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Linkage Mapping of Beta 2 EEG Waves via Non-Parametric Regression

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Parametric linkage methods for analyzing quantitative trait loci are sensitive to violations in trait distributional assumptions. Non-parametric methods are relatively more robust. In this article, we modify the non-parametric regression procedure proposed by Ghosh and Majumder [2000: Am J Hum Genet 66:1046–1061] to map Beta 2 EEG waves using genome-wide data generated in the COGA project. Significant linkage findings are obtained on chromosomes 1, 4, 5, and 15 with findings at multiple regions on chromosomes 4 and 15. We analyze the data both with and without incorporating alcoholism as a covariate. We also test for epistatic interactions between regions of the genome exhibiting significant linkage with the EEG phenotypes and find evidence of epistatic interactions between a region each on chromosome 1 and chromosome 4 with one region on chromosome 15. While regressing out the effect of alcoholism does not affect the linkage findings, the epistatic interactions become statistically insignificant.

KEY WORDS: quantitative trait; alcoholism; epistatic interaction

INTRODUCTION

The Collaborative Study on the Genetics of Alcoholism (COGA) is a multicenter research program to detect and map susceptibility genes for alcohol dependence and related phenotypes. Studies have revealed that many regions on the genome have significant linkage with alcohol related phenotypes [Reich et al., 1998; Foroud et al., 2000] like event-related potentials (ERP) [Begleiter et al., 1998; Williams et al., 1998; Almasy et al., 2001] and maximum number of drinks in a 24 h period [Saccone et al., 2000].

Electroencephalogram (EEG) is a term used to describe recordings of potential difference fluctuations in the brain that can be detected via electrodes attached to the scalp. EEG waves reflect the mean excitation of pools of neurons. Excitatory inputs at synapses generate electric currents that flow in closed loops within the recipient neuron towards its axon, across the cell membrane into the extracellular space and, in that space, back to the synapse. Inhibitory inputs generate loops moving in the opposite direction. The cell body summates all the inputs and, if the threshold is reached, fires an action potential. Electrodes placed on the scalp record these currents after they leave the cell. Beta 2 EEG waves are associated with an alert state of mind [Porjesz et al., 2002]. An increase in the frequency of these waves can be detected when the attention of a person is focussed.

In this article, we analyze genome-wide scan data generated in the COGA project to identify regions which show evidence of linkage with Beta 2 EEG phenotypes. We also investigate the presence of epistatic interactions between regions exhibiting significant linkage. We modify the non-parametric regression method proposed by Ghosh and Majumder [2000] to perform our linkage scan. The advantage of the method is that it does not assume any probability distribution for the trait values

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or a specific functional relationship between squared sib-pair trait differences and estimated identity-by-descent (ibd) scores at marker loci and hence, is robust to violations in distributional assumptions.

MATERIALS AND METHODS

Subjects and Genotyping

The COGA dataset is a collection of two distinct sets of phenotyped and genotyped families designated as the initial sample and the replication sample. The initial sample consists of 105 extended families (Genetic Analysis Workshop 11, Begleiter et al., 1999), while the replication sample comprises 157 extended families. In all, the data involve 1,553 subjects ranging from 7 to 70 years of age. For our analysis, we consider the combined sample. COGA sites providing data for this study include SUNY Downstate Medical Center, New York; University of Connecticut Health Science Center; Indiana University School of Medicine, University of Iowa School of Medicine, University of California School of Medicine, San Diego, and Washington University School of Medicine, St. Louis. Ascertainment and assessment procedures have been described in Bucholz et al. [1994] and Begleiter et al. [1995]. The laboratory and data collection procedures were identical at each of the sites [Begleiter et al., 1998].

A total of 405 markers have been genotyped with the average intermarker distance and the average heterozygosity of the markers being 10.9 and 0.74 cM, respectively, although the marker coverage in some regions is denser than 5 cM. Genotyping was performed at Washington University and at Indiana University [Foroud et al., 2000]. Most markers were tri- and tetranucleotide repeat polymorphisms developed by the Cooperative Human Linkage Center, with additional marker from Genethon, the Marshfield Clinic, M.I.T., and the University of Utah. The program CRI-MAP [Lander and Green, 1987] was used to calculate marker order and distances. The maximum likelihood estimates of the allele frequencies were obtained using USERM13 [Boehnke, 1991].

