Am. J. Hum. Genet. 59:1343–1362, 1996

A Follow-Up Report of a Genome Search for Affective Disorder Predisposition Loci in the Old Order Amish

Michele C. LaBuda,[1] Mady Maldonado,[2] Dianna Marshall,[2] Kevin Otten,[2] and Daniela S. Gerhard[2,3]

[1]Division of Child and Adolescent Psychiatry, Johns Hopkins Medical Institutions, Baltimore; and Departments of [2]Genetics and [3]Psychiatry, Washington University School of Medicine, St. Louis

Summary

Progress of a full-genome scan for predisposition loci for affective disorder in the Old Order Amish is reported. LOD-score results have been previously published for 51 loci on chromosomes 1 and 11, collectively. The present report contains results for an additional 367 loci throughout the genome with extensive coverage on chromosomes 1, 2, 3, 4, 6, 7, 9, 10, 13, 14, 18, 19, and 21 (average marker density for these chromosomes = 10.7 cM). Analyses were conducted in a four-stage process: (1) two-point LOD scores were calculated for all loci under a dominant model with reduced penetrance, consistent with results of segregation analyses of these pedigrees; (2) a screen for the sharing of alleles in similarly affected individuals was used to highlight areas potentially important for further analysis; (3) the preceding areas and markers on densely covered chromosomes were analyzed using the affected-pedigree-member (APM) method; and (4) the sharing of extended haplotypes in affected individuals was examined in areas showing apparent clustering of significant allele sharing as assessed by the APM method. Of the 367 markers analyzed, no statistically significant LOD scores resulted. Some degree ($P < .05$) of allele sharing was found at 74 loci, and 3.8% of all markers analyzed ($N = 14$) passed more stringent significance criteria suggestive of linkage ($P \leq .001$ for at least one of the weighting functions). Multilocus APM and detailed exploration of extended haplotype sharing in areas highlighted by the APM analyses provided methods for more informative exploration of potentially suggestive results but did not identify areas clearly involved in the etiology of affective disorder in this population.

Received June 7, 1996; accepted for publication September 3, 1996.

Address for correspondence and reprints: Dr. Daniela S. Gerhard, Department of Genetics, Box 8232, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110. E-mail: gerhard@genetics.wustl.edu

0002-9297/96/5906-0022$02.00

Introduction

Affective disorders are characterized primarily by disturbances in mood ranging from extreme elation, or mania, to severe depression. These alterations of mood can be associated with symptoms of sleep disturbances, hyperactivity, flight of ideas, weight changes, feelings of worthlessness, and/or suicidal ideation. It is estimated that 5%–10% of the population will meet criteria for affective disorder sometime in life (Goodwin and Guze 1989). Because the financial cost for treatment and loss of productivity is estimated at $16.3 billion each year, affective disorder represent a significant public health issue (Jarret 1990).

For decades, the tendency for mood disorders to cluster within families has been documented. Data from blinded, controlled family studies have been consistent with a hypothesis of a genetic vulnerability to both bipolar disorder (mania and depression) and unipolar disorder (depression without mania; Tsuang and Faraone 1990). The genetic relationship between bipolar and unipolar disorder is less clear, however, since family studies of bipolar probands generally find elevated rates of bipolar and unipolar depression in first-degree relatives, whereas studies of unipolar probands generally find elevated rates of unipolar but not bipolar disorder (Heun and Maier 1993). Data from twin and adoption studies provide more direct evidence of the involvement of genetic factors in the transmission of affective disorders and are consistent with a greater familiality of bipolar than unipolar disorder as observed in family-study data (Tsuang and Faraone 1990).

In light of the evidence from family, twin, and adoption studies in support of a genetic basis for affective disorder (particularly bipolar disorder), several attempts have been made to delineate the mode of inheritance. The results of these attempts are varied; however, there is evidence that a major locus may underlie bipolar disorder in at least some families (Rice et al. 1987; Sham et al. 1992; Spence et al. 1994), including the Old Order Amish (OOA) (Pauls et al. 1995). Studies aimed at pinpointing the location of genes of major effect for susceptibility to affective disorder have been undertaken by many research groups worldwide. A survey of investiga-

tors in 1992–93 determined that there were 16 separate groups engaged in linkage analysis of affective disorder (Nurnberger 1993). Although there have been indications of significant findings (Baron et al. 1987; Egeland et al. 1987; Berrettini et al. 1994; Straub et al. 1994), no result has yet clearly passed the test of independent replication (see Risch and Botstein 1996). Linkage to Xq28, for example, has had a long history of both positive and negative findings (Baron et al. 1987, 1993; De bruyn et al. 1994). Also, excess allele sharing between affected siblings has been in found two studies for a region on chromosome 18 (Berrettini et al. 1994; Stine et al. 1995), although it is not clear that the second study (Stine et al. 1995) is truly a replication of the first. Although some markers for which excess allele sharing was originally found showed similar excess sharing in the second study, there were additional significant findings in the first study that were not replicated in the second study. Second, stronger evidence for linkage was observed in the second study (Stine et al. 1995) in a region 30 cM away in paternally—but not maternally—transmitting pedigrees. Additional study of chromosome 18 provides mixed results. De bruyn et al. (1996) were not able to exclude the pericentric region of chromosome 18 in their study of two large pedigrees. Likewise, Coon et al. (1996) found no linkage in the pericentric region but small positive LOD scores at 18q23.

Study of the familiality of affective disorders in the OOA began with the ascertainment of cases of mental illness during the period 1976–87 in Lancaster County, Pennsylvania (Egeland and Hostetter 1983; Pauls et al. 1992). Ascertainment was accomplished through (1) a survey of inpatient psychiatric facilities in the area and (2) a community epidemiological survey (details of each of which are given in Egeland and Hostetter 1983). Direct interviews were undertaken of first-degree relatives of 38 probands who were diagnosed with bipolar I disorder by Research Diagnostic Criteria (RDC). Family members were found to be at increased risk for affective disorders (Pauls et al. 1992). Specifically, risk for first-degree relatives compared to population prevalence estimates were found to be increased 7.3-fold for bipolar I (8.7% in relatives vs. 1.2% in the general Amish community), 18.5-fold for bipolar II (3.7% vs. 0.2%), and 7.7-fold for major depressive disorder (11.6% vs. 1.5%). Risk of illness in relatives was not found to differ on the basis of either the sex of the proband or the sex of the relative. Segregation analyses of the family data show the pattern of inheritance to differ depending on the diagnostic scheme applied to relatives and the subset of families analyzed; however, support for a major locus was provided by the analysis of bipolar disorder only in the more closely related families who comprise the linkage sample (Pauls et al. 1995).

The first formal linkage analysis of affective disorder in the OOA was published in 1984 (Kidd et al. 1984). Since the early 1980s, diagnostic data and cell lines have resided in a public repository, and several groups have been or are currently engaged in linkage efforts. A complete genome screen has been undertaken, utilizing data from this family, and details of the screen are presented in the Methods section of this paper. Two-point LOD-score results for markers on chromosomes 1 and 11 were previously published (Gerhard et al. 1994). The present report contains the LOD-score results for an additional 367 markers throughout the genome, along with allele- and haplotype-sharing analyses on chromosomes sufficiently saturated with markers.

Methods

Pedigree Structure and Diagnostic Data

Figure 1 depicts members of the OOA extended pedigree genotyped. The pedigrees correspond to those published by the National Institutes of Health (NIH) (Egeland 1992/1993, appendix F, pp. 841–848). The pedigree is "anonymous" in order to protect the confidentiality of its members. Details of the pedigree structure are available from the authors on request. Figure 1*A* includes the latest addition of 49 individuals to pedigree 210 (Coriell Institute for Medical Research [CIMR], family 1075, panels 2 and 3), together with the 27 members of pedigree 210 (CIMR family 1075, panels 1 and 2); figure 1*B* shows 18 members of pedigree 110 (CIMR family 884, panels 1 and 2); figure 1*C* shows 31 members of pedigree 110 (CIMR family 884/885, panel 3).

Bipolar I (BPI) probands and members of the extended family have been followed since 1976. Diagnostic evaluations were made with information obtained from multiple interviews conducted using the Schedule for Affective Disorders and Schizophrenia—Lifetime version (Endicott and Spitzer 1978) and from abstraction of all available medical records. Diagnoses were made using RDC (Spitzer et al. 1978) by a panel composed of four psychiatrists and one psychologist. The panel was kept blind to patient identity, biological relationships, and previous diagnostic information. Annual follow up of all subjects continues to be conducted by interviewers who are blind to genotype status. Of the 41 subjects with major affective disorders, 30 had some form of bipolar disorder: 24 were diagnosed with bipolar I or schizoaffective disorder (bipolar type), 6 were diagnosed with bipolar II, and 11 were diagnosed with recurrent major depression. An additional 20 individuals were diagnosed with minor psychiatric conditions.

Genotypings/Genetic Maps

Initially, genotyping efforts were focused on the typing of RFLPs, while the latest typings utilize the more

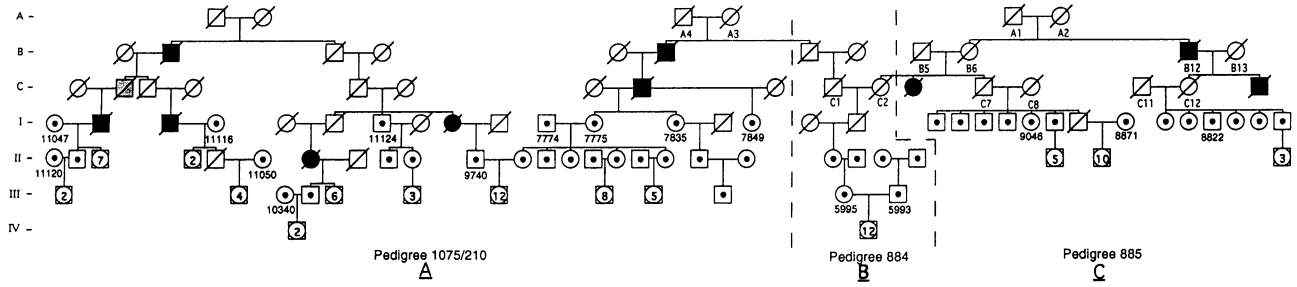

Figure 1 Genotyped members of the OOA pedigree. The individuals for whom DNA exists are indicated by dots or by a circle within a square, within which is the number of individuals in that sibship. The diagnostic status is unknown to the individuals doing the genotyping and is therefore not shown, except in some members of the earlier generations for whom DNA does not exist.

polymorphic PCR-based markers. Results from both types of markers are included in the present report. Areas yielding potentially interesting results will be subsequently fully saturated with markers. The present report includes progress to date on the genome scan, excluding the loci on chromosomes 1 and 11 previously published (Gerhard et al. 1994) and excluding chromosomes 5 and 16, which were omitted because of prior arrangement for study by another investigator (J. Kelsoe, personal communication). The few chromosome 5 and 16 markers shown were done by request.

Results from 367 polymorphic genetic markers are included in the present report. PCR-based markers were chosen to have observed heterozygosity or PIC values exceeding 70%. Oligonucleotide primer pairs were obtained from Research Genetics, except for 30 pairs that were synthesized by the Washington University Clinical Research Center. Golf primer sequences were provided by Dr. W. Berrettini prior to publication. All primer pairs were first tested to determine the optimal amplification conditions. The desired criteria were the sharpness of bands and the highest signal-to-noise ratio: noise being band stutter or lane-specific general background. Fifty nanograms of genomic DNA were amplified with locus-specific primers by either of two methods for 35 cycles, electrophoresed on 4% or 6% denaturing acrylamide gels, and exposed to X-ray Hyperfilm MP (Amersham) for 1–3 d with or without a Dupont intensifying screen (Gerhard et al. 1994). In PCR method one, the DNA was denatured at 92°C for 30 s, annealed at the temperature determined during the testing phase for 1 min, and extended at 72°C for 1 min by using either Perkin-Elmer 9600 or MJ PTC 200 thermocyclers. To detect the product, one primer was either end-labeled or radioactivity was incorporated during the extension step. PCR method two was "touchdown" performed exactly as described by Don et al. (1991). It was utilized when crisp and strong bands were not obtained during the primer-testing phase under standard conditions.

