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A Genome-Wide Search for Genes That Relate to a Low Level of Response to Alcohol

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Background: The low level of response (LR) to alcohol is genetically influenced in both humans and animals, and a low LR is a characteristic of offspring of alcoholics that has been reported to predict alcoholism 10 and 15 years later. The genes that contribute to a low LR have not yet been identified.

Methods: A 12-item questionnaire that measures LR, the Self Rating of the Effects of Alcohol (SRE) instrument, was filled out by 745 individuals from the Collaborative Study on the Genetics of Alcoholism (COGA) for whom genetic material was available. These subjects were genotyped by using 336 markers with an average heterozygosity of 0.74 and an average intermarker distance of 10.5 cM. Both quantitative and qualitative nonparametric, sib-pair analyses were carried out for the SRE measure related to early drinking experiences.

Results: Correlations of SRE scores across related individuals were significant and between 0.16 and 0.22 for most values, compared with nonsignificant correlations of 0.03 or less among unrelated individuals. Linkage analyses performed by using the FIRST 5 variables (first five times alcohol is consumed) identified four chromosomal regions with lod scores $\geq$2.0 whose maximum was also near a marker. One of these chromosomal regions previously was linked to alcohol dependence in the COGA sample.

Conclusions: These data document the familial nature of a low LR to alcohol as measured by the SRE and suggest several chromosomal regions that might contribute to the phenomenon.

Key Words: Genetics, Alcoholism, Reaction.

ALCOHOL DEPENDENCE IS a complex genetic disorder (Foroud et al., 1998; Reich et al., 1998; Schuckit, 1998). Typical of such syndromes in psychiatry and general medicine, it is likely that a number of different clinical phenomena (or endophenotypes) contribute to the risk, and all genetic influences combined explain 40% to 60% of the phenotypic variance (Burmeister, 1999; Schuckit, 1998). Relevant characteristics include antisocial personality disorder, several brain electrophysiological measures (which include event-related potentials and background cortical electroencephalograph results), and alcohol metabolizing enzymes (Begleiter et al., 1998; Ehlers et al., 1999; Lappalainen et al., 1998; Li, