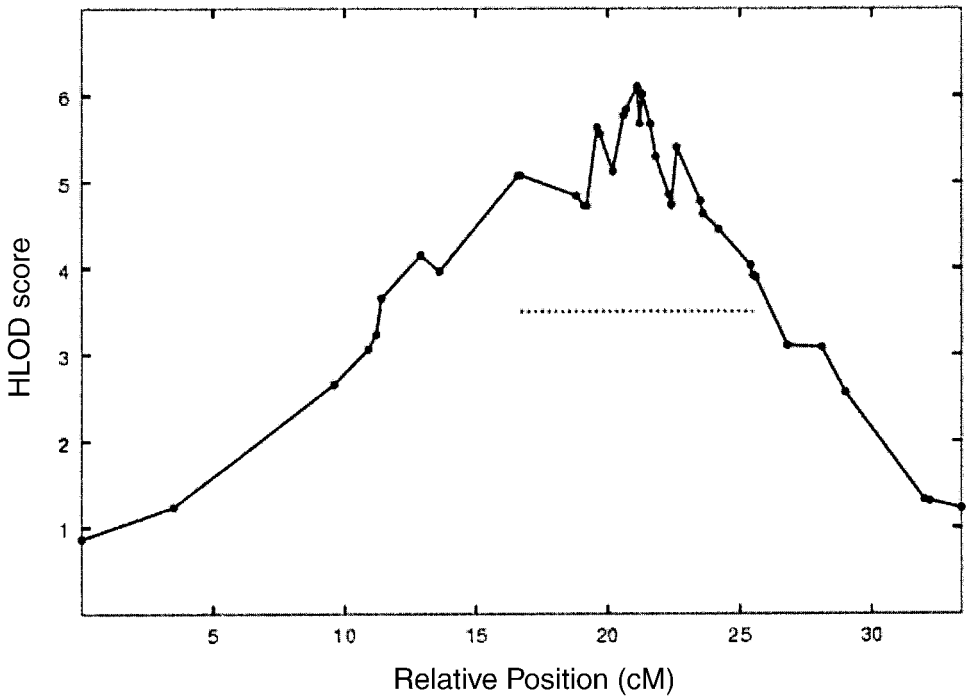

Figure 4 Linkage analyses of chromosomal region 12q21.1-q23.3 with additional markers (dominant model, DEPM phenotype). Black dots correspond to the position of markers used in the analysis. The dashed line indicates the region within boundaries determined by recombination events in three pedigrees with the strongest linkage evidence (see fig. 5).

females are considered informative; and, in the third one (DEPM), only affected males are considered informative. Although all 110 pedigrees had at least four affected individuals with the DEP phenotype, the number of informative pedigrees with the DEPF and the DEPM phenotypes was significantly lower: 94 pedigrees had at least four affected individuals with the DEPF phenotype and only 32 pedigrees had at least four affected individuals with the DEPM phenotype.

Results

Genomewide Search

We performed a genomewide scan for loci linked to phenotypes DEP, DEPF, and DEPM through use of a set of 628 highly polymorphic microsatellite repeat markers. Results of linkage analyses for the genome scans obtained using dominant and recessive models are shown in figures 1 and 2, respectively. Because our pedigrees were multigenerational, with several affected individuals in each generation, we did not expect to observe recessive linkage evidence. Consistent with this expectation, no significant recessive linkage signals were detected. However, we found strong evidence of linkage on chromosome 12q23.1 for the DEPM phenotype at marker D12S1300 (heterogeneity LOD score [HLOD] 4.6) when the dominant mode of inheritance was used. Results of linkage analyses for chromosome 12, obtained using the dominant model, are shown in figure 3. In this study, we used the guidelines proposed by Lander and Kruglyak (1995) to distinguish among "highly significant," "significant," and "suggestive" linkage evidence (it should be mentioned that such categorization is only approximate). However, the present study employed three phenotypes and two models for each of the phenotypes. Therefore, we adjusted the thresholds proposed by Lander and Kruglyak (1995) to account for performing six tests. To be conservative, we assumed that these models and phenotypes were not correlated, requiring an adjustment of $\log_{10}(6)$ LOD score units (~0.8). Accordingly, we used the threshold of 5.7 for a "highly significant" LOD score, 4.1 for "significant," and 2.7 for "suggestive" evidence for linkage. Using these thresholds, we can characterize the linkage evidence to chromosome 12q23.1 obtained in the genome scan as significant, with corresponding *P* value equal to .00003. There were no other regions that reached the significant or suggestive thresholds.