EEG Data

Subjects were seated comfortably in a dimly lit sound attenuated temperature regulated booth (Industrial Acoustics Company, Bronx, NY). They were instructed to keep their eyes closed and remain relaxed, but not to fall asleep. Each subject wore a fitted electrode cap (Electro-Cap International, Inc., Eaton, OH) using the 19-channel montage as specified according to the 10–20 international system [FP1, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2]. The nose was used as a reference and a forehead electrode served as the ground electrode. Both vertical and horizontal eye-movements were monitored with electrodes that were placed supraorbitally and at the outer canthus of the right eye to perform ocular artifact correction. Electrode impedances were maintained below 5 kΩ. Electrical activity was amplified 10,000 times by Sensorium EPA-2 Electrophysiology amplifiers (Charlotte, VT), with a bandpass between 0.02 and 50 Hz and digitized on a Concurrent 55/50 computer (Concurrent Computer Corp., Atlanta, GA). EEG data were collected in the awake, eyes-closed condition at a sampling rate of 256 Hz for 4.25 min.

The raw data were subjected to wavelet filtering and reconstruction to eliminate very high and low frequencies [Bruce and Gao, 1994; Strang and Nguyen, 1996]. The s12 wavelet was used to perform a six level analysis, and the output signal was reconstructed with levels d6 through d3, roughly equivalent to applying a bandpass filter with a range of 2–64 Hz to the data. Subsequently, eye movements were removed using the method developed by Gasser et al. [1986], [1987]. This method subtracts a portion of the observed ocular activity from the observed EEG to obtain the true EEG, where the proportionality is based on the difference between the cross-spectral values of trials with high ocular activity and those with low ocular activity. Visual inspection of corrected data showed satisfactory artifact removal. The filtered, artifact-free data were transformed into 31 bipolar derivations (FP1–F3, FP2–F4, FP1–F7, FP2–F8, F7–F3, F8–F4, F7–T7, F8–T8, F3–C3, F4–C4, FZ–CZ, CZ–PZ, T7–C3, T8–C4, T7–P7, T8–P8, C3–P3, C4–P4, P7–P3, P8–P4, P7–O1, P8–O2, P3–O1, P4–O2, PZ–O1, PZ–O2, O1–O2, CZ–C3, CZ–C4, PZ–P3, PZ–P4) in order to improve sensitivity to local electrical sources [Nunez, 1995; Nunez et al., 1997; Cook et al., 1998]. The 19-channel montage used in this study would not be sufficient for current source density (CSD) analyses. Bipolar derivations using closely adjacent electrodes provide a high pass spatial filter (i.e., counteract some of the smearing of cortical potentials), and are more effective in capturing a greater amount of cerebral energy output than other referencing strategies. Bipolar derivations were analyzed in 254 overlapping 2 s epochs by use of a Fourier transform.

After windowing effects were minimized by application of a Hamming function [Hamming, 1983], the resulting spectral densities, sampled at 0.5 Hz intervals, were aggregated into bands, divided by the bandwidth, and then averaged across epochs as follows: (a) theta (3–7 Hz), (b) alpha 1 (7–9 Hz), (c) alpha 2 (9–12 Hz), (d) beta 1 (12–16 Hz), (e) beta 2 (16–20 Hz), and (f) beta 3 (20–28 Hz). For this study, we analyze the waves only in the frequency range 16–20 Hz. The average pair-wise correlation between Beta 2 EEG waves at the different bipolar electrodes was 0.61 and the correlations ranged between 0.47 and 0.72. Our analysis is based on 99 independent sib-pairs belonging to distinct families and having at least one informative parent (i.e., genotyped) at least at one marker locus on each chromosome. To ensure independence of observations, only one sib-pair was chosen from each sibship (the sib-pair with the maximum number of marker genotypes available for both sibs) and no two distinct sib-pairs were first degree relatives.

Data are also available on three covariates: age, sex, and diagnosis of alcoholism by COGA (DSM-III-R and Feighner) criterion (dichotomised as 1 or 5). We regress out the effects of sex and age from the phenotypic values using least squares linear regression. We analyze the

data both with and without regressing out the effect of alcoholism.