Genotypes were determined independently by two persons blind to diagnoses. Whenever possible, ambiguities were resolved by repeated genotyping; otherwise they remained as missing data. The genotyping error rate in the laboratory has been estimated at <1% and is periodically reassessed. In addition to the OOA pedigree, DNA from 10 individuals not belonging to these kindreds were genotyped for the exact determination of allele sizes. Estimates of allele frequencies are computed from a sample of married-in individuals from the OOA analysis and reserve pedigrees combined. This estimation procedure was used in order to avoid potential false-positive results due to misspecification of marker allele frequencies (Williamson and Amos 1995).

CRIMAP (Lander and Green 1987) was used to establish the order of markers on chromosomes nearing a 10-cM density map. Empirical maps were developed with the requirement that the odds for placement exceed 1,000:1. Rare cases where this criterion was relaxed are noted in the figure legends. Maps based on genotyping data from the OOA were compared to CHLC (Murray et al. 1994), NIH-CEPH (NIH-CEPH Collaborative Mapping Group 1992), and Généthon (Gyapay et al. 1994; Dib et al. 1996) published maps and as such provide a measure of quality control over the genotyping process. Graphic presentation of genetic maps generated using data from the OOA, comparison with other published maps, and LOD-score exclusion results from the present report can be viewed on the Internet at http://genome.wustl.edu/gerhard/mss/mss_figures.html.

Phenotypic Genetic Analyses

Statistical relationships between the phenotypic or clinical data and genetic marker data were examined in a four-stage process. Initially, two-point LOD scores were computed using the MLINK program from the LINKAGE package of programs (Lathrop et al. 1984). Second, the frequency of allele sharing was calculated in a subset of seven individuals selected because of their high degree of clinical similarly, to highlight potentially interesting chromosomal areas for follow up. These regions were pursued with the more statistically rigorous APM method (Weeks and Lange 1988). All markers on

reasonably saturated chromosomes were also analyzed with the APM method. Finally, allele sharing across loci in affected individuals was examined via multilocus APM and by the creation of extended haplotypes by using the SIMWALK program of Weeks and colleagues (Weeks et al. 1995).

Two-point LOD-score analyses were run under three different diagnostic schemes (the breakdown of affected individuals within these schemes is available from the authors on request):

1. Only those individuals meeting criteria for bipolar I or schizoaffective disorder, bipolar type, were considered affected. Individuals with other disorders potentially within the affective spectrum were considered of "unknown" phenotype. This resulted in 24 "affected" individuals and 37 "unknown" individuals.
2. Affected individuals met criteria for bipolar I or II or schizoaffective disorder, bipolar type (N = 30). Other diagnoses were coded as unknown (N = 31).
3. Affected individuals met criteria for bipolar I or II or schizoaffective disorder, bipolar type, or recurrent major depressive disorder (N = 41). Other diagnoses were coded as unknown (N = 20).

Parameters used for the LOD-score analyses included population prevalences of 0.8% for the first scheme, 1.0% for the second scheme, and 2.5% for the third scheme; inheritance was set as autosomal dominant, with an age-dependent penetrance (maximum = 50% at ≥30 years of age), and 12.5% phenocopies, on the basis of results of the segregation analyses of this population (Pauls et al. 1995). Results are presented in the present report for the second diagnostic scheme only; other results are available from the authors on request.

Recent simulation work has shown that, even when segregation analysis indicates the presence of a major gene effect, use of the resulting major gene parameters may affect the results of LOD-score analyses for some types of two-locus inheritance models (Dizier et al. 1993, 1996). Under such circumstances, nonparametric approaches provide an important complementary methodology. For these reasons, allele-sharing methods were incorporated in the present study. The initial screen for allele sharing among affected individuals employed a frequency count of alleles in common within the group of individuals diagnosed with bipolar I disorder. Subsequently, allele sharing was formally analyzed using the APM method for these markers and markers on all chromosomes densely saturated. The significance of allele sharing was computed using three standard functions of the allele frequencies (f[p]): f(p) = 1, where no weight is applied to the allele frequencies; f(p) = $1/\sqrt{p}$, which gives greater weight to the sharing of more rarely occurring alleles and produces a generally normal distribution of the test statistic; and f(p) = $1/p$, which also gives greater weight to the sharing of more rarely occurring alleles but more frequently produces a non-normal distribution of the test statistic. Results from all three weighting schemes are presented, but the results using f(p)=$1/p$ are generally considered the most reasonable for interpretation. Empirical P-values of the test statistic at each locus for each weighting scheme were calculated using 1,200 replicates of the pedigree structure. Multilocus APM statistics were calculated for select areas on the basis of the results of the single-locus APM results, and extended haplotypes that encompassed these areas were examined. All APM and extended haplotype analyses were conducted with the second diagnostic scheme described above.

Results

LOD Scores—Genome Screen

Two-point LOD scores under the diagnostic scheme that considered individuals diagnosed with bipolar I or II, or schizoaffective disorder as affected (other diagnoses were considered "unknown"), are presented for 367 markers in table 1. The results are listed in order of the markers on the chromosomes (chromosomal locations listed). In order to evaluate the potential magnitude of LOD scores capable of being produced under conditions of linkage by the pedigree used in the present report, simulation analyses were undertaken. These analyses were based on autosomal dominant transmission with parameters as detailed above for the second diagnostic scheme. In addition, the simulation assumed a six-allele marker (of equal allele frequencies) linked with recombination set at 0.05 (roughly corresponding to a marker map density of 10 cM). In simulation analyses of 1,000 replicates, the resulting average maximum LOD score was 4.09. Furthermore, 70.2% of overall LOD scores exceeded a threshold of 3.0, 87.9% of overall LOD scores exceeded 2.0, and 98.2% of LOD scores exceeded 1.0. Simulations based on similar conditions but assuming no linkage produced no LOD scores exceeding 3.0, and only 0.1% and 2% of LOD scores exceeded thresholds of 2.0 and 1.0, respectively. A total of four (1.1%) markers yielded LOD scores >1 (table 1). In contrast, data from 304 (82.8%) markers produced LOD scores generally accepted as evidence of exclusion of genetic linkage under the model tested (LOD <−2.0). Regions of exclusion on 13 chromosomes with heavy marker coverage are accessible on the Internet (http://genome.wustl.edu/gerhard/mss/mss_figures.html). These figures are a graphical representation of the data in table 1, and the reader is cautioned that these areas of exclusion pertain only to the particular diagnostic and genetic model conditions under which the analyses were conducted.

Positive LOD scores were pursued with the placement of flanking markers (excepting MAOB; see Discussion). The maximum LOD score for D2S123 was 1.70 (at θ = .094). This region was further pursued by two markers (D2S119 and D2S136) ~10 cM on either side of D2S123 (CHLC maps these markers to be 9 cM distal and 13 cM proximal, while mapping within the OOA would place them 14 cM and 10 cM, respectively). LOD-score analysis of the flanking markers resulted in exclusion regions of 20 cM around D2S119 and 17 cM around D2S136. These exclusion regions nearly completely overlap with D2S123, although the results are not strong enough to exclude unequivocally D2S123 under the model tested. Second, the region indicated by the positive LOD score for D17S80 (maximum LOD score = 1.26 at θ = .00) was pursued by the reportedly tightly linked marker D17S250. The LOD-score analysis of D17S250 resulted in an exclusion region of 18 cM centered around this marker. D17S80 is a poorly informative marker in the OOA, which may have resulted in a spurious positive LOD score at this locus. Finally, the region around D22S29 (maximum LOD score = 2.02 at θ = .00) was further studied with the analysis of D22S281. This additional marker showed no recombination with D22S29 (LOD score >10) and resulted in an exclusion region extending nearly 10 cM to either side of the marker.

Genetic Maps

Markers genotyped for the 13 most densely typed chromosomes were analyzed using CRIMAP to establish order and intermarker distance within the OOA. In general, most markers were placed with odds of 10^3:1. The order and intermarker distances agreed well with information available from other sources (CHLC [Murray et al. 1994], Généthon [Dib et al. 1996], and the NIH-CEPH Collaborative Maps [1992]). Complete details of the genetic maps are accessible on the Internet (http://genome.wustl.edu/gerhard/mss/mss_figures.html) and are summarized below.

Twelve additional markers have been genotyped in the OOA since the publication from our group of some initial results on chromosome 1 (Gerhard et al. 1994). These markers provide coverage in areas otherwise unexplored, and therefore the full complement of chromosome 1 was mapped. This resulted in the placement of 36 markers in 28 unique locations over an estimated 356-cM region, thereby yielding a marker every 13.2 cM, on average. In addition, three markers were analyzed that were not able to be unequivocally placed in relation to the other chromosome 1 markers on the basis of data from the OOA.

Twenty markers on chromosome 2 identified unique locations along the 299 cM spanned, yielding an average marker density for this chromosome of 15.7 cM. Eight markers were not unequivocally placed on the map, because of low informativeness of the markers and moderate intermarker distances on this chromosome. The typing of additional markers will undoubtedly allow the incorporation of these markers into the OOA chromosome 2 map. All markers on chromosome 3 were mapped by the OOA genotypes: 36 markers were placed in 31 unique locations over 280 cM (average marker density 9.3 cM). For chromosome 4, 30 markers were placed in 27 unique locations over a region of ~251 cM, yielding an average marker density of 9.7 cM. Three markers were not able to be placed on the map with sufficient confidence in this pedigree. For chromosome 6, an average marker density of 11.6 cM resulted from the placement of 17 uniquely localized markers over a distance of 185 cM. Three markers were not unequivocally mapped on chromosome 6. A total of 39 markers were ordered on chromosome 7, resulting in 33 unique marker sites over 201 cM (average marker density 6.3 cM), with 1 marker left unlocalized. Thirty-two genotyped markers on chromosome 9 were unequivocally placed and defined 25 unique loci with an average marker density of 7.3 cM. One marker was not placed with sufficient confidence on chromosome 9. All 20 chromosome 10 markers were uniquely localized, yielding an average marker density of 9.8 cM. Eighteen markers (16 locations) were placed on chromosome 13, and 14 markers (12 locations) were placed on chromosome 14, yielding marker densities of 9.9 and 13.8 cM for these chromosomes, respectively. Thirteen markers in 11 unique locations were placed on chromosome 18 (marker density 15.0 cM). All 14 markers on chromosome 19 and all 9 markers on chromosome 21 were unequivocally placed and resulted in empirical marker densities of 8.6 cM for chromosome 19 and 9.4 cM for chromosome 21. The average marker density for these 13 highlighted chromosomes equals 10.7 cM.