Linkage Analyses of the 12q21.1-q23.3 Region

We genotyped an additional 33 markers in the 33-cM interval between markers D12S303 and D12S353, where the strongest evidence for linkage was observed. The link-

Table 1

Markers and Linkage Scores in Chromosomal Region 12q21.1-q23.3 (DEPM Phenotype, Dominant Model)

Marker[a]	Relative Position (cM)	HLOD
D12S303	.0	.9
D12S1684	3.5	1.2
D12S1667	9.6	2.7
D12S1710	10.9	3.1
D12S1064	11.2	3.2
D12S322	11.4	3.7
D12S1345	12.9	4.2
12-MYR0285	13.6	4.0
12-MYR0255	16.6	5.1
12-MYR0256	16.7	5.1
D12S309	18.9	4.8
D12S1716	19.1	4.7
12-MYR0284	19.2	4.7
D12S1051	19.6	5.6
D12S2081	19.7	5.6
12-MYR0288	20.2	5.1
D12S1300	20.6	5.8
D12S1671	20.7	5.8
D12S1706	21.1	6.1
12-MYR0254	21.2	5.7
D12S1600	21.3	6.0
D12S346	21.6	5.7
12-MYR0289	21.8	5.3
12-MYR0283	22.3	4.9
D12S1058	22.4	4.7
D12S1588	22.6	5.4
D12S1041	23.5	4.8
12-MYR0286	23.6	4.6
12-MYR0287	24.3	4.5
D12S318	25.4	4.0
D12S1607	25.5	3.9
D12S1074	25.6	3.9
PAH	26.8	3.1
D12S338	28.1	3.1
D12S1636	29.0	2.6
D12S1335	32.0	1.3
D12S84	32.2	1.3
D12S353	33.4	1.2

[a] Markers denoted "12-MYR" were developed at Myriad Genetics. Primer sequences are available on request.

age results (when the dominant model and DEPM phenotype were used) including these added markers are shown in figure 4 and in table 1. The highest HLOD score for the dominant model, 6.1 (corresponding *P* value is equal to .0000007 after adjustment for multiple testing) at marker D12S1706, meets the criteria for highly significant linkage after adjustment. Linkage evidence is very sensitive to phenotype definition: HLOD for the DEP and DEPF phenotypes is <0.1 everywhere in the region. If only individuals with MDD are considered affected and those with BPD are considered uninformative, the highest HLOD score is 4.7. This indicates, as expected, that individuals affected with MDD and BPD in our pedigrees share the same haplotypes and that, although linkage evidence comes mainly from individuals with MDD, individuals with BPD substantially increase it. It is interesting to note that the LOD score increased sharply after more markers were added to the region, even though we used a higher marker density in the genome scan than in most previously published studies. This suggests that important regions could be missed altogether in genomic scans performed with low marker density.

Discussion

In the present study, we have conducted a genomewide search for genes predisposing to MDD and have found highly significant linkage evidence for such a gene in the region 12q22-q23.2. Seven of 32 pedigrees with four or more affected male individuals show evidence of linkage in this region (LOD >0.5). In these pedigrees, ~86% of affected males (excluding affected spouses) share the segregating haplotypes. In comparison, only 39% of affected females share these haplotypes. This clearly indicates that the effect of the MDD predisposition gene in this region is much stronger among males than among females. We used recombination events in the three pedigrees showing the strongest linkage evidence (pedigree multipoint LOD >1.5) to determine the boundaries of the region. Individuals with these recombinants were affected with MDD. However, it should be mentioned that the use of recombination events for the determination of the region's boundaries is tentative, especially given the fact that only 86% of affected males within linked pedigrees share the segregating haplotypes. By requiring at least two different recombination events per boundary, we were able to narrow the region to 6.5 Mb, between markers 12-MYR0256 and D12S1607 (fig. 5).

