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Linkage for Platelet Monoamine Oxidase (MAO) Activity: Results from a Replication Sample

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Background: Monoamine oxidase B (MAO-B) degrades catecholamines in presynaptic nerve endings and is also active in platelets. There is evidence to suggest that platelet MAO-B activity level is controlled by a major genetic locus distinct from the structural gene on the X chromosome. To expand on a prior report, new linkage analyses for platelet MAO-B activity have been performed on the previously analyzed sample (designated the initial sample), on a new sample of families (the replication sample), and on the combined sample. These families were recruited as part of the Collaborative Study on the Genetics of Alcoholism (COGA).

Methods: The initial sample consists of 105 extended families providing 1002 nonindependent (412 independent) sib pairs that have been phenotyped for MAO activity and genotyped. The replication sample of 157 extended families contains 608 nonindependent (309 independent) phenotyped and genotyped sib pairs. Analyses were conducted using Haseman-Elston based regression on sib pairs and variance component analysis on extended pedigrees, and the importance of cigarette smoking and gender as covariates of platelet MAO-B activity was taken into account.

Results: Regions on chromosomes 2, 9, and 12 indicated consistent evidence for linkage across the two distinct datasets by at least one analysis method. Under Haseman-Elston regression of independent sib pairs, only the chromosome 2 region gave lod scores above 1 in both the initial and replication samples. Using all possible pairs, unweighted, for the regression, chromosome 12 gave lod scores above 1 in both samples. For variance component analysis, only the chromosome 9 region gave lod scores above 1 in both samples.

Conclusions: The consistency across datasets of these findings is encouraging. In particular, variance component analysis of extended pedigrees supports a potential linkage of MAO-B activity to chromosome 9, with a lod over 3 at 115 cM near D9S261 in the combined sample. Sib-pair regression supports this finding with modest lod scores in the region. Suggestive linkage to chromosomes 2 and 12 from sib-pair analysis is only weakly supported by variance component analysis.

Key Words: Quantitative Trait, Linkage, Sib-Pair Analysis, Variance Component Analysis, Smoking.

MONOAMINE OXIDASE (MAO) is a mitochondrial enzyme that degrades catecholamines in presynaptic nerve endings. Two different forms of the enzyme, MAO-A and MAO-B, are each encoded by structural genes on the X-chromosome (Bach et al., 1988; Hsu et al., 1989). MAO-B is the sole isoform in human platelets and the primary isoform in the human brain. MAO-B activity can be measured in platelets, and studies using positron emission tomography (PET) to assess inhibition of MAO-B activity have shown that brain and platelet MAO-B activity are highly correlated (Bench et al., 1991).

The structural genes on the X-chromosome do not appear to regulate platelet MAO-B activity level (Parsian et al., 1995; Saccone et al., 1999; Suarez et al., 1995). However, there is evidence that platelet MAO activity is influenced by genetic factors. This evidence comes from twin studies (Hussein et al., 1980; Nies et al., 1973; Pedersen et al., 1993; Winter et al., 1978) and family studies (Pandey et al., 1979) indicating high heritability of the enzyme activity. Segregation analyses and commingling analyses (Cloninger et al., 1985; Devor et al., 1993; Goldin et al., 1982; Rice et al., 1982; Rice et al., 1984) show evidence for the existence of a major genetic locus controlling MAO activity.

Since the time of many of the above studies, it has become increasingly evident that platelet MAO activity is influenced by cigarette smoking (Daw et al., 2001; Fowler et al., 1996; Norman et al., 1982; Oreland et al., 1981; Simpson et al., 1999; Whitfield et al., 2000), and that this

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should be taken into account in studies of the genetics of platelet MAO activity. Recently, Whitfield et al. (2000) studied twins and determined that current smoking reduced platelet MAO activity in a significant and dose-related manner, with no evidence of lower MAO in ex-smokers or in nonsmoking co-twins of smokers. Daw et al. (2001) found similar effects among current smokers, ex-smokers, and nonsmoking individuals measured in the Collaborative Study on the Genetics of Alcoholism (COGA). A commingling analysis also performed in that study notably controlled for cigarette smoking status of individuals and still found admixture in the MAO levels consistent with the presence of a major genetic locus.