Results of Allele- and Haplotype-Sharing Analyses

An initial step in conducting nonparametric linkage analyses was the identification of markers that showed allele sharing in 7 BPI individuals of similar disease manifestations. The individuals are separated by approximately four generations from a common ancestor. The chromosomal regions identified by this procedure were analyzed using the APM method (Weeks and Lange 1988), along with all the markers on the 13 chromosomes presented in figures 2–14 on the Gerhard Web site and loci on chromosome 11 for which LOD-score results have been previously published (Gerhard et al. 1994). Results are presented in table 2. For consistency with table 1, analyses are presented for the diagnostic scheme that included as affected those individuals diagnosed with bipolar I or II or schizoaffective disorder,

Table 1

LOD Score Results

Locus	Location[a]	Heterozygosity or PIC[b]	LOD Score at θ = .00	.05	.10	.15	.20
D1S468	1	.75	−2.17	−.05	.39	.54	.55
D1S548	1	.76	−4.36	−2.01	−1.11	−.56	−.23
D1S228	1	.78	−4.53	−2.30	−1.51	−.98	−.59
D1S436	1	.69	−7.01	−3.04	−1.74	−1.02	−.59
D1S199	1	.81	−6.68	−3.67	−2.46	−1.68	−1.14
D1S60	1	.48	−3.96	−2.32	−1.55	−1.13	−.83
D1S551	1	.73	−8.04	−4.48	−3.03	−2.07	−1.42
D1S226	1	.84	−7.51	−2.82	−1.60	−.96	−.59
D1S435	1	.73	−3.54	−.12	.56	.77	.77
D1S518	1	.88	−13.2	−5.88	−3.65	−2.28	−1.38
pHHH212	1	.50	.44	.35	.29	.23	.18
D1S102	1q32-q44	.56	−3.63	−1.49	−.75	−.33	−.08
D2S207	2	.80	−7.53	−4.04	−2.64	−1.79	−1.21
D2S162	2	.75	−6.77	−4.59	−3.25	−2.34	−1.67
D2S149	2	.88	−5.33	−3.45	−2.51	−1.83	−1.32
D2S144	2p24-p21	.85	−8.50	−3.67	−2.16	−1.31	−.79
D2S119	2	.80	−7.82	−3.72	−2.14	−1.28	−.77
D2S123	2p16	.77	.45	1.55	1.69	1.57	1.34
D2S136	2	.50	−6.69	−2.90	−1.69	−1.04	−.65
D2S45	2p13	.41	−3.16	−1.37	−.68	−.31	−.09
D2S38 (CRI-L625B)	2p12	.25	−1.06	−.65	−.44	−.30	−.21
D2S38 (CRI-L625C)	2p12	.48	−2.97	−1.58	−.99	−.65	−.42
D2S436	2	.90	−5.92	−3.42	−2.32	−1.58	−1.07
D2S410	2	.81	−7.88	−3.71	−2.28	−1.40	−.83
D2S95	2q14-q21	.85	−4.56	−2.33	−1.54	−1.07	−.74
D2S222	2	.92	−8.87	−5.55	−3.92	−2.84	−2.06
D2S118	2	.78	−4.65	−2.37	−1.36	−.83	−.55
D2S433	2	.76	−1.38	−.70	−.47	−.37	−.32
D2S128	2q35	.80	−9.05	−4.05	−2.41	−1.48	−.89
D2S159	2q33-q37	.77	−3.16	−1.39	−.77	−.42	−.21
D2S407	2	.73	−5.29	−2.14	−1.09	−.53	−.22
D2S53 (*Msp*I)	2q37.3	.74	−4.74	−2.27	−1.33	−.78	−.42
D2S53 (*Rsa*I)	2q37.3	.50	−2.83	−1.22	−.76	−.50	−.33
D2S140	2	.75	−7.71	−4.67	−3.41	−2.49	−1.77
D2S51	2q14.3-q21.1	.17	−2.18	−1.20	−.78	−.51	−.34
D2S54	2q14-q21	.49	.17	.13	.09	.06	.05
D2S44	2q21.3-q22	.97	−5.18	−2.78	−1.79	−1.22	−.87
D2S55	2q36-37.1	.50	−3.55	−1.95	−1.30	−.90	−.62
D2S61 (*Pvu*II)	2q37.1	.32	−2.63	−1.36	−.89	−.60	−.41
D2S61 (*Taq*I)	2q37.1	.24	−.78	−.26	−.11	−.04	−.00
D2S48	2pter-q32	.50	−3.52	−1.89	−1.20	−.79	−.53
pYNZ9.2	2	.26	−1.63	−.89	−.61	−.44	−.31
D3S2387	3pter-p24.2	.83	−12.9	−8.25	−5.83	−4.22	−3.05
D3S1297	3pter-p25	.84	−11.9	−5.35	−3.25	−2.03	−1.24
D3S1304	3p25-p24.2	.81	−7.73	−2.90	−1.37	−.60	−.17
D3S1350	3q	.70	−6.79	−3.45	−2.18	−1.38	−.84
RAF1	3p25	.50	−1.36	−.23	.05	.18	.22
D3S1263	3	.86	−7.22	−3.04	−1.56	−.74	−.26
D3S1255	3	.88	−2.72	−1.07	−.36	.00	.19
D3S86	3	.48	−2.93	−1.02	−.52	−.28	−.15
THRB	3p24.1-p22	.69	−2.16	−1.29	−.80	−.50	−.30
D3S1266	3	.72	−6.72	−3.94	−2.69	−1.86	−1.28
D3S1211	3	.89	−7.15	−3.29	−1.89	−1.09	−.58
D3S1289	3p21.1-p21.1	.82	−6.06	−2.56	−1.28	−.58	−.17
D3S32	3q21.3-p21.3	.50	−2.36	−1.04	−.57	−.31	−.16

(*continued*)

Table 1 (continued)

Locus	Location[a]	Heterozygosity or PIC[b]	LOD Score at θ = .00	.05	.10	.15	.20
D3S1766	3p21.1-p14.2	.86	−5.60	−2.40	−1.33	−.76	−.42
D3S1287	3p14.2-p14.1	.69	−3.04	−1.18	−.50	−.14	.04
D3S30 (*Pvu*II)	3p12	.50	−1.10	−.36	−.09	.01	.05
D3S1284	3	.75	−6.07	−2.52	−1.42	−.80	−.42
D3S2386	3p14.1-p12	.88	−7.81	−3.69	−2.19	−1.32	−.77
D3S1215	3q11-q13.1	.82	−6.86	−3.40	−2.16	−1.41	−.92
D3 Receptor	3	.50	.06	.04	.01	−.00	−.01
D3S1769	3	.71	−2.22	−1.16	−.74	−.43	−.22
D3S1269	3q21	.84	−6.43	−2.09	−.96	−.42	−.15
D3S1316	3q21.3-q25.2	.72	−6.58	−3.14	−2.03	−1.35	−.89
D3S1744	3	.82	−2.97	−.67	.04	.36	.48
D3S1746	3q25.1-q25.2	.76	−6.38	−2.02	−.91	−.34	−.01
D3S1243	3q25.2-q26.2	.60	−.04	.13	.24	.29	.30
D3S1281	3q13	.67	−4.48	−1.74	−.76	−.24	.03
D3S1574	3q26.2-q27	.78	−5.66	−2.75	−1.62	−.99	−.60
D3S1754	3q26.2-q27	.81	−4.71	−1.79	−.84	−.36	−.11
D3S1262	3q27	.81	−4.36	−1.74	−.93	−.50	−.24
D3S1314	3q27	.87	−5.03	−1.89	−.72	−.08	.25
D3S43	3q	.31	.78	.70	.61	.52	.42
D3S30[c]	3p12	.64	−3.41	−1.84	−1.22	−.82	−.54
D3S45	3	.69	−1.63	−.69	−.19	.07	.19
D3S1311	3q27-qter	.84	−4.57	−1.93	−.87	−.29	.02
D3S44	3	.68	−1.73	−1.01	−.64	−.40	−.25
D4S412	4	.81	−6.64	−2.07	−.72	−.08	.22
D4S2366	4	.83	−4.97	−2.37	−1.50	−.98	−.64
D4S124	4p	.27	−4.56	−2.20	−1.41	−.94	−.62
D4S394	4	.81	−7.16	−2.96	−1.71	−1.01	−.57
D4S1567	4	.69	−5.37	−2.71	−1.69	−1.08	−.67
D4S51	4	.32	−1.44	−.81	−.51	−.32	−.20
D4S1632	4	.80	−4.83	−2.35	−1.35	−.76	−.39
D4S174	4p15-p11	.90	−10.4	−4.70	−2.83	−1.80	−1.14
D4S190	4p15-q23	.60	−6.58	−2.34	−.95	−.21	.21
D4S1630	4	.85	−5.05	−2.54	−1.57	−.96	−.54
D4S189	4p15-q23	.60	−5.65	−2.48	−1.30	−.62	−.21
D4S1645	4	.81	−7.85	−4.41	−2.96	−2.05	−1.41
D4S2456	4	.71	−1.63	−.29	.10	.25	.30
D4S395	4	.85	−6.96	−3.62	−2.38	−1.62	−1.08
D4S423	4	.94	−7.67	−3.71	−2.49	−1.74	−1.20
D4S1628	4	.76	.93	.87	.76	.63	.51
D4S1572	4	.94	−10.2	−5.25	−3.53	−2.44	−1.66
D4S25	4	.38	−3.11	−1.86	−1.24	−.86	−.60
D4S1651	4	.62	−1.14	−.44	−.25	−.15	−.10
D4S193	4q21-q25	.90	−5.13	−2.03	−1.04	−.53	−.23
D4S430	4	.69	−5.69	−3.19	−2.31	−1.74	−1.32
D4S429	4	.88	−3.32	−2.01	−1.20	−.69	−.37
D4S175	4q21-qter	.85	−7.00	−3.13	−1.92	−1.20	−.74
D4S1625	4	.76	−8.78	−5.06	−3.42	−2.36	−1.62
D4S192	4q25-q31	.90	−5.42	−3.09	−2.17	−1.54	−1.07
D4S1596	4	.38	−3.63	−2.41	−1.70	−1.22	−.89
D4S415	4	.81	−10.6	−4.85	−3.03	−1.95	−1.24
D4S408	4	.87	−5.18	−2.16	−1.14	−.57	−.24
D4S171	4q33-q35	.70	−6.18	−2.75	−1.53	−.87	−.48
D4S1652	4	.56	−2.76	−.73	−.19	.05	.16
D4S23	4	.34	−2.12	−1.28	−.88	−.62	−.44
D4S49	4	.50	−4.70	−2.44	−1.50	−.94	−.58
D4S46	4	.45	−2.29	−1.23	−.81	−.54	−.35

(*continued*)

Table 1 (continued)

Locus	Location[a]	Heterozygosity or PIC[b]	LOD Score at θ = .00	.05	.10	.15	.20
D5S71	5	.15	.02	.00	.00	.00	.00
D5S107	5q11.2-q13.3	.80	−10.1	−5.46	−3.82	−2.75	−1.99
D5S678	5	.69	−8.80	−4.64	−2.97	−1.97	−1.32
D5S2488	5	.73	−6.52	−2.84	−1.69	−1.03	−.64
D6S277	6pter-p23	.85	−7.10	−4.19	−2.95	−2.12	−1.53
D6S259	6p	.75	−3.57	−.87	−.07	.32	.49
D6S285	6p	.75	−4.61	−2.75	−1.82	−1.25	−.89
D6S105	6p	.87	−8.41	−4.92	−3.24	−2.20	−1.50
D6S10	6p21.3	.53	−.04	−.05	−.05	−.04	−.03
D6S291	6p	.56	−3.97	−1.65	−.80	−.32	−.04
D6S426	6	.75	−7.53	−3.04	−1.75	−1.01	−.55
D6S438	6	.62	−3.77	−1.36	−.68	−.35	−.18
D6S272	6p	.62	−3.25	−1.72	−1.04	−.63	−.37
D6S493	6	.71	−2.44	−.95	−.36	−.01	.20
D6S482	6	.53	−8.76	−3.97	−2.43	−1.55	−.97
D6S501	6	.75	−2.93	−1.41	−.60	−.15	.08
D6S447	6	.69	−3.43	−1.85	−1.09	−.65	−.37
D6S292	6q	.88	−4.41	−1.63	−.67	−.21	.01
D6S495	6	.65	−2.26	−1.19	−.85	−.63	−.47
D6S37	6q27	.81	−6.84	−3.76	−2.53	−1.77	−1.23
D6S39	6q27	.64	−4.41	−1.96	−1.13	−.67	−.38
D6S41	6p21-cen	.25	−2.38	−1.21	−.80	−.55	−.38
D6S44	6	.72	−3.79	−2.27	−1.50	−1.01	−.66
D6S29	6p21	.45	−2.62	−1.32	−.82	−.54	−.35
D7S517	7pter-p15	.75	−5.22	−2.87	−1.95	−1.35	−.92
D7S481	7pter-p15	.75	−3.90	−1.46	−.79	−.44	−.24
D7S513	7pter-p15	.87	−5.92	−2.72	−1.77	−1.25	−.91
D7S507	7p21-p15	.90	−2.82	−1.11	−.31	.08	.25
D7S488	7p21-p15	.75	−4.10	−.84	−.07	.24	.33
D7S503	7p21-p15	.75	−1.89	−.42	−.05	.09	.15
D7S493	7p21-p15	.97	−3.47	−1.10	−.40	−.04	.14
D7S529	7p21-p15	.81	−5.64	−3.55	−2.57	−1.91	−1.41
D7S516	7p21-p15	.75	−4.14	−1.55	−.80	−.42	−.21
D7S370	7p21-p15	.56	−.74	−.25	−.11	−.06	−.05
D7S460	7	.77	−3.08	−1.10	−.37	−.01	.17
D7S484	7p21-p15	.62	−4.09	−2.12	−1.16	−.60	−.25
D7S555	7	.78	−3.34	−1.79	−1.07	−.62	−.33
D7S478	7p15-q22	.56	−3.72	−1.85	−1.07	−.61	−.31
D7S519	7p15-q22	.75	−5.47	−3.74	−2.55	−1.73	−1.14
D7S371	7p21-q11	.31	−1.58	.28	.74	.86	.83
D7S499	7p15-q22	.81	−5.16	−2.73	−1.60	−.94	−.53
D7S645	7	.69	−2.66	−.95	−.47	−.22	−.08
pthh27-1	7	.43	−4.55	−3.03	−2.25	−1.67	−1.21
pthh27-2	7	.31	−5.32	−2.77	−1.92	−1.37	−.97
D7S524	7p15-q22	.87	−3.65	−1.11	−.38	−.05	.07
D7S2417	7	.60	−3.65	−1.67	−.90	−.47	−.22
D7S492	7p15-q22	.69	−1.02	.53	.80	.84	.77
D7S491	7q21-q22	.80	−4.04	−2.24	−1.29	−.68	−.29
D7S496	7q31	.56	−4.84	−2.88	−2.00	−1.44	−1.06
D7S466	7	.86	−7.77	−3.29	−2.08	−1.40	−.98
D7S487	7q31-q35	.69	−3.50	−1.93	−1.18	−.71	−.42
D7S530	7q31-q35	.62	−2.09	−.90	−.66	−.48	−.32
D7S514	7q31-q35	.69	−6.82	−4.11	−2.82	−1.97	−1.36
D7S500	7q31-q35	.94	−5.68	−2.44	−1.23	−.57	−.20
D7S684	7	.75	−5.12	−2.09	−1.13	−.62	−.32

(*continued*)

Table 1 (continued)

Locus	Location[a]	Heterozygosity or PIC[b]	LOD Score at θ = .00	.05	.10	.15	.20
D7S498	7q31-qter	.69	−4.49	−2.62	−1.92	−1.44	−1.08
D7S505	7q31-qter	.75	−.24	.59	.72	.70	.61
D7S372	7q35-q36	.44	−1.00	−.40	−.09	.05	.11
D7S798	7	.69	−2.66	−.87	−.30	−.03	.10
D7S2447	7	.66	−3.41	−1.84	−1.15	−.76	−.51
D7S550	7q31-qter	.75	−6.08	−2.60	−1.48	−.86	−.49
D7S396	7q35-q36	.79	−1.02	−.38	−.17	−.07	−.03
D7S2423	7	.17	−6.63	−3.29	−2.10	−1.37	−.88
D7S1794	7	.29	−9.37	−4.57	−2.96	−1.99	−1.35
D8S17	8pter-p22	.25	−.55	−.48	−.38	−.27	−.18
D8S19	8q	.27	−1.48	−.81	−.53	−.35	−.23
D8S207	8	.74	−4.85	−1.95	−1.02	−.55	−.29
D8S208	8	.71	−6.53	−3.75	−2.45	−1.63	−1.08
D8S512	8	.62	−3.11	−1.49	−.78	−.40	−.18
penk	8q11.23-q12	.58	−3.56	−1.44	−.91	−.64	−.47
D9S132	9	.61	−6.56	−2.44	−1.29	−.68	−.32
D9S324	9	.75	−3.31	−1.25	−.65	−.32	−.13
D9S157	9	.81	−6.26	−3.85	−2.66	−1.87	−1.31
D9S171	9	.62	−4.61	−3.17	−2.44	−1.88	−1.42
D9S43	9p21-q21	.83	−7.84	−3.22	−1.60	−.70	−.18
D9S18	9pter-p13	.38	−3.90	−1.88	−1.16	−.72	−.44
D9S200	9	.83	−8.27	−4.94	−3.59	−2.66	−1.94
D9S15	9q21	.70	−4.25	−2.68	−1.98	−1.50	−1.14
D9S9	9	.38	−3.11	−1.67	−1.13	−.78	−.53
D9S284	9	.81	−2.68	−.81	−.36	−.18	−.11
D9S175	9	.90	−8.46	−4.79	−3.42	−2.50	−1.83
D9S153	9	.69	−1.02	.14	.46	.56	.53
D9S152	9	.88	−7.09	−3.14	−1.97	−1.29	−.85
D9S303	9	.86	−.57	.40	.67	.74	.69
D9S318	9	.50	−5.63	−2.62	−1.42	−.71	−.29
D9S176	9	.88	−8.49	−4.18	−2.55	−1.58	−.95
D9S53	9	.85	−6.63	−3.16	−1.82	−1.04	−.55
D9S58	9q22.3-q31	.90	−5.34	−2.41	−1.39	−.80	−.44
D9S59	9	.70	.62	.68	.62	.54	.45
D9S302	9	.89	−2.95	−.64	−.04	.22	.34
D9S51	9q22.2-q33	.81	−3.67	−1.13	−.36	.00	.18
D9S60	9q33-q34.1	.90	−4.95	−2.03	−1.07	−.55	−.26
D9S61	9	.81	−8.18	−4.51	−3.00	−2.04	−1.38
D9S63	9	.89	−6.55	−3.09	−1.95	−1.31	−.89
D9S64	9	.82	−4.29	−1.31	−.48	−.09	.09
dbh	9q34.3	.41	−4.87	−1.95	−.98	−.48	−.22
D9S10	9q34.3	.43	−3.42	−2.14	−1.45	−1.00	−.68
D9S30	9q34	.64	.72	.55	.40	.28	.18
D9S7	9q34	.65	−4.34	−1.37	−.59	−.21	−.01
D9S67	9q34-qter	.60	−7.05	−3.34	−2.11	−1.37	−.88
D9S11 (*Hin*fI)	9q34	.69	−5.21	−1.86	−.88	−.37	−.10
D9S11 (*Pst*I)	9q34	.72	−3.05	−.77	−.20	.08	.22
D9S31	9q34	.45	−3.52	−2.09	−1.38	−.90	−.58
D10S249	10	.62	−8.16	−3.92	−2.62	−1.81	−1.25
D10S591	10	.94	−6.18	−2.38	−1.21	−.61	−.28
D10S189	10	.75	−5.26	−1.75	−.82	−.40	−.18
D10S172	10	.70	−5.05	−1.90	−.93	−.45	−.19
D10S674	10	.73	−3.20	−.82	−.23	.01	.12
D10S89	10pter-p11.2	.87	−2.19	−.84	−.32	−.06	.06

(*continued*)

Table 1 (continued)

Locus	Location[a]	Heterozygosity or PIC[b]	LOD Score at θ = .00	.05	.10	.15	.20
D10S174	10	.83	−5.76	−2.61	−1.47	−.79	−.40
D10S220	10	.83	−8.22	−4.00	−2.44	−1.53	−.94
D10S464	10	.82	−7.25	−3.41	−1.83	−.96	−.46
D10S676	10	.77	−7.12	−2.53	−1.02	−.25	.14
D10S537	10	.88	−9.09	−3.76	−2.12	−1.28	−.81
D10S580	10	.69	−1.33	−.06	.19	.27	.27
D10S219	10	.81	−5.29	−1.59	−.57	−.11	.09
D10S215	10	.88	−6.73	−2.75	−1.51	−.89	−.53
D10S677	10	.86	−6.40	−2.29	−1.03	−.38	−.04
D10S173	10	.79	−6.07	−2.87	−1.61	−.93	−.51
D10S221	10	.81	−3.75	−1.67	−1.02	−.62	−.36
D10S190	10	.81	−4.47	−2.11	−1.21	−.71	−.43
D10S587	10	.88	−3.72	−.02	.66	.91	.95
D10S169	10q11.2-qter	.78	−2.45	.04	.50	.63	.62
D11S910	11q24-qter	.77	−5.93	−2.48	−1.37	−.75	−.37
TH	11p15.5	.30	−5.25	−3.14	−2.00	−1.27	−.80
D12S2	12p12.2-p12.1	.22	−2.73	−1.64	−1.09	−.75	−.51
D12S6 (*Bam*HI)	12q14	.21	−1.41	−.44	−.22	−.11	−.05
D12S6 (*Msp*I)	12q14	.62	−1.11	−.50	−.28	−.16	−.10
D12S7	12q14-q24.1	.65	−2.79	−.79	−.53	−.79	−.36
D12S8	12q14-q24.1	.29	.21	.17	.13	.10	.07
D12S14	12q12-q24.1	.65	−.66	.34	.57	.62	.59
D12S16	12q12	.57	−1.91	−.71	−.35	−.17	−.07
D12S18	12q12-q24.1	.24	−.89	−.36	−.16	−.06	−.00
D12S70	12p13.3-p12.1	.72	−7.77	−3.39	−1.91	−1.09	−.59
D12S71	12	.72	−6.74	−3.67	−2.51	−1.78	−1.27
D12S72	12	.64	−7.03	−3.54	−2.27	−1.50	−.98
D12S354	12	.69	−2.40	−1.22	−.70	−.36	−.15
D12S372	12	.69	−6.71	−3.34	−2.05	−1.30	−.83
D12S392	12	.75	−4.27	−1.82	−.88	−.39	−.12
D13S175	13	.44	−2.84	−1.50	−.85	−.44	−.18
D13S115	13pter-q12.1	.77	−5.56	−3.31	−2.34	−1.75	−1.34
D13S217	13	.75	−7.53	−3.55	−1.98	−1.09	−.53
D13S171	13	.81	−3.94	−2.43	−1.54	−.97	−.59
D13S765	13	.75	−3.42	−1.49	−.81	−.43	−.21
D13S325	13	.69	−2.77	−2.16	−1.76	−1.38	−1.04
D13S126	13q14.1	.79	−2.24	−.86	−.46	−.25	−.12
D13S118	13q14.1	.60	−3.11	−1.06	−.49	−.19	−.03
RB1	13q14.2	.30	−.90	−.33	−.13	−.03	.01
D13S321	13	.79	−5.44	−3.03	−1.94	−1.30	−.88
D13S318	13	.83	−2.92	−1.69	−1.05	−.62	−.33
D13S162	13	.88	−8.19	−4.79	−3.18	−2.16	−1.46
D13S317	13	.87	−3.74	−1.61	−.87	−.46	−.24
D13S4	13q31	.67	−2.74	−.92	−.49	−.28	−.15
D13S322	13	.62	−8.75	−5.19	−3.66	−2.66	−1.95
D13S173	13	.73	−6.02	−3.57	−2.53	−1.80	−1.27
D13S3	13q34	.33	−4.22	−2.69	−2.07	−1.59	−1.19
D13S285	13	.81	−10.3	−5.78	−3.96	−2.78	−1.94
D13S5	13q21.3-q32	.39	−3.54	−2.20	−1.56	−1.10	−.77
D13S49	13q	.45	−1.61	−.52	−.23	−.08	−.01
D13S54 (cMCOC46-1)	13q	.50	−3.57	−1.71	−1.13	−.80	−.57
D13S54 (cMCOC46-2)	13q	.46	−4.81	−2.73	−1.84	−1.29	−.91

(*continued*)

Table 1 (continued)