There is strong supporting evidence for the presence of a gene involved in psychiatric disorders in this region. Significant (Jones et al. 2002) and suggestive (Craddock et al. 1994) linkages were obtained between the Darier disease gene (ATP2A2) at 12q23-q24.1 and major affective disorder (a mixture of MDD and BPD cases). Moreover, there is strong support for this region from studies of other psychiatric diseases, especially from BPD. Observations of linkage evidence in chromosomal region 12q23-q24 are displayed in figure 6 (some of which are from published abstracts, not yet reported in peer-reviewed journals). In a review article, Detera-Wadleigh et al. (1999) described highly significant linkage obtained in an unpublished report by Barden et al., for BPD at D12S366. Significant linkage evidence was observed by Ewald (2002) for BPD at D12S1639 and by Fullerton et al. (2003) for neuroticism at D12S346.

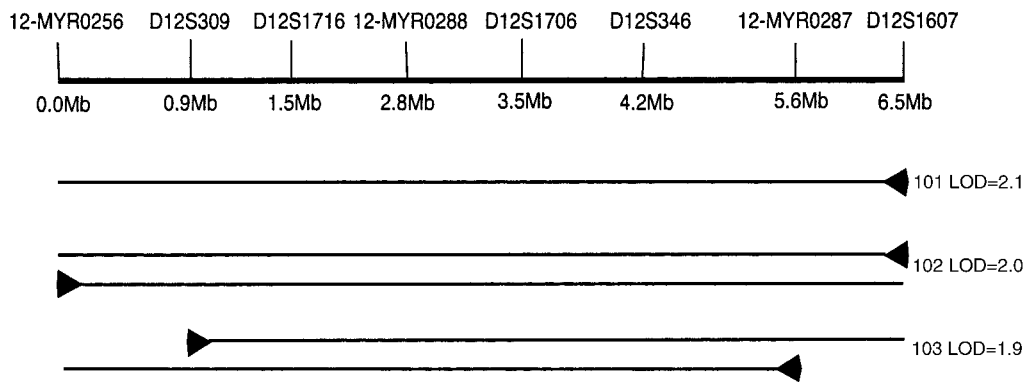

Figure 5 Recombinations in three pedigrees with the strongest linkage evidence (>1.5 LOD score units) to chromosomal region 12q22-q23.2. Four affected males share the haplotype with recombination at marker D12S1607 in pedigree 101. One affected male shares the haplotype with recombination at marker D12S1607 in pedigree 102. Three affected males share the haplotype with recombination at marker 12-MYR0256 in pedigree 102. One affected male shares the haplotype with recombination at marker 12-MYR0287 in pedigree 103. Two affected males share the haplotype with recombination at marker D12S309 in pedigree 103.

Suggestive linkage evidence for BPD was obtained by Morissette et al. (1999) at D12S84, Degn et al. (2001) at D12S342, Ekholm et al. (2001) at PAH, and Maziade et al. (2002) at IGF1. In their review article, Detera-Wadleigh et al. (1999) described suggestive linkage for BPD obtained in an unpublished report by McQuillin et al. at D12S342. Suggestive linkage evidence for schizophrenia was obtained by Brzustowicz et al. (2000) at PAH and by Wilcox et al. (2002) at D12S1300.

All of these studies (including the present study) revealed evidence for linkage within a 30-Mb region; however, it is not yet possible to conclude whether a single gene or multiple genes are responsible for all of these observations. There are certain characteristics that distinguish our study from the others. First, while the strongest linkage evidence obtained in the studies mentioned above (including ours) appears within a relatively small region, our strongest linkage evidence is closer to the centromere. Second, there is a distinct difference in the phenotype considered in the present study compared with other studies. Although, in the majority of genetic studies of BPD, individuals with recurrent MDD are also considered affected, individuals with BPD constitute the majority of the affected individuals. In our study, on the other hand, individuals affected with BPD constituted <15% of all affected individuals. This difference originates from the ascertainment of pedigrees. In our study, all probands were affected with MDD, whereas, in genetic studies of BPD, all probands are affected with BPD. In addition, 15% of the affected individuals in our study had only a single episode of MDD. These individuals are usually not included in genetic studies of even the broad phenotype of BPD and recurrent MDD. The similarity of the affected individuals used in this study as compared with schizophrenia studies is even lower. Schizophrenia and MDD are generally considered to be caused by different genetic factors. Individuals with MDD typically are not considered affected in schizophrenia studies (with one notable exception: Blackwood et al. [2001]). The third distinct difference from other studies of psychiatric disorders in which linkage in chromosomal region 12q23-q24 was observed is the use of sex-specific phenotypes. Linkage evidence obtained in the present study is very sensitive to phenotype definition, since no evidence for linkage was observed when either the DEP or the DEPF phenotypes were used.