Previously, Saccone et al. (1999) controlled for cigarette smoking status in the initial COGA sample and used sib-pair based Haseman and Elston (1972) regression for linkage analysis of platelet MAO activity. That genome scan of 291 markers found modest evidence for linkage to two regions of chromosome 2 and a region of chromosome 6. The present study expands on the previous work in three areas. In addition to the initial sample, a new independent sample of families (denoted the replication sample) is analyzed, as is the combined sample. The present analysis uses an updated, denser marker map. Finally, the present study performs genome-wide scans using both Haseman-Elston sib-pair methods and also whole-pedigree variance component methods (Almasy and Blangero, 1998; Amos, 1994). The importance of cigarette smoking status and gender as covariates of MAO activity is again taken into account in these analyses.

MATERIALS AND METHODS

Subjects

Participants were recruited as part of the Collaborative Study on the Genetics of Alcoholism (COGA), a multi-site program to map genes influencing susceptibility to alcohol dependence and related phenotypes. The COGA ascertainment scheme consists of single ascertainment on an alcohol dependent proband to obtain a preliminary sample, followed by multiplex ascertainment to obtain the sample used for genotyping and linkage analysis. The ascertainment protocols for COGA have been described previously in papers reporting genome screen results for alcohol dependence (Foroud et al., 2000; Reich et al., 1998). All subjects participated with informed consent.

Three sets of phenotyped families were analyzed for MAO activity. The previously reported sample (Saccone et al., 1999), designated the initial sample, is composed of 105 extended families. Of these, 95 extended families have genotype and phenotype information for sib-pair analyses of MAO activity, providing 147 nuclear families and a total of 1002 nonindependent (412 independent) sib pairs that have been phenotyped for platelet MAO activity and genotyped. The replication sample is a distinct sample of 157 extended families. Of these, 144 extended families have phenotype and genotype information for at least two members. A total of 120 extended families have genotype and phenotype information for sib-pair analyses, giving 143 nuclear families and 608 nonindependent (309 independent) phenotyped and genotyped sib pairs. The initial and replication samples were combined to form the combined sample.

These data exclude one nuclear family of three individuals whose MAO activity measurements were extreme outliers and who were removed before beginning any linkage analyses.

Genotyping

A total of 351 markers were genotyped; the average intermarker distance was 10.9 cM and the average heterozygosity was 0.74. Most markers were trinucleotide and tetranucleotide repeat polymorphisms developed by the Cooperative Human Linkage Center, with additional markers from Genethon, the Marshfield Clinic, M.I.T., and the University of Utah (Murray et al., 1994). Details of the genotyping protocols are described in Foroud et al. (2000) and Reich et al. (1998).

Mendelian inheritance of markers was confirmed using the database manager Genemaster (Rice, Washington University, 1997, personal communication) as well as the programs CRIMAP (Green, 1990) and USERM13 (Boehnke, 1991). Maximum likelihood estimates of marker allele frequencies were obtained from data on all genotyped individuals in the COGA combined dataset using the USERM13 program. CRIMAP was used to calculate marker order and distances, also using the combined family genotype data in COGA.

Platelet MAO Activity Measurements

Platelet MAO activity levels were determined as detailed in Anthenelli et al. (1998). Briefly, blood was drawn from participants at their respective COGA sites and collected in vacutainer tubes containing 0.10 ml of 15% EDTA solution. Platelets were extracted using multiple centrifuge spins at room temperature (22°C) following a modified method of Corash (1980). To determine stability of MAO activity, whole blood in the vacutainer tubes was kept up to 5 hr at room temperature and up to 24 hr in the refrigerator. Values were stable (±5%) under the conditions of storage. MAO activity in platelets was determined at pH 7.4 with tryptamine (0.1 mM) as substrate using a modification of the method of Wurtman and Axelrod (1963). Activity levels were recorded as nmol/mg protein/hr.