Locus	Location[a]	Heterozygosity or PIC[b]	LOD Score at θ = .00	.05	.10	.15	.20
D14S261	14	.81	−6.16	−4.11	−2.98	−2.20	−1.62
D14S276	14	.81	−3.53	−1.69	−1.04	−.65	−.40
D14S258	14	.75	−2.80	−.58	.13	.44	.55
D14S284	14	.69	−6.94	−2.96	−1.84	−1.20	−.78
D14S302	14	.62	−5.53	−2.89	−2.00	−1.44	−1.06
D14S280	14	.69	−5.65	−2.92	−1.96	−1.35	−.94
D14S605	14	.59	−8.28	−4.73	−3.23	−2.28	−1.63
D14S18	14q32.1-q32.32	.30	−1.48	−.94	−.60	−.39	−.25
D14S13	14q32.1-q32.3	.81	−6.32	−2.63	−1.50	−.87	−.47
D14S21	14q32.1-q32.32	.11	−1.44	−.84	−.55	−.38	−.26
D14S1	14q33.33	.50	−.83	.07	.30	.37	.36
D14S17	14q32.33	.46	−.17	−.00	.12	.19	.21
D14S16	14q32.32-q32.33	.35	−4.14	−2.14	−1.39	−.95	−.66
D14S19	14q32.33-q32.32	.67	−2.38	−.93	−.27	.05	.21
D14S22	14	.50	−3.53	−2.20	−1.48	−1.02	−.69
ighj	14q32.32-q32.33	.82	−2.85	−1.16	−.62	−.35	−.20
D15S26	15	.15	−.76	−.26	−.13	−.07	−.04
D15S27	15	.50	−3.23	−1.06	−.57	−.29	−.12
D15S28	15	.27	.18	.16	.14	.13	.12
D15S33	15	.50	.26	.19	.13	.07	.03
D15S34	15	.22	−1.53	−.67	−.36	−.19	−.09
D15S37	15	.50	−3.53	−1.73	−.98	−.54	−.28
D15S45	15q11-qter	.40	−2.46	−1.46	−.90	−.56	−.34
D15S87	15	.86	−8.50	−4.31	−2.76	−1.86	−1.30
D15S24	15q13	.42	−.91	−.49	−.34	−.24	−.16
D15S97	15	.85	−3.25	−1.54	−.76	−.35	−.12
D15S107	15	.67	−4.75	−.94	−.03	.29	.36
D15S117	15	.82	−4.36	−2.02	−.96	−.35	.01
D15S172	15q	.82	−5.16	−2.83	−1.88	−1.30	−.91
D15S230	15	.89	−4.12	−2.45	−1.59	−1.02	−.65
D15S1232	15	.70	−9.09	−1.98	−.46	.21	.49
D15S11	15q11-q12	.58	−8.14	−2.80	−1.34	−.61	−.21
D16S510	16	.81	−3.00	−1.15	−.64	−.37	−.21
D17S24 (*Pvu*II)	17q	.65	−3.48	−1.29	−.63	−.30	−.13
D17S24 (*Taq*I)	17q	.65	−2.25	−.94	−.62	−.46	−.37
D17S27	17q	.32	−2.02	−1.13	−.63	−.34	−.17
D17S28	17p13.3	.58	−1.52	−.66	−.07	.23	.38
D17S32	17q	.50	−.73	−.11	.02	.07	.08
D17S33	17q11.1-q12	.31	−2.77	−1.30	−.81	−.54	−.36
D17S35	17	.50	.71	.62	.53	.44	.35
D17S74	17	.91	−7.30	−3.46	−2.12	−1.36	−.88
D17S80	17q	.35	1.26	1.07	.89	.72	.56
D17S846	17	.83	−4.22	−1.02	−.20	.14	.29
D17S849	17	.75	−2.05	−.76	−.23	.06	.24
D17S969	17	.81	−6.24	−3.17	−1.92	−1.22	−.79
D17S1289	17	.58	−7.06	−2.77	−1.41	−.67	−.24
pthh32	17	.34	−2.71	−1.35	−.81	−.50	−.30
D17S250	17q11.2-q12	.83	−5.70	−3.10	−1.82	−1.07	−.59
D18S59	18	.61	−10.8	−4.88	−2.70	−1.48	−.74
D18S452	18	.75	−5.69	−3.15	−1.98	−1.18	−.65
D18S542	18	.88	−8.64	−4.88	−3.34	−2.36	−1.67
Golf	18	.77	−7.17	−3.73	−2.43	−1.66	−1.15
D18S53	18	.81	−7.17	−3.98	−2.71	−1.92	−1.37

(*continued*)

Table 1 (continued)

Locus	Location[a]	Heterozygosity or PIC[b]	LOD Score at θ = .00	.05	.10	.15	.20
D18S535	18	.92	−7.34	−3.64	−2.31	−1.53	−1.00
D18S450	18	.88	−3.56	−1.26	−.51	−.15	.00
D18S64	18	.81	−5.72	−4.19	−3.08	−2.27	−1.66
D18S537	18	.74	−6.19	−2.81	−1.72	−1.08	−.68
D18S541	18	.79	−6.40	−2.67	−1.52	−.92	−.60
D18S17	18q23	.73	−5.68	−3.14	−2.14	−1.54	−1.15
D18S70	18	.86	−11.1	−5.02	−3.13	−2.06	−1.36
D18S24	18	.50	−.99	−.46	−.32	−.25	−.21
D18S45	18q11.1-q11.2	.50	−3.60	−1.90	−1.28	−.92	−.67
D18S464	18	.50	−.28	−.24	−.14	−.09	−.05
D19S20	19p13.3	.82	−8.54	−4.05	−2.62	−1.83	−1.33
INSR	19p13.3	.58	−3.51	−1.79	−1.14	−.74	−.49
D19S179	19p13.2-p13.1	.67	−1.53	−1.19	−.83	−.56	−.37
D19S433	19	.85	−2.84	−1.89	−1.15	−.66	−.36
D19S49	19q12-q13.1	.82	−5.66	−3.58	−2.51	−1.82	−1.32
D19S191	19q13.1	.92	−5.42	−2.54	−1.39	−.69	−.25
D19S200	19	.92	−9.57	−5.51	−3.80	−2.67	−1.86
D19S178	19q13.2	.80	−5.56	−3.27	−2.42	−1.77	−1.26
D19S246	19	.83	−5.79	−3.77	−2.59	−1.77	−1.18
D19S22	19q13.4	.42	−3.08	−1.52	−.95	−.62	−.41
D19S601	19	.81	−3.25	−.93	−.19	.16	.32
D19S180	19q	.61	−2.97	−1.87	−1.36	−.91	−.57
D19S254	19	.73	−3.20	−1.32	−.52	−.10	.08
APOC2			−6.77	−3.85	−2.35	−1.42	−.83
D20S4 (*MspI*)	20q13.2	.47	−5.21	−3.17	−2.24	−1.62	−1.17
D20S4 (*RsaI*)	20q13.2	.46	−2.13	−.97	−.54	−.30	−.15
D20S19	20q	.84	−7.87	−3.99	−2.48	−1.59	−1.02
D20S66	20	.80	−10.3	−5.02	−3.27	−2.24	−1.54
D21S1256	21	.62	−8.37	−4.89	−3.35	−2.36	−1.65
D21S8	21	.49	−1.98	−1.01	−.64	−.41	−.27
D21S214	21q	.96	−9.28	−4.01	−2.37	−1.42	−.82
D21S265	21	.75	−8.38	−3.34	−1.82	−.99	−.49
D21S1270	21	.86	−5.63	−2.29	−1.22	−.66	−.33
D21S65	21q11.2-q22.2	.92	−4.51	−2.05	−1.21	−.73	−.43
D21S231	21q	.67	−2.61	−1.09	−.40	−.05	.12
PFKL	21	.70	−3.97	−1.26	−.40	.00	.19
D21S171	21q22.3	.67	−4.94	−2.36	−1.46	−.93	−.59
D22S29	22q13.1-qter	.38	2.02	1.77	1.52	1.28	1.05
D22S32	22	.48	−1.31	−.39	−.05	.11	.18
D22S281	22	.75	−4.67	−2.60	−1.80	−1.29	−.91
pdgfb	22q12.3-q13.1	.69	−.81	−.06	.27	.42	.47
MAOB	Xp11.4-p11.3	.82	.13	1.23	1.32	1.27	1.15
3r45	X	.38	−3.29	−1.36	−.84	−.51	−.29

[a] According to the Genome Data Base and CHLC Integrated Maps.
[b] PIC values are underlined. All others are heterozygosity values.
[c] An undocumented second set of polymorphisms was found for this marker.

bipolar type. The pattern of results are similar for the two diagnostic models.

Some degree of allele sharing ($P < .05$) was observed for 74 loci, as indicated by underlining in table 2. Furthermore, 3.8% of the markers in table 2 passed more stringent significance criteria ($P \leq .001$ for at least one of the weighting functions). For allele-sharing analyses involving several types of affected relative pairs (i.e., not solely sib pairs), pointwise *P*-values in the range of .0005–.001 have been defined as suggestive of linkage (Lander and Kruglyak 1995).

Table 2 shows clustering of allele sharing in several chromosomal regions. Multilocus APM analyses were conducted in these areas and results are presented in table 3. Using the criteria for "suggestive" findings established by Lander and Kruglyak (1995) and the weighting function $1/p$, only two chromosomal regions warrant further consideration: the telomeric portion of the short arm of chromosome 6 (D6S277 through D6S285) and a 10-cM region on chromosome 9p (D9S43 through D9S18). Extended haplotypes in these regions were created using the SIMWALK program (Weeks et al. 1995). In each case, haplotype sharing was noted, although fewer than half of the affected individuals shared the most-common haplotype. For the region on 9p, only ~1/3 of the affecteds shared the same haplotype, but the significant multilocus APM finding was reflective of the fact that the haplotype sharing in this region involved one of the rarest alleles for D9S43. The results on chromosome 6p were not the result of sharing the rarest allele(s); however, only half of the affected individuals inherited the same extended haplotype in this region.

Discussion

This report presents the results of 367 genetic markers within the OOA. Combined with previously published work (Egeland et al. 1987; Pauls et al. 1991; Gerhard et al. 1994), a total of 426 markers have been included in the genome screen. Two-point LOD-score and allele-sharing results from a genome screen for affective disorder did not identify any areas clearly important in the etiology of this psychiatric disorder within the OOA. Although some positive LOD scores did result, follow-up placement of flanking markers in these regions indicated the original LOD scores to be within the realm of expectation even in the absence of linkage. Allele- and extended haplotype–sharing analyses, likewise, did not result in any significant findings, although some suggestive areas were defined.

Review of the world literature on linkage and affective disorder yields several areas implicated to various degrees in the etiology of the disorder. For example, chromosome 5q35 (marker D5S62) showed some evidence of linkage in a genome screen published by Coon et al. (1993). A potential significance of this area was the localization of the D1 dopamine receptor gene to the same region. This group of investigators subsequently performed a mutation scan of the D1 dopamine receptor gene but found nothing (Shah et al. 1995). The short arm of chromosome 5 has also been implicated in the etiology of bipolar disorder because of to a positive LOD score resulting for markers in the region of the dopamine-transporter gene in a set of 18 families (maximum LOD scores >1.5 under a dominant model, and $P < .005$ for APM analyses; Kelsoe et al. 1995). The present report contains two markers in this region: D5S2488 and D5S678. The two markers are tightly linked to each other (LOD > 30 at $\theta = .00$) and are located <1 cM from D5S392 (Dib et al. 1996), one of the markers used by Kelsoe et al. (1995). Analysis of D5S2488 and D5S678 excludes regions of 16 cM and 30 cM, respectively, and therefore does not replicate the findings of Kelsoe and colleagues in this region.