Statistical Methods

Following Ghosh and Majumder [2000], we assume a non-parametric regression model of y_j and $\hat{\pi}_{jp}$ at any arbitrary point p on the genome:

$$y_j = \psi(\hat{\pi}_{jp}) + e_j;\ j = 1, 2, \ldots, 99;$$

where, y_j, is the squared difference in EEG value for the jth sib-pair, $\hat{\pi}_{jp}$ is the multipoint estimated estimated ibd score at a point p on the genome for the jth sib-pair computed using the linear regression method proposed by Fulker et al. [1995], and ψ is a real valued function of $\hat{\pi}_{jp}$ and e_js are random errors.

The functional form of ψ is estimated using a kernel-smoothing technique [Silverman, 1986]. The kernel function used is:

$$\kappa(t) = \begin{array}{l} \frac{3}{4}(1 - t^2), \quad \text{if } |t| < 1; \\ 0, \text{ otherwise.} \end{array} \tag{1}$$

In this technique of non-parametric regression, the domain of the explanatory variable $\hat{\pi}_{jp}$ is divided into a number of windows. Local smoothing using the kernel function is carried out within each window (as given in Eq. 2 below) and appropriate adjustments are made to ensure continuity at window boundaries. The procedure is repeated for different window lengths and the "optimal" window length is obtained by minimizing the residual sum of squares for the nonparametric regression. The predictor of y_j is given by:

$$\hat{y}_j = \hat{\psi}(\hat{\pi}_{jp}) = \frac{\sum_{i \neq j} \kappa\left(\frac{\hat{\pi}_{jp} - \hat{\pi}_{ip}}{h}\right) y_i}{\sum_{i \neq j} \kappa\left(\frac{\hat{\pi}_{jp} - \hat{\pi}_{ip}}{h}\right)},$$

where, h is the "optimal" window length in the kernel smoothing procedure. To assess the significance of our regression, we use a diagnostic measure as follows:

$$\Delta = 1 - \frac{\sum_{j=1}^{n} \{y_j - \hat{\psi}(\hat{\pi}_j)\}^2}{\sum_{j=1}^{n} (y_j - \bar{y})^2}.$$

One has to use resampling techniques such as bootstrap to obtain empirical thresholds under the null hypothesis of no linkage.

In order to investigate the presence of epistatic interaction between putative QTLs, we define two non-parametric additive regression models as follows:

Suppose there are two significant peaks at positions p_1 and p_2 on the genome. Then,

$$\text{Model I}: y_j = \psi_1(\hat{\pi}_{jp_1}) + \psi_2(\hat{\pi}_{jp_2}) + e_j; j = 1, 2, \ldots, 99.$$

$$\text{Model II}: y_j = \psi_1(\hat{\pi}_{jp_1}) + \psi_2(\hat{\pi}_{jp_2}) + \psi_3(\hat{\pi}_{jp_1}\hat{\pi}_{jp_2}) + e_j; j = 1, 2, \ldots, 99;$$

where $\hat{\pi}_{jp_1}$ and $\hat{\pi}_{jp_2}$ are estimated marker ibd scores at the two peaks, respectively, and ψ_1, ψ_2, and ψ_3 are real-valued functions, which are estimated sequentially using kernel smoothing (see Ghosh and Majumder, 2000 for details) based on the kernel function given in Equation 1.

A significant increase in Δ for Model II over Model I would indicate the presence of epistatic interaction. As before, empirical thresholds are determined using bootstrap.

RESULTS

We perform the proposed non-parametric regression based on kernel smoothing at every centimorgan of the genome. The significant peak positions (when alcoholism is not regressed out) throughout the genome for the different electrode locations (statistical significance <0.00001, evaluated using bootstrap) are given in Table I. For clarity, graphs corresponding to the non-parametric regressions of P8–P4 on estimated ibd scores at different points on chromosomes 1, 4, 5, and 15 are presented in Figure 1a–d, respectively.