Statistical Methods

Prior to linkage analyses, linear regression was performed on the MAO activity values (measured in nmol/mg protein/hr) using variables for gender, smoking status, and COGA site at which the subjects' blood samples were drawn. These variables were chosen in accordance with the findings of Daw et al. (2001), who showed these to be the significant covariates of MAO activity measurements in the COGA data. Several other variables (e.g., ethnicity, age) were tested by Daw and found to be not significant in the overall model. After correction, the quantitative trait of MAO activity was recorded as a residual from the predicted value.

Two-point and multi-point Haseman-Elston regression analyses were conducted on all sib pairs and on independent sib pairs, using version 2.0 of MAPMAKER/SIBS (Kruglyak and Lander, 1995). This method regresses the squared trait difference on a true maximum likelihood estimate for alleles shared identical by descent (i.b.d.).

Variance component analyses were performed using the SOLAR software package (Almasy and Blangero, 1998). Variance component analysis allows the use of all relative pairs by building likelihood functions for whole pedigrees, assuming multivariate normality within pedigrees. The appropriate variance-covariance matrix for a pedigree depends in part on the predicted proportion of genes shared i.b.d. by the relative pairs at a hypothesized QTL location; this proportion depends in turn on the proportion-shared i.b.d. at genotyped markers, and on the type of relative pair. Maximum likelihood estimates for the variance component parameters are obtained, and a lod score is computed as log_{10} of the likelihood ratio comparing two models: the model where the additive genetic variance σ_a^2 for the QTL is estimated versus the model where σ_a^2 is constrained to be 0 (corresponding to no linkage).

Variance component analyses of MAO activity were initially performed without ascertainment correction. Ascertainment for COGA was based on alcohol dependence, not on MAO activity values, but correction for nonrandom sampling could nevertheless increase power in our analysis of MAO. Following the example of Comuzzie and Williams (1999), additional analyses corrected for ascertainment by conditioning on each of the 105 initial probands' (corrected) MAO activity values. Comuzzie and

Table 1. Regions with Peak LOD > 1 in Either Sample by at Least One Analysis Method

		H-E regression (ip)		H-E regression (ap)		Variance components	
Chr	Flanking markers	cM position	LOD	cM position	LOD	cM position	LOD
Initial sample							
2	D2S436-D2S1328	131	2.04*	135	1.18	—	—
2	D2S1334-D2S399	—	—	—	—	178	1.02
2	D2S408	—	—	255	2.36	—	—
2	D2S1363	262	2.32	—	—	—	—
3	D3S2387-D3S2405	—	—	—	—	16	1.47
3	D3S2432	56	1.26	—	—	—	—
6	D6S1006-D6S1019	29	1.12	—	—	—	—
6	D6S1019-D6S1018	52	1.26	50	1.50	—	—
6	D6S1009-GATA30	—	—	—	—	137	1.42
9	GATA62F-GATA175	—	—	—	—	20	1.47
9	D9S261	—	—	—	—	115	1.50*
12	D12S375-D12S379	—	—	—	—	87	1.01
12	D12S379-D12S393	—	—	113	1.17*	—	—
18	D18S542-D18S877	—	—	—	—	31	1.37
19	D19S254	98	1.30	—	—	—	—
20	D20S42	—	—	—	—	31	1.16
Replication sample							
1	D1S235	—	—	—	—	284	2.66
2	D2S1790	110	2.43*	—	—	—	—
3	D3S1311	—	—	—	—	229	1.35
8	D8S1106	—	—	—	—	0	1.55
8	D8S1102-D8S1136	—	—	70	1.30	—	—
9	D9S261-D9S53	119	1.12	123	1.17	122	2.40*
9	D9S930-D9S302	—	—	—	—	143	1.22
10	D10S610-D10S1213	—	—	128	1.18	—	—
10	D10S1213-D10S590	—	—	153	1.02	149	1.36
11	D11S2002-D11S1354	83	1.46	—	—	—	—
12	D12S375-D12S379	99	2.51	—	—	—	—
12	D12S379-D12S393	—	—	110	1.19*	—	—
12	D12S393-D12S395	—	—	128	1.07	—	—
12	D12S395-D12S2078	—	—	—	—	147	1.86
13	D13S321-D13S318	—	—	—	—	53	1.66
13	D13S318-D13S121	—	—	—	—	62	1.66
16	D16S539	—	—	—	—	151	1.06
17	D17S969-D17S975	48	2.25	—	—	—	—
17	D17S975	—	—	—	—	56	1.30
17	D17S975-D17S250	—	—	57	1.15	—	—
22	AF8VWFP-D22S533	—	—	8	1.13	19	2.71

* Region gives LOD > 1 in both samples (initial and replication) by this analysis method; H-E, Haseman-Elston; (ip), independent pairs; (ap), all pairs unweighted.