Study has also focused on chromosome 16p13 because of an original report of potential linkage of this region and affective disorder in a large Danish family (Eiberg et al. 1993; Ewald et al. 1995). Because the original marker, PGP, was not fully informative, the Danish researchers placed 12 additional markers in the region. As reported at the 1995 World Congress on Psychiatric Genetics, results were less significant under the previously assumed dominant model but reached a maximum LOD score of 2.52 for marker D16S510 for two families, assuming a recessive model of inheritance. Although the evidence in these two regions is interesting, it is weak. D16S510 has been typed in the OOA, and, as shown in table 1, it reaches criterion for exclusion under the dominant model and diagnostic scheme employed (LOD = −3.00 at $\theta = .00$). Further analyses (not shown) do not exclude this locus under a recessive model assuming 50% penetrance and 12.5% phenocopies; however, neither is evidence for linkage obtained under this recessive model (a maximum LOD score of 0.16 at $\theta = .05$ is reached). In contrast, nonparametric analysis of these data yields empirical *P*-values that are in closer agreement with that expected for a region suggestive of linkage ($P = .009$ for $f[p] = 1$; $P = .009$ for $f[p] = 1/p$; and $P = .292$ for $f[p] = 1/p$). At this time, no other markers have been typed in the OOA in this region for multilocus analyses or the examination of extended haplotypes.

Several areas cited in other published works as indicative of weak to moderate linkage to affective disorder can be examined within the OOA. Linkage to chromosome 12q23-24.1 was examined in 45 English and German bipolar pedigrees on the basis of the previous independent identification of a family with significant cosegregation of affective disorder and Darier disease,

Table 2

Empirical *P*-Values Resulting from APM Analyses under Three Alternative Weighting Schemes

	Weight				Weight				Weight		
Marker	1	$1/\sqrt{p}$	$1/p$	Marker	1	$1/\sqrt{p}$	$1/p$	Marker	1	$1/\sqrt{p}$	$1/p$
D1S76	.704	.014	.000	D2S407	.264	.352	.614	D4S174	.922	.840	.575
D1S80	.868	.676	.059	D2S53 (*Msp*I)	.917	.928	.805	D4S190	.948	.633	.157
D1S77	.691	.696	.475	D2S53 (*Rsa*I)	.899	.324	.004	D4S1630	.126	.176	.390
D1S468	.026	.158	.672	D2S140	.597	.723	.760	D4S189	.828	.551	.126
D1S548	.522	.610	.445	D2S51[a]	.727	.002	.011	D4S1645	.000	.002	.200
D1S228	.629	.760	.871	D2S54[a]	.035	.042	.095	D4S2456	.000	.010	.126
D1S436	.380	.374	.539	D2S44[a]	.416	.163	.149	D4S395	.186	.408	.819
D1S199	.567	.639	.711	D2S55[a]	.985	.981	.976	D4S423	.554	.357	.181
D1S60	.587	.589	.568	D2S61[a] (*Pvu*II)	.279	.471	.789	D4S1628	.003	.008	.211
D1S79	.012	.021	.153	D2S61[a] (*Taq*I)	.220	.000	.000	D4S1572	.921	.954	.877
D1S57	.004	.007	.034	D2S48[a]	.875	.825	.755	D4S25	.707	.785	.762
MYCL1	.974	.920	.438	pYNZ9.2[a]	.363	.004	.014	D4S1651	.361	.365	.604
D1S62	.006	.007	.010					D4S193	.681	.191	.009
D1S162	.935	.787	.312	D3S2387	.416	.532	.592	D4S430	.849	.665	.599
D1S21	.742	.305	.086	D2S1297	.955	.904	.729	D4S429	.445	.610	.786
D1S17	.016	.019	.062	D3S1304	.223	.276	.397	D4S175	.119	.077	.160
D1S551	.268	.356	.578	D3S1350	.598	.477	.320	D4S1625	.311	.315	.503
D1S226	.205	.344	.624	RAF1	.564	.557	.365	D4S192	.903	.885	.021
D1S435	.298	.387	.555	D3S1263	.786	.907	.923	D4S1596	.475	.441	.538
D1S64	.920	.971	.974	D3S1255	.314	.139	.207	D4S415	.313	.301	.329
D1S73	.000	.000	.000	D3S86	.220	.279	.529	D4S408	.346	.461	.511
NRAS	.384	.347	.528	THRB	.272	.369	.557	D4S171	.768	.006	.007
D1S13	.280	.280	.280	D3S1266	.553	.471	.288	D4S1652	.175	.241	.359
D1S67	.526	.529	.579	D3S1211	.637	.877	.974	D4S23[a]	.779	.792	.701
D1S104	.390	.234	.144	D3S1289	.900	.456	.112	D4S49[a]	.965	.960	.947
D1S61	.457	.768	.957	D3S32	.437	.535	.578	D4S46[a]	.393	.548	.783
D1S518	.555	.727	.774	D3S1766	.198	.314	.602				
D1S65	.427	.448	.546	D3S1287	.225	.260	.392	D6S277	.074	.103	.154
D1S58	.008	.008	.033	D3S30	.940	.974	.946	D6S259	.134	.068	.162
pHHH212	.013	.014	.035	D3S1284	.399	.556	.669	D6S285	.001	.001	.030
REN	.292	.397	.524	D3S2386	.694	.774	.814	D6S105	.561	.805	.932
D1S59	.779	.889	.967	D3S1215	.825	.914	.963	D6S10	.023	.010	.020
D1S103	.691	.183	.000	D3 Receptor	.011	.014	.028	D6S291	.140	.126	.411
D1S81	.463	.133	.034	D3S1769	.026	.039	.263	D6S426	.103	.107	.262
D1S102	.416	.601	.851	D3S1269	.314	.525	.736	D6S438	.017	.014	.203
D1S14[a]	.221	.290	.504	D3S1316	.088	.144	.297	D6S272	.319	.240	.359
D1S20[a]	.000	.199	.381	D3S1744	.804	.766	.530	D6S493	.564	.259	.200
D1S66[a]	.361	.409	.556	D3S1746	.508	.554	.605	D6S482	.899	.240	.004
				D3S1243	.062	.030	.193	D6S501	.672	.383	.074
D2S207	.654	.723	.670	D3S1281	.219	.279	.485	D6S447	.257	.306	.490
D2S162	.346	.223	.170	D3S1574	.415	.293	.270	D6S292	.193	.341	.751
D2S149	.421	.568	.759	D3S1754	.556	.378	.177	D6S495	.225	.276	.404
D2S144	.975	.886	.064	D3S1262	.141	.088	.195	D6S37	.619	.662	.687
D2S119	.909	.893	.504	D3S1314	.448	.681	.837	D6S39	.762	.914	.995
D2S123	.302	.091	.392	D3S43	.373	.000	.000	D6S41[a]	.477	.655	.936
D2S136	.609	.740	.767	D3S30 (*Pvu*II)	.985	.955	.041	D6S44[a]	.227	.283	.378
D2S45	.943	.972	.896	D3S45	.188	.345	.591	D6S29[a]	.498	.490	.497
D2S38 (CRI-L625B)	.861	.699	.087	D3S1311	.815	.173	.337				
D2S38 (CRI-L625C)	.818	.579	.252	D3S44	.189	.289	.311	D7S517	.443	.583	.582
D2S436	.201	.428	.767					D7S481	.261	.205	.222
D2S410	.945	.935	.743	D4S412	.931	.884	.659	D7S513	.193	.078	.024
D2S95	.103	.264	.682	D4S2366	.308	.512	.756	D7S507	.040	.013	.023
D2S222	.793	.763	.607	D4S124	.439	.422	.331	D7S488	.247	.098	.137
D2S118	.528	.785	.793	D4S394	.443	.494	.650	D7S503	.139	.162	.203
D2S433	.036	.031	.214	D4S1567	.013	.035	.247	D7S493	.481	.365	.265
D2S128	.833	.891	.751	D4S51	.119	.136	.300	D7S529	.550	.362	.348
D2S159	.491	.324	.344	D4S1632	.073	.107	.358	D7S516	.170	.341	.629

(*continued*)

Table 2 (continued)

Marker	Weight 1	Weight $1/\sqrt{p}$	Weight $1/p$	Marker	Weight 1	Weight $1/\sqrt{p}$	Weight $1/p$	Marker	Weight 1	Weight $1/\sqrt{p}$	Weight $1/p$
D7S370	.196	.286	.480	DBH	.706	.321	.110	D13S175	.788	.841	.851
D7S460	.243	.461	.724	D9S10	.749	.687	.657	D13S115	.755	.750	.235
D7S484	.708	.012	.002	D9S30	.025	.035	.089	D13S217	.847	.944	.973
D7S555	.578	.027	.025	D9S7	.694	.803	.829	D13S171	.310	.277	.306
D7S478	.125	.101	.249	D9S67	.059	.127	.567	D13S765	.286	.401	.695
D7S519	.283	.109	.045	D9S11 (*PstI*)	.351	.501	.749	D13S325	.018	.012	.098
D7S371	.865	.436	.057	D9S11 (*Hin*dIII)	.878	.884	.855	D13S126	.446	.104	.271
D7S499	.075	.104	.329	D9S31[a]	.574	.735	.812	D13S118	.350	.352	.534
D7S645	.081	.090	.251					RB1	.457	.532	.618
pthh27-1	.900	.948	.853	D10S249	.903	.878	.610	D13S321	.874	.959	.925
pthh27-2	.921	.989	.999	D10S591	.015	.065	.294	D13S318	.074	.061	.110
D7S524	.941	.827	.375	D10S189	.771	.754	.699	D13S162	.055	.142	.392
D7S2417	.157	.247	.664	D10S172	.226	.274	.598	D13S317	.172	.200	.444
D7S492	.270	.253	.251	D10S674	.014	.013	.134	D13S4	.498	.529	.534
D7S491	.522	.361	.203	D10S89	.037	.183	.388	D13S322	.747	.741	.810
D7S496	.939	.382	.026	D10S174	.950	.001	.000	D13S173	.342	.533	.652
D7S466	.513	.505	.238	D10S220	.166	.157	.488	D13S3	.373	.416	.465
D7S487	.259	.480	.891	D10S464	.902	.658	.101	D13S285	.764	.728	.814
D7S530	.003	.009	.157	D10S676	.855	.471	.147	D13S5[a]	.538	.482	.180
D7S514	.591	.509	.461	D10S537	.062	.089	.289	D13S49[a]	.887	.716	.224
D7S500	.439	.133	.052	D10S580	.302	.073	.134	D13S54 (cMCOC46-1)[a]	.867	.801	.521
D7S684	.553	.274	.016	D10S219	.208	.444	.710	D13S54 (cMCOC-46-2)[a]	.857	.865	.662
D7S498	.501	.138	.023	D10S215	.103	.245	.542				
D7S505	.401	.645	.903	D10S677	.463	.224	.076	D14S261	.850	.848	.550
D7S372	.717	.752	.663	D10S173	.726	.741	.690	D14S276	.220	.288	.677
D7S798	.168	.342	.593	D10S221	.730	.659	.555	D14S258	.663	.418	.212
D7S2447	.788	.726	.533	D10S190	.341	.535	.692	D14S284	.233	.358	.667
D7S396	.702	.786	.749	D10S587	.408	.370	.372				
D7S550	.128	.177	.357	D10S169	.061	.185	.632	D14S302	.101	.094	.268
D7S2423	.486	.717	.891					D14S280	.291	.511	.806
D7S1794[a]	.208	.412	.658	D11S26	.653	.527	.201	D14S605	.957	.911	.668
				D11S12	.973	.885	.117	D14S18	.946	.558	.013
D9S132	.578	.454	.154	D11S16	.180	.255	.369	D14S13	.298	.413	.600
D9S324	.021	.059	.372	D11S149	.947	.930	.084	D14S21	.278	.339	.599
D9S157	.943	.810	.581	D11S288	.325	.369	.448	D14S1	.944	.338	.061
D9S171	.216	.056	.081	CD20	.899	.208	.008	D14S17	.297	.072	.009
D9S43	.993	.003	.000	PGA	.974	.101	.000	D14S16	.575	.688	.762
D9S18	.583	.072	.002	D11S817	.028	.044	.069	D14S19	.844	.000	.000
D9S200	.570	.658	.777	PYGM	.354	.457	.502	D14S22	.721	.721	.721
D9S15	.091	.135	.370	FAEEIIIS	.468	.116	.024	ighj	.674	.705	.727
D9S9	.852	.880	.814	INT2	.336	.410	.468				
D9S284	.533	.465	.353	D11S527	.502	.001	.000	D18S59	.779	.825	.876
D9S175	.417	.078	.103	D11S84	.412	.224	.126	D18S452	.243	.391	.512
D9S153	.256	.093	.080	STMY	.429	.555	.520	D18S542	.417	.010	.022
D9S152	.632	.509	.409	DRD2	.843	.527	.029	GOLF	.193	.454	.762
D9S303	.087	.028	.128	D11S821	.000	.000	.000	D18S53	.276	.061	.020
D9S318	.989	.984	.293	D11S490	.535	.591	.427	D18S535	.093	.089	.206
D9S176	.860	.302	.033	D11S29	.899	.867	.412	D18S450	.507	.381	.236
D9S53	.179	.383	.570	D11S147	.466	.591	.778	D18S64	.017	.022	.217
D9S58	.023	.180	.640	THY1	.576	.649	.929	D18S537	.133	.045	.131
D9S59	.005	.003	.017	ETS	.609	.474	.363	D18S541	.428	.656	.784
D9S302	.221	.271	.035	D11S144	.652	.761	.830	D18S17	.445	.835	.978
D9S51	.005	.053	.497	D11S387	.579	.350	.317	D18S70	.962	.906	.724
D9S60	.331	.609	.745	D11S910	.901	.569	.137	D18S24[a]	.206	.206	.206
D9S61	.975	.951	.333	TH	.194	.283	.668	D18S45[a]	.020	.042	.266
D9S63	.728	.231	.041					D18S464	.161	.362	.827
D9S64	.048	.043	.177								