TABLE I. Chromosomal Positions of the Linkage Peaks for Beta 2 EEG Waves at Different Electrode Locations

Chr #	Interval (cM)	Electrode locations
1	95–115	P8–P4*, F3–C3*, P7–P3*, CZ–PZ, T8–P8*, C3–P3*, PZ–P3, P4–O2, PZ–P4*, FZ–CZ*, F7–F3*, F8–F4, F7–T7*, F8–T8*, FP2–F4*, PZ–O1*, FP1–F7*, FP2–F8*, T7–P7, P7–O1*, P3–O1*, PZ–O2*, O1–O2*, CZ–C3*
2	95–103	T8–C4, FP1–F3
4	54–63	P8–P4*, P7–P3*, F4–C4, T8–P8, C3–P3*, T8–C4, C4–P4, FZ–CZ, CZ–C4, F7–T7*, T7–C3*, FP1–F3*, FP1–F7*, FP2–F8, P8–O2, P3–O1*, PZ–O1, O1–O2*, CZ–C3*
4	118–128	P8–P4, F3–C3, CZ–PZ, T8–P8, T8–C4, PZ–P3*, PZ–P4, FZ–CZ, F7–T7*, F8–T8, FP2–F4, FP1–F7, P7–O1*, P8–O2, PZ–O2*, O1–O2, CZ–C3
5	230–243	P8–P4, P7–P3*, CZ–PZ, C3–P3, PZ–P3, FZ–CZ, CZ–C4, F7–F3, F8–T8, FP2–F4, FP1–F7, FP2–F8*, P3–O1, P4–O2, CZ–C3
7	37–42	C3–P3, P8–O2
15	5–10	P8–P4, P7–P3, C4–P4, PZ–P3*, PZ–P4, CZ–C4*, F8–F4, T7–C3, FP1–F3, FP1–F7, P8–O2, P4–O2, O1–O2
15	48–59	P8–P4*, F3–C3*, P7–P3*, F4–C4*, C3–P3*, T8–C4*, C4–P4, PZ–P4*, CZ–C4, F7–F3*, F8–F4*, F7–T7, T7–C3*, FP1–F3*, FP2–F4*, FP1–F7*, T7–P7*, P7–O1, P8–O2*, P3–O1*, P4–O2*, PZ–O2*, O1–O2, CZ–C3*
15	86–93	P8–P4, F4–C4, T8–C4, PZ–P4*, F7–T7, T7–C3, P7-O1, P4–O2, O1–O2

All P-values < 0.00001.
*Implies P-value < 0.000001.