Williams (1999) examined various approximate ascertainment corrections in variance component analyses of alcohol dependence in the COGA data. They found that correction on the 105 initial probands best recovered the population prevalence of the alcohol dependence phenotype in males, and also resulted in the most power when analyzing a region of chromosome 4, which had previously been linked to alcohol dependence (Reich et al., 1998).

This study was designed to identify those chromosomal regions that provide evidence for linkage across both the initial and replication samples. The combined dataset was also analyzed. While the initial and replication samples are distinct samples, the same ascertainment protocol was used for both.

RESULTS

The only regions of the genome that attained maximal lod scores above 1 in both the initial and replication samples by a given multipoint method were: chromosome 2 near D2S436 (Haseman-Elston regression with independent pairs), chromosome 9 near D9S261 (variance component analysis), and chromosome 12 near D12S393 (Haseman-Elston regression with all possible pairs, unweighted). In the combined data, these regions resulted in lod scores of 2.85 on chromosome 2 at 126 cM, 3.27 on chromosome 9 at 115 cM, and 2.27 on chromosome 12 at 112 cM, under the respective analysis methods. Weighted Haseman-Elston analysis of all pairs resulted in no regions with lod scores above 1 in both samples.

Table 1 shows all regions with maximal lod scores above 1 in either the initial or the replication sample, for Haseman-Elston regression (independent pairs), Haseman-Elston regression (all pairs unweighted), and variance component analyses. Table 2 shows all regions with peak lod scores above 1.5 in the combined data, by each method, so that support across methods can be recognized. The chromosome 9 finding from variance component analysis is supported by the second highest lod score (1.62) from sib-pair regression with independent pairs. The second highest lod (1.64) from regression with all pairs unweighted also supports the chromosome 9 result. The chromosome 2 finding from analysis of independent sib pairs is only somewhat supported by variance component results, for which the fourth highest lod peak of 1.61 is on chromosome 2, near D2S399,

Table 2. All Regions with Peak LOD ≥ 1.5 in the Combined Sample, by Each Method

Chromosome	Flanking markers	cM position	LOD score
Multipoint Haseman-Elston regression, independent pairs			
2	D2S436-D2S1328	126	2.85
9	D9S1120-D9S261	108	1.62
Multipoint Haseman-Elston regression, all pairs unweighted			
12	D12S379-D12S393	112	2.27
9	D9S261-D9S53	119	1.64
Multipoint variance components with ascertainment correction			
9	D9S261	115	3.27
3	D3S1311	228	1.83
22	AF8VWFP-D22S533	22	1.79
12	D12S395-D12S2078	156	1.64
2	D2S1334-D2S399	178	1.61
13	D13S121-D13S779	76	1.58

about 40 cM from the peak of the sib-pair signal, with a smaller peak of 1.31 closer to D2S436. The chromosome 12 evidence from unweighted analysis of all sib pairs appears to find modest consensus, with variance component analysis indicating lods of 1.39 near the peak of the sib-pair signal, and independent sib pairs giving the third best genome-wide signal with a lod of 1.41 near the region. Finally, although chromosome 22 did not indicate strong evidence for linkage in both the initial and replication sample by any method, in the combined data all three methods obtain a LOD over 1 at markers AF8VWFP-D22S533.

Figures 1A and 1B show the lod score graphs from Haseman-Elston independent-pairs analyses of chromosomes 2 and 9. These two chromosomes gave the two highest lod scores over the genome for the combined data, under this analysis method. Figure 1C shows the lod curve from analysis of all sib pairs, unweighted, on chromosome 12.