(*continued*)

Table 2 (continued)

Marker	Weight			Marker	Weight			Marker	Weight		
	1	$1/\sqrt{p}$	$1/p$		1	$1/\sqrt{p}$	$1/p$		1	$1/\sqrt{p}$	$1/p$
D19S20	.858	.870	.668	D21S1256	.403	.383	.284	Additional loci identified through common allele screen of subset of affecteds (see text for details):			
INSR	.418	.610	.395	D21S8	.562	.519	.216				
D19S179	.570	.640	.808	D21S214	.562	.158	.098				
D19S433	.177	.283	.551	D21S265	.150	.247	.489				
D19S49	.343	.340	.021	D21S1270	.694	.421	.283	D17S1289	.302	.515	.864
D19S191	.707	.620	.605	D21S65	.150	.121	.295	D17S969	.299	.349	.434
D19S200	.743	.647	.455	D21S231	.381	.404	.360				
D19S178	.652	.407	.135	PFKL	.260	.290	.382				
D19S246	.868	.644	.415	D21S171	.145	.312	.657				
D19S22	.997	.982	.885								
D19S601	.472	.494	.322								
D19S180	.279	.186	.115								
D19S254	.105	.154	.369								
APOC2	.866	.770	.549								

NOTE.—Underlined values indicate a P-value $\leq .05$.
[a] Marker without unequivocal map location within the OOA.

an autosomal dominant skin disorder (Dawson et al. 1995). Small positive LOD scores (<1.0) were obtained for five markers in the region when allowance was made for genetic heterogeneity and extended sib-pair analyses showed interesting but nonsignificant findings ($P = .05$–.08). The authors note that the power of their sample to detect linkage in the presence of heterogeneity is not substantial and call for other researchers to examine this area in their work. In the present OOA analyses, there are four markers that are of interest: D12S7 and D12S8, which are localized to 12q14-24.1, and D12S14 and D12S18, which are localized to 12q12-24.1. D12S7 is the only marker showing exclusion in table 1; other markers are less conclusive. Analysis of D12S14 yields a maximum LOD score of just over 0.6 at a distance of ~15 cM. Closer examination of the contribution to the total LOD score by pedigree indicates small positive LOD scores occur in all portions of the kindred at this

Table 3

Results from Multilocus APM Analyses

Region	Intermarker Distances (cM)	Weight		
		1	$1/\sqrt{p}$	$1/p$
D1S79–D1S57–MYCL1–D1S62	8 5 0	.001	.003	.007
D1S65–D1S58–pHHH212–RENIN	9 0 0	.005	.013	.036
D3 receptor–D3S1279–D3S1269	0 5	.0002	.006	.412
D4S189–D4S1645–D4S2456–D4S295–D4S1628	0 10 10 7	.000	.002	.541
D6S277–D6S259–D6S285–D6S105–D6S10	16 7 6 4	.009	.008	.279
D6S277–D6S259–D6S285	16 7	.0001	.0001	.236
D7S513–D7S507	11	.045	.012	.0003
D7S555–D7S478–D7S519	5 0	.205	.028	.170
D7S496–D7S466–D7S487–D7S530	7 1 1	.238	.129	.121
D7S530–D7S514–D7S500–D7S684–D7S498	0 12 7 6	.164	.028	.006
D7S684–D7S498	6	.498	.188	.003
D9S171–D9S43–D9S18–D9S200–D9S15	14 10 0 4	.560	.001	.0000
D9S43–D9S18	10	.882	.0004	.0000
D9S176–D9S53–D9S58–D9S59–D9S302	2 8 8 2	.026	.002	.0001
D18S542–Golf–D18S53–D18S535	0 0 22	.082	.014	.007
D18S64–D18S537	14	.009	.002	.205

marker. Nonparametric APM analyses result in $P < .03$ for D12S18 (for f[p] = 1/p and f[p] = 1/p) and $P < .003$ for D12S14 (for f[p] = 1/p and f[p] = 1/p). The multilocus APM results for these two markers are suggestive of linkage ($P = .160$ for f[p] = 1; $P = .000$ for f[p] = 1/p; and $P = .000$ for f[p] = 1/p). Extended haplotype analysis shows a common inherited haplotype of ~12 cM in length that occurs in 63% of the affected individuals but also in 51% of unaffected individuals.

Receiving considerable attention recently with regard to linkage and affective disorder are the short and long arms of chromosome 18 (Berrettini et al. 1994; Stine et al. 1995). An original report (Berrettini et al. 1994) highlighted the pericentromeric region of chromosome 18. Subsequent results by other researchers have varied (Coon et al. 1996; De bruyn et al. 1996), yet significant evidence for linkage to chromosome 18, in the presence of a parent-of-origin effect, has been published by Stine et al. (1995). The confidence intervals surrounding the putative linkage area are so large as to implicate both arms and the majority of the chromosome. Although a few markers were analyzed in the present report, the area was extensively analyzed in the OOA (Pauls et al. 1995) without finding much support for linkage to this area except in the portion of the pedigree included in the Berrettini et al. report. The results presented in the present report agree.

Another area holding the interest of multiple research groups is chromosome 21q22.3. In 1994, Straub and colleagues reported 1 family of a total sample of 47 bipolar disorder families from the United States and Israel that provided in a two-point LOD score of 3.4 at the PFKL locus, under a dominant model. APM analyses also suggested in a significant finding ($P < .0003$). Although the result is particular only to 2% of families, it was shown to be robust to changes in the underlying genetic parameters and diagnostic status. A smaller positive LOD score (1.28, two-point; 1.33, multipoint) was reported in this same region (D21S171) in a sample of 6 Icelandic and 17 English pedigrees (Gurling et al. 1995*a*). Twenty-two multiplex families (Detera-Wadleigh et al. 1996) exhibited excess allele sharing in multilocus analyses involving these two markers, suggestive of linkage. The present report contains both of the markers of interest: PFKL from the Straub et al. study and D21S171 from the Gurling study. Analyses within the OOA show exclusion of a region ~10 cM in length, and no apparent heterogeneity is evident from examining the contribution of different portions of the overall pedigree to the total LOD score. Furthermore, APM results are not suggestive of linkage.

Although it is most likely that affective disorder within the OOA pedigrees is inherited as an autosomal disorder, two markers on the X chromosome were included in the genome scan. It is interesting, in light of two earlier positive association studies involving MAOB (Lim et al. 1994, 1995; Kawada et al. 1995) and the two methodologically more recent studies (Craddock et al. 1995; Nöthen et al. 1995), one employing the more powerful haplotype relative risk analysis (Nöthen et al. 1995), which do not support an association at this locus. Analysis of the OOA data yield a positive LOD score, but this is within the realm of type 1 error.

An area still receiving intermittent attention is the one was originally highlighted by analysis of the OOA: chromosome 11p15. Although the original significant LOD score within the OOA within this region (Egeland et al. 1987) was significantly diminished with the subsequent onset of disorder in two individuals, the LOD score remains positive in the core pedigree (Kelsoe et al. 1989). Additional support for the region comes from at least three reports: Leboyer et al. (1990); Meloni et al. (1995); and most recently Gurling et al. (1995*b*), who found evidence to support a model involving two single major-locus subtypes of affective disorder, one linked to chromosome 21q22.3 as previously discussed and the other to chromosome 11p15. LOD-score analysis of the extended OOA pedigree in the present report shows exclusion of a 20-cM region around the TH locus under an autosomal dominant model. Likewise, APM analysis indicated nonsignificant allele sharing at this locus (empirical $P = .205$ for f[p] = 1; $P = .278$ for f[p] = 1/p; and $P = .662$ for f[p] = 1/p).

Since the compilation of results of the genome screen from our group, three publications on linkage and affective disorder were presented simultaneously in the journal *Nature Genetics* (Blackwood et al. 1996; Freimer et al. 1996; Ginns et al. 1996). The paper written by Freimer and colleagues details the results from two pedigrees obtained in a Costa Rican genetic isolate that indicate significant haplotype sharing for chromosome 18q22-q23 in 23 of 26 individuals affected with BPI. This region may have a small degree of overlap with the region identified in the report of Stine and colleagues (1995) but continues for ~40 cM toward the telomere of 18q. As already described, our data do not support a locus for predisposition to affective disorder in the OOA on chromosome 18.

Blackwood et al. (1996) report a maximum LOD score for marker D4S394 of 4.1 ($\theta = .00$) with significant heterogeneity ($\alpha = 0.35$) in 12 bipolar families, on the assumption of a dominant model of inheritance. This marker was included in the OOA genome screen, and, as shown in table 1, the marker and a region of ~15 cM are excluded in our sample, under similar diagnostic definitions and genetic model parameters. LOD-score analysis using two highly informative flanking markers (D4S2366 and D4S1567) also provides exclusion of this region. No heterogeneity is apparent, because contributions to the LOD score from all parts of the larger OOA

pedigree are negative. APM results are not indicative of any notable degree of allele sharing at this region; *P*-values exceed .30 for all weighting functions for markers D4S2366 and D4S394, while the *P*-value for D4S1567 is $\leq .05$, but not close to criteria for suggestive finding ($P \leq .001$).

The third linkage article published in the *Nature Genetics* series was an independent genome screen in the OOA (Ginns et al. 1996). The report presented results for 14 genetic markers in three chromosomal regions defined by the markers D6S7, D13S1, and D15S45. These three markers were noted to be suggestive of linkage, on the basis of LOD-score analysis and/or the analysis of affected sibling pairs. Of the three markers, only D15S45 was genotyped in our genome screen. Although the analysis of D15S45 in the present report does not result in a positive LOD score, the present report includes a smaller subset of the OOA pedigree. The second marker suggestive of linkage in the genome screen reported by Ginns et al. (1996), D6S7, is an extremely telomeric 6p marker. It is located ~17 cM from D6S277, the most telomeric 6p marker typed for the present report. The most-distal 6p marker in the present report, D6S277, is estimated to be ~17 cM from the telomere. Our findings in this region were suggestive with multilocus APM analyses. LOD-score analyses, however, resulted in the exclusion of a 30-cM region centered around D6S277. A more definitive comparison cannot be made. The third marker, D13S1, is most likely in the 11-cM interval defined by D13S325 and D13S765 genotyped in the present report is but closer to D13S325. The results for D13S325 are not striking, although it is the only chromosome 13 marker showing any degree of allele sharing (empirical $P < .05$).