Linkage evidence for a predisposition gene was observed only for the DEPM phenotype and points to a deleterious allele (or alleles) predisposing only males to develop MDD and sometimes BPD. However, linkage evidence can be deceiving. Even a moderately complex relation between genotypes and phenotypes can suppress LOD scores. For example, the gene detected in this study might have an effect on females as well, but the effect (penetrance) may be much weaker than for males. It is also possible that the effect of this gene is sex-independent but that the environmental effect on females (sporadic rate) is stronger than on males or that other genes might have a stronger effect on females. For example, Zubenko et al. (2002*b*) reported highly significant linkage on chromosomal region 2q33-q35 exclusively among females within families with recurrent, early-onset MDD. It is also possible that the gene we have detected has a very strong sex-specific effect on MDD. Only with the discovery of the disease-causing allele(s) can we provide a certain answer regarding the role of this gene in male and female depression. What-

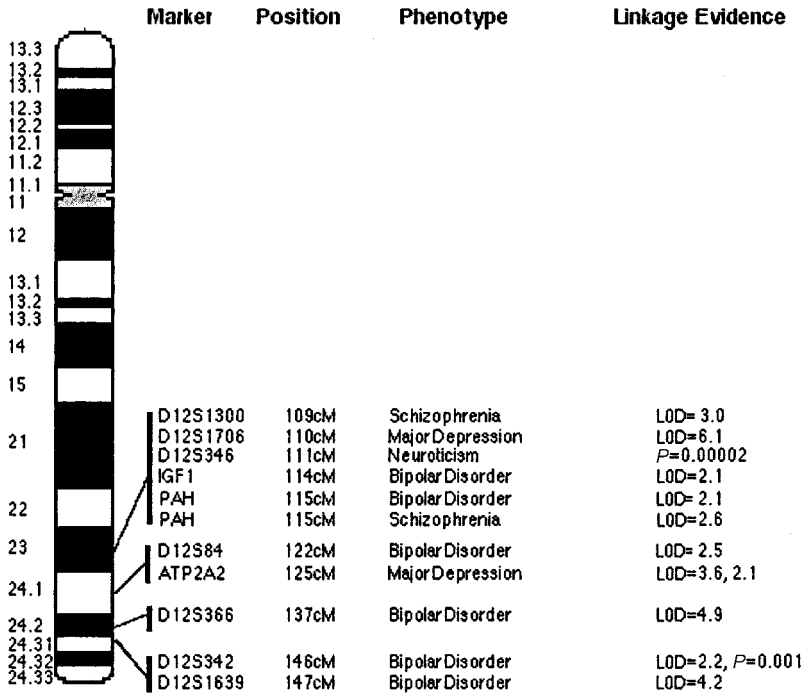

Figure 6 A map of chromosomal region 12q22-q24, showing relevant markers for different psychiatric diseases and corresponding linkage evidence. Markers and references are as follows: D12S1300 (Wilcox et al. 2002); D12S1706 (present study); D12S346 (Fullerton et al. 2003); IGF1 (Maziade et al. 2002); PAH (Brzustowicz et al. 2000; Ekholm et al. 2001); D12S84 (Morissette et al. 1999); ATP2A2 (Craddock et al. 1994; Jones et al. 2002); D12S366 (Barden et al., cited by Detera-Wadleigh et al. 1999); D12S342 (McQuillin et al., cited by Detera-Wadleigh et al. 1999; Degn et al. 2001), D12S1639 (Ewald 2002). The *P* value of .001 corresponds to a LOD score of 2.4, and the *P* value of .00002 corresponds to LOD score of 4.0.

ever the reason, overall haplotype sharing among affected females was substantially lower than among affected males, and the HLOD scores for the phenotypes DEP and DEPF were not significant.

In conclusion, our results strongly suggest the presence of an MDD predisposition gene on chromosome 12q22-q23.2. This gene has an especially important effect on MDD among males. This represents, to our knowledge, the first highly significant linkage evidence of a male-specific MDD gene.

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