Figures 2A and 2B show the lod curves from variance component analyses of chromosomes 2 and 9, respectively. In these analyses, ascertainment correction gave only a negligible increase in the lod scores for the above-indicated regions, compared to noncorrected analyses. We thus report results from ascertainment corrected analyses only. Heritability estimates ranged from 0.2–0.3 for QTL placements at the chromosome 2 signal and 0.3–0.4 for QTL placements on chromosome 9.

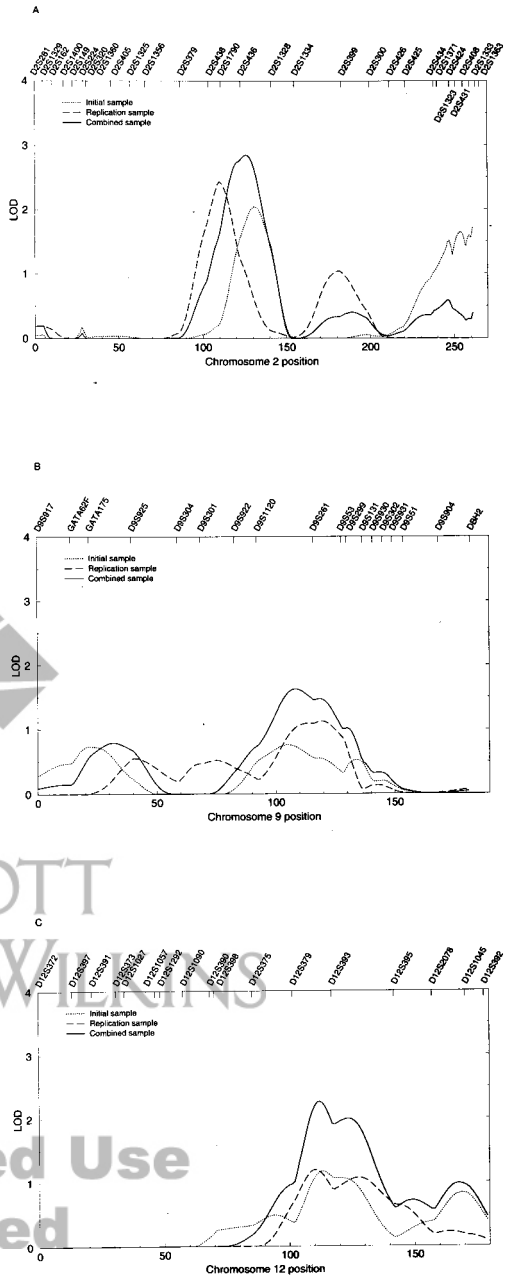

Fig. 1. Multipoint LOD scores for MAO platelet activity, from traditional Haseman-Elston regression for (A) chromosome 2 (independent sib pairs), (B) chromosome 9 (independent sib pairs) and (C) chromosome 12 (all sib pairs, unweighted).

DISCUSSION

The observed consistency across datasets is encouraging; in addition, some consensus across analysis methods was observed. In particular, the lod of 3.27 attained by variance component methods on chromosome 9 gives good evidence for linkage, and is backed by modest evidence from Haseman-Elston regression. Evidence for linkage to this region of chromosome 9 is supported in each distinct sample when analyzed separately. Haseman-Elston sib-pair analysis of the combined data resulted in lod scores above 2.2 on chromosomes 2 and 12, indicating suggestive linkage according to criteria proposed by Lander and Kruglyak (1995). However, linkage to these regions was only somewhat supported by variance component analysis. There was no evidence for linkage to the X chromosome in these data.

Two regions on chromosome 2 and one region on chromosome 6 were previously reported in sib-pair linkage analyses of the initial sample (Saccone et al., 1999). As described above, the chromosome 2 region near D2S436 again indicated modest evidence for linkage in the replication sample from sib-pair analyses. However, evidence in