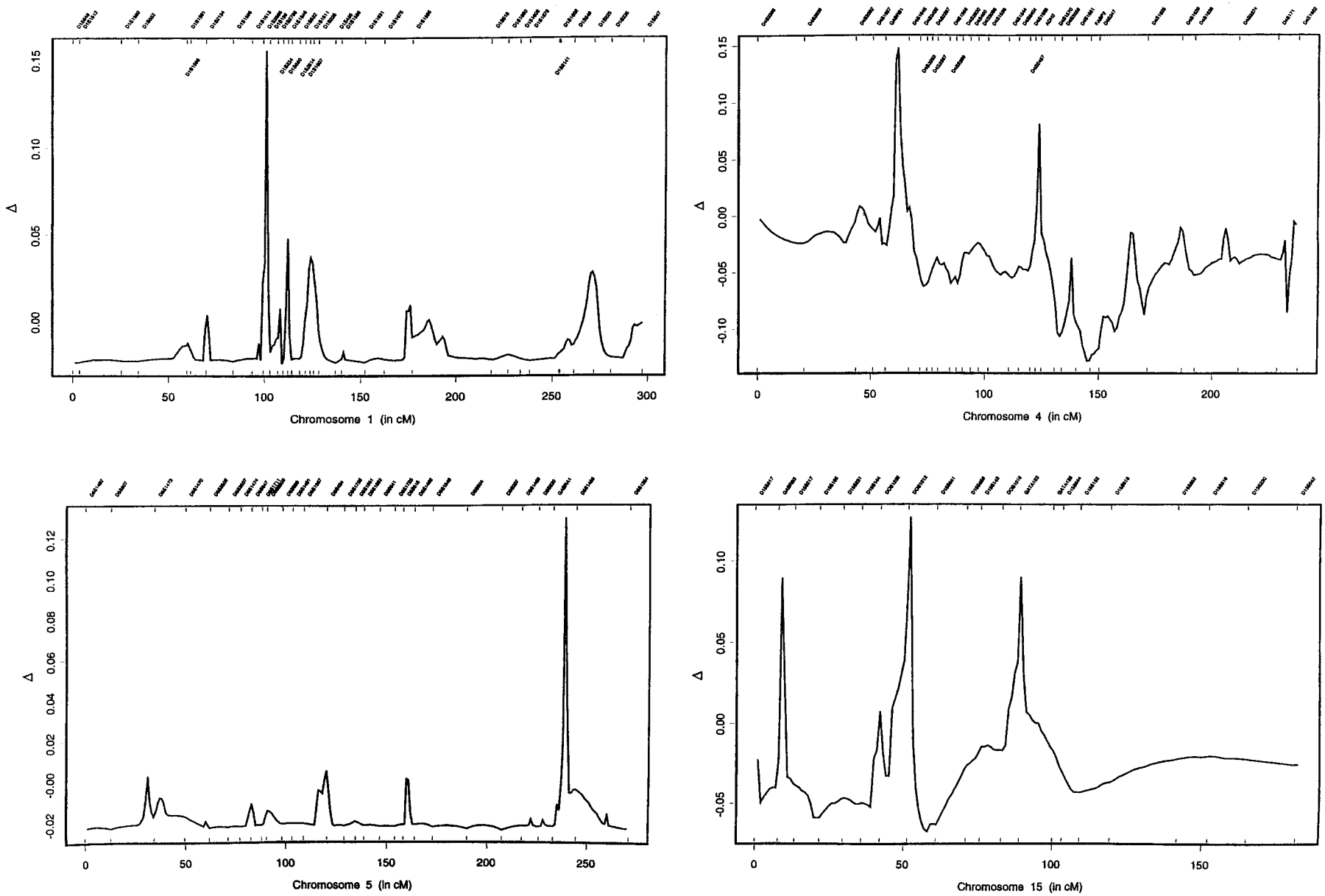

Fig. 1. **a**: Genome-wide scan on chromosome 1 for P8–P4 using kernel smoothing. **b**: Genome-wide scan on chromosome 4 for P8–P4 using kernel smoothing. **c**: Genome-wide scan on chromosome 5 for P8–P4 using kernel smoothing. **d**: Genome-wide scan on chromosome 15 for P8–P4 using kernel smoothing.

We obtain significant linkage findings on chromosomes 1, 4, 5, and 15 for a majority of the electrode locations. The positions of the peaks on these chromosomes appear to be consistent across different electrode locations. The peak on chromosome 1 is near the markers *D1S2866* (99.3 cM) and *D1S198* (102.9 cM); there are two regions showing significant linkage on chromosome 4: one near the *GABRB1* receptor (56.5 cM) and the other near the *ADH3* gene (124.9 cM); the peak on chromosome 5 is near the *GABRA1* receptor (233 cM) and there are three regions of interest on chromosome 15: near the *GABRB3* receptor (7.8 cM), near the marker *D15S1012* (51.3 cM), and near the *GATA153* marker (88.8 cM). Given that the EEG realizations at the different locations are highly correlated, we emphasize that we choose a stringent *P*-value criterion to correct for multiple tests.

When the effect of alcoholism is regressed out as a covariate, we find that the linkage findings are hardly altered. The positions of the peaks are almost identical (within 5 cM) to those obtained when the effect of alcoholism is not regressed out. Moreover, the *P*-values corresponding to these peaks are only changed marginally.

When alcoholism is not regressed out, we observe two pairs of epistatic interaction: (1) between chromosome 1 (around 100 cM) and chromosome 15 (around 50 cM) and (2) between chromosome 4 (around 56 cM) and chromosome 15 (around 50 cM). We find that at $P < 0.00001$, the first type of interaction is significant for the electrode locations P8–P4, P7–P3, PZ–P4, F7–F3, FP2–F4, P3–O1, and CZ–C3; while the second type of interaction is significant for the electrode locations P8–P4, P7–P3, T7–C3, FP1–F7, and PZ–O2. In all these cases, epistasis (in terms of increase in Δ for Model II over Model I) explains between 3 and 5% of the variance in the squared difference in sib-pair EEG values. However, none of these interactions are significant at $P < 0.001$ when the effect of alcoholism is regressed out.