In sum, the present report details the results of a genome screen involving 367 markers. LOD-score and allele- and haplotype-sharing methods were used to explore fully the genome for potential linkage. LOD scores and exclusion maps based on these results were included in the present report, in an effort to make available all data to other groups for comparison. The inclusion of nonparametric results and the inconsistency that can occur between these results and results of LOD-score analyses illustrate the need to use a comprehensive assortment of analytic methods when dealing with complex behavioral phenotypes. In the present report, no definitive loci were implicated in the etiology of affective disorder; however, several areas of small effect were noted. Future analytic efforts within the OOA will incorporate two-gene models, and the examination of extended haplotypes in the manner used by Freimer and colleagues for the analysis of benign recurrent intrahepatic cholestasis (Houwen et al. 1994).

Acknowledgments

This work was supported in part by NIH grant MH51673 (to D.S.G.). We would like to acknowledge the invaluable contributions of Janice A. Egeland, Ph.D., for the initiation and maintenance of the Amish study. The genome scan would not have been possible without her continued involvement to assure the inclusion of the most accurate and up-to-date clinical information available. In addition, we thank both Dr. Egeland and Cleona Allen, as well as Dr. D. Pauls, for careful reading and comments on earlier drafts of this manuscript and their constant collegial interactions and encouragement throughout the course of this project. We thank Dr. Eric Green for the use of his chromosome 7 in situ hybridization results and primers and acknowledge the contribution of Dr. Abbas Parsian for PCR primer synthesis. Last, we thank Haroon Taqi and Jose Aquilar for construction of the World Wide Web page.

References

Baron M, Freimer NF, Risch N, Lerer B, Alexander JR, Straub RE, Asoka S, et al (1993) Diminished support for linkage between manic depressive illness and X-chromosome markers in three Israeli pedigrees. Nat Genet 3:49–55

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

Berrettini WH, Ferraro TN, Goldin LR, Weeks DE, Detera-Wadleigh S, Nurnberger JI, Gershon ES (1994) Chromosome 18 DNA markers and manic-depressive illness: evidence for a susceptibility gene. Proc Natl Acad Sci USA 91: 5918–5921

Blackwood DHR, He L, Morris SW, McLean A, Whitton C, Thomson M, Walker MT, et al (1996) A locus for bipolar affective disorder on chromosome 4p. Nat Genet 12:427–430

Coon H, Hoff M, Holik J, Hadley D, Fang N, Reimherr F, Wender P, et al (1996) Analysis of chromosome 18 DNA markers in multiplex pedigrees with manic depression. Biol Psychiatry 39:689–696

Coon H, Jensen S, Hoff M, Holik J, Plaetke R, Reimherr F, Wender P, et al (1993) A genome-wide search for genes predisposing to manic-depression, assuming autosomal dominant inheritance. Am J Hum Genet 52:1234–1249

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 60:322–324

Dawson E, Parfitt E, Roberts Q, Daniels J, Lim L, Sham P, Nöthen M, et al (1995) Linkage studies of bipolar disorder in the region of the Darier's disease gene on chromosome 12q23-241. Am J Med Genet 60:94–102

De bruyn A, Raeymaekers P, Mendelbaum K, Sandkuijl LA, Raes G, Delvenne V, Hirsch D, et al (1994) Linkage analysis of bipolar illness with X-chromosome DNA markers: a susceptibility gene in Xq27-q28 cannot be excluded. Am J Med Genet 54:411–419

De bruyn A, Souery D, Mendelbaum K, Mendlewicz J, Van Broeckhoven C (1996) Linkage analysis of families with bipolar illness and chromosome 18 markers. Biol Psychiatry 39:679–688

Detra-Wadleigh SD, Badner JA, Goldin LR, Berrettini WH, Sanders AR, Rollins DY, Turner G, et al (1996) Affected-sib-pair analyses reveal support of prior evidence for a susceptibility locus for bipolar disorder, on 21q. Am J Hum Genet 58:1279–1285

Dib C, Faure S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, et al (1996) A comprehensive genetic map of the human genome based on 5,264 microsatellites. Nature 380:152–154

Dizier MH, Babron MC, Clerget-Darpoux F (1996) Conclusions of LOD-score analysis for family data generated under two-locus models. Am J Hum Genet 58:1338–1346

Dizier MH, Bonaïti-Pellié C, Clerget-Darpoux F (1993) Conclusions of segregation analysis for family data generated under two-locus models. Am J Hum Genet 53:1338–1346

Don H, Cox PT, Wainwright BJ, Baker K, Mattick JS (1991) "Touchdown" PCR to circumvent spurious priming during gene amplification. Nucleic Acids Res 19:4008

Egeland JA (1992/1993) Catalog of cell lines: NIGMS Human Genetic Mutant Cell Repository. Publication no 92-2011. NIH, Bethesda

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

Egeland JA, Hostetter AM (1983) Amish Study. I. Affective disorders among the Amish, 1976–1980. Am J Psychiatry 40:56–61

Eiberg H, Ewald H, Mors O (1993) Suggestion of linkage between manic-depressive illness and the enzyme phosphoglycolate phosphatase (PGP) on chromosome 16p. Clin Genet 44:254–257

Endicott J, Spitzer RL (1978) A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 35:837–844

Ewald H, Mors O, Flint T, Koed K, Eiberg H, Kruse TA (1995) A possible locus for manic-depressive illness on chromosome 16p13. Psychiatr Genet 5:S25

Freimer NB, Reus VI, Escamilla MA, McInnes LA, Spesny M, Leon P, Service SK, et al (1996) Genetic mapping using haplotype, association and linkage methods suggests a locus for severe bipolar disorder (BPI) at 18q22-q23. Nat Genet 12:436–441

Gerhard DS, LaBuda MC, Bland SD, Allen C, Egeland JA, Pauls DL (1994) Initial report of a genome search for the affective disorder predisposition gene in the Old Order Amish pedigrees: chromosomes 1 and 11. Am J Med Genet 54: 398–404

Ginns EI, Ott J, Egeland JA, Allen CR, Fann CSJ, Pauls DL, Weissenbach J, et al (1996) A genome-wide search for chromosomal loci linked to bipolar affective disorder in the Old Order Amish. Nat Genet 12:431–435

Goodwin DW, Guze SB (1989) Psychiatric diagnosis. Oxford University Press, New York

Green ED, Braden RS, Fulton R, Lim MS, Ueltzen DC, Peluso RM, Mohr-Tidwell JR, et al (1995) A human chromosome 7 yeast artificial chromosome (YAC) resource: construction, characterization, and screening. Genomics 25:170–183

Gurling H, Smyth C, Kalsi G, Moloney E, Rifkin L, O'Neill J, Murphy P, et al (1995*a*) Linkage findings in bipolar disorder. Nat Genet, 10, 8–9

Gurling HMD, Kalsi G, Smyth C, Brynjolfsson J, Petursson H, Curtis D, Rifkin L, et al (1995*b*) Linkage analysis in 23 mixed bipolar and unipolar (manic-depression) pedigrees supports an admixture of two single major locus subtypes of affective disorder. Psychiatr Genet 5:25S

Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, et al (1994) The 1993–1994 Généthon human genetic linkage map. Nat Genet 7:246–339

Heun R, Maier W (1993) The distinction of bipolar II disorder from bipolar I and recurrent unipolar depression: results of a controlled family study. Acta Psychiatr Scand 87:279–284

Houwen RH, Baharloo S, Blankenship K, Raeymaekers P, Juyn J, Sandkuijl LA, Freimer NB (1994) Genome screening by searching for shared segments: mapping a gene for benign recurrent intrahepatic cholestasis. Nat Genet 8:380–386

Jarrett RB (1990) Psychosocial aspects of depression and the role of psychotherapy. J Clin Psychiatry Suppl 5:26–35

Kawada Y, Hattori M, Dai XY, Nanko S (1995) Possible association between monoamine oxidase A gene and bipolar affective disorder. Am J Hum Genet 56:335–336

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

Kelsoe JR, Sadovnick AD, Dristbjarnarson H, Bergesch P, Mroczkowski-Parker Z, Flodman P, Rapaport MH, et al (1995) Evidence for a possible susceptibility locus for bipolar disorder near the dopamine transporter on chromosome 5. Psychiatr Genet 5:S26

Kidd KK, Egeland JA, Molthan L, Pauls DL, Kruger SD, Messner KH (1984) Amish study. IV. Genetic linkage study of pedigrees of bipolar probands. Am J Psychiatry 141: 1042–1048

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

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

Lathrop GM, Lalouel J-M, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Leboyer M, Malafosse A, Boularand S, Campion D, Gheysen F, Samolyk D, Henriksson B, et al (1990) Tyrosine hydroxylase polymorphisms associated with manic-depressive illness. Lancet 335:1219

Lim LC, Powell JF, Murray R, Gill M (1994) Monoamine oxidase A gene and bipolar affective disorder. Am J Hum Genet 54:1122–1124

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 bipolar affective disorder. Am J Med Genet 60:325–331

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 345:932

Murray JC, Buetow KH, Weber JL, Ludwigsen S, Schlerpbier-Heddema T, Manion F, Quillen J, et al (1994) A comprehensive human linkage map with centimorgan density. Science 265:2049–2054

NIH/CEPH Collaborative Mapping Group (1992) A comprehensive genetic linkage map of the human genome. Science 258:67–86

Nöthen MM, Eggerman K, Albus M, Borrmann M, Rietschel M, Körner J, Maier W, et al (1995) Association analysis of the monoamine oxidase A gene in bipolar affective disorder by using family-based internal controls. Am J Hum Genet 57:975–977

Nurnberger JI (1993) Status report on linkage studies of affective disorders. Psychiatr Genet 3:207–214

Pauls DL, Bailey JN, Carter AS, Allen CR, Egeland JA (1995) Complex segregation analyses of Old Order Amish families ascertained through bipolar I individuals. Am J Med Genet 60:290–297

Pauls DL, Gerhard DS, Lacy LG, Hostetter AM, Allen CR, Bland SD, LaBuda MC, et al (1991) Linkage of bipolar affective disorders to markers on chromosome 11p is excluded in a second lateral extension of Amish pedigree 110. Genomics 11:730–736

Pauls DL, Morton LA, Egeland JA (1992) Risks of affective illness among first-degree relatives of bipolar I Old-Order Amish probands. Arch Gen Psychiatry 49:703–708

Rice JP, Reich T, Andreason NC, Endicott J, Van Eerdewegh M, Fishman R, Hirschfeld RMA, et al (1987) The familial transmission of bipolar illness. Arch Gen Psychiatry 44: 441–447

Risch N, Botstein D (1996) A manic-depressive history. Nat Genet 12:351–353

Shah M, Coon H, Holik J, Hoff M, Helmer V, Panos P, Byerley W (1995) Mutation scan of the D1 dopamine receptor gene in 22 cases of bipolar disorder. Am J Med Genet 60:150–153

Sham PC, Morton NE, Rice JP (1992) Segregation analysis of the NIMH collaborative study: family data on bipolar disorder. Psychiatr Genet 2:175–184

Spence MA, Flodman P, Sadovnick AD, Remick RA, Yee IML, Bailey-Wilson JE, Rice JP (1994) Reanalysis of the NIMH collaborative bipolar family data: results of complex segregation analysis. Am J Hum Genet Suppl 55:A166

Spitzer RL, Endicott J, Robins EL (1978) Research diagnostic criteria. Arch Gen Psychiatry 35:773–782

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

Straub RE, Lehner T, Luo Y, Loth JE, Shao W, Sharpe L, Alexander JR, et al (1994) A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. Nat Genet 8:291–296

Tsuang MT, Faraone SV (1990) The genetics of mood disorders. Johns Hopkins University Press, Baltimore

Weeks DE, Lange K (1988) The affected-pedigree-member method of linkage analysis. Am J Hum Genet 42:315–326

Weeks DE, Sobel E, O'Connell JR, Lange K (1995) Computer programs for multilocus haplotyping of general pedigrees. Am J Hum Genet 56:1506–1507

Williamson JA, Amos CI (1995) Guess LOD approach: sufficient conditions for robustness. Genet Epidemiol 12:163–176