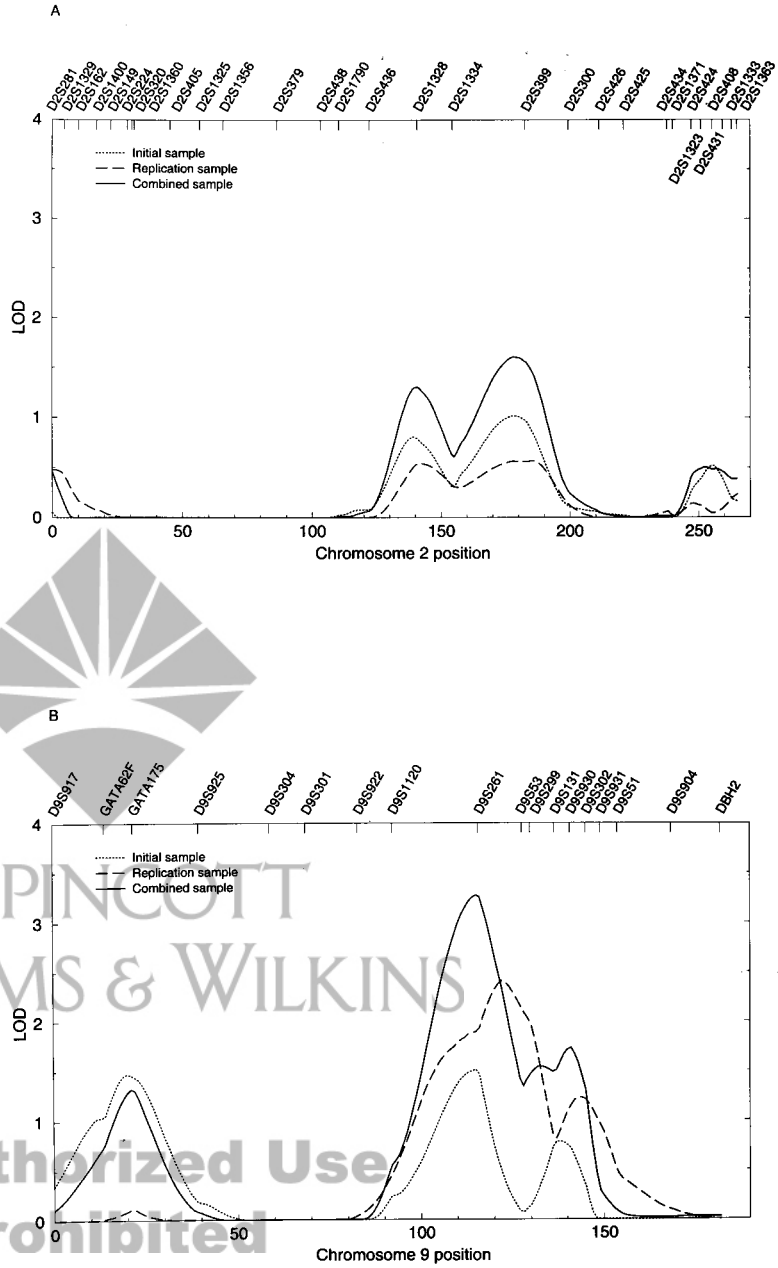

Fig. 2. Multipoint LOD scores for MAO platelet activity, from variance component analysis with ascertainment correction in extended families, for (A) chromosome 2 and (B) chromosome 9.

the chromosome 6 region was not supported in the replication sample. Similarly, the second region on chromosome 2 at 261 cM was detected in the initial sample only and did not replicate.

Consensus across analysis methods in this study was not necessarily expected. The sib-pair and variance component analyses used here are quite distinct methods, and may make use of different information available in our sample. Nevertheless, there is some concordance in findings across both approaches on chromosome 9, with variance component analysis evidencing more power than sib-pair regression to detect this region.

The majority of families in our study are Caucasian or primarily Caucasian. Genetic heterogeneity can be a concern when studying ethnically diverse samples. However, while affected sib-pair analyses can be greatly affected by allele misspecification (Hauser et al., 1996) when parents are ungenotyped, analyses of quantitative traits across a spectrum, or of both affected and affected-unaffected pairs, are more robust in this regard. The analyses used here are appropriate for this phenotype and sample, and the results are unlikely to be artifacts of stratification.

As the region of chromosome 9 appears to be the most likely candidate to harbor a gene for platelet MAO activity, further work will include study of possible candidate genes in this region. In addition, genotyping of the control families in COGA is underway, and genetic analyses of MAO activity in these families will be conducted in the future.

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