DISCUSSION

We used a non-parametric method to map Beta 2 EEG waves at 31 bipolar electrode locations using genome-wide data on sib-pairs generated in the COGA project. We obtained statistically significant evidence for linkage on chromosomes 1, 4, 5, and 15. The finding on chromosome 1 is in the 1p22.3 region (University of Southhampton map, http://cedar.genetics.soton.ac.uk/pub/chrom1/gmap). This region contains genes like *PDE4B* (phosphodiesterase 4B), a human homologue of the *Dunce* gene in *Drosophila*, which has been shown to be involved in the processes of normal learning and memory [Davis, 1996] and regulation of ethanol intoxication by the cAMP signaling pathway [Moore et al., 2000]. The linkages on chromosome 4 are in the 4p11 and the 4q22.3 regions (/chrom4/gmap). The 4p11 region contains the gamma amino-butyric acid A beta 1 (*GABRB1*) receptor, which is a multisubunit chloride channel that mediates the fastest inhibitory synaptic transmission in the central nervous system [Haenschel et al., 2000; Tobler et al., 2001]. The gamma amino-butryic acid A alpha 2 and alpha 4, respectively (*GABRA2* and *GABRA4*) receptors are also present in this region. The 4q22.3 region contains the alcohol dehydrogenase gene cluster (*ADH1–ADH7*). Variants in the class I *ADH* genes affect enzyme kinetic properties and have been reported to reduce the risk of alcoholism in Chinese and Japanese populations [Edenberg and Bosron, 1997]. This region has produced a linkage finding with alcohol dependence in an American Indian population [Long et al., 1998]. The finding on chromosome 5 is in the 5q35.2 region (/chrom5/gmap) and those on chromosome 15 are in the 15q11.1, 15q21.1, and 15q21.2 regions (/chrom15/gmap). The 5q35.2 and 15q11.1 regions contain two other clusters of gamma amino-butyric acid A receptors: alpha 1, alpha 2, beta 2, and gamma 2 subunits on 5q35.2; and beta 3, alpha 5, and gamma 3 subunits on 15q11.1. The 15q21.1 region contains the cholinergic receptor nicotinic alpha polypeptide 7 (*CHRNA7*) gene, which is believed to be responsible for heavy smoking among schizophrenic patients [Stassen et al., 2000].

Oscillations of brain activity play an important role in the functional organization of neuronal activity that underlies sensory and cognitive processing. Oscillations within the EEG gamma and beta bands have been linked to sensory perception and memory and have been shown to be modified by anesthetic agents. An increasingly large body of data exists which demonstrates that oscillations of frequency 12–80 Hz (Beta and Gamma) are a consequence of, and are inextricably linked to, the behavior of inhibitory interneurons in the central nervous system. The pharmacological profile of these oscillations reveal a strong influence on those rhythms by drugs that have direct effects on GABRA receptor-mediated synaptic transmission. These oscillations are of particular interest as they are found to be aberrant in abstinent alcoholics [Rangaswamy et al., 2002] and their offspring [Rangaswamy et al., submitted]. Since these oscillations appear to be trait as opposed to state-related, we have used these traits as endophenotypes in the search for genes predisposing individuals to develop alcohol dependence. The high correlations between EEG waves at the different bipolar electrodes may tempt one to use data reduction techniques like principal components to obtain fewer phenotypes, but linear combinations of EEG waves at different bipolar locations carry no biological significance and hence would not be interpretable from an electrophysiological point of view. We are currently exploring a trilinear method of representing brain potentials as a data reduction strategy [Wang et al., 2000] to analyze EEG waves simultaneously at multiple locations.

Since the proposed Δ statistic does not consider the direction of relationship between squared sib-pair trait difference and estimated ibd scores, there may be concern that the rate of false positives is inflated due to random positive relationship between the variables under the null hypothesis of no linkage. One way to circumvent this problem is to ensure that the rank correlation between the variables is negative at the significant linkage regions. We found that the rank

correlations were significantly negative (evaluated by an asymptotic normal test) at all our linkage peaks.

We note that our linkage analyses after regressing out the effect of alcoholism yielded very similar results to those obtained without regressing out the effect of alcoholism. However, the epistatic interactions between regions exhibiting significant linkage were found only when the effect of alcoholism was not regressed out. This raises the possibility that though alcoholism may have a small main effect on the EEG phenotypes, it may have a strong interaction effect. Since the genes discussed in the preceding paragraph have provided evidence of linkage with alcohol related phenotypes, one needs to carry out further analysis to evaluate their roles as potential candidate genes for Beta 2 EEG waves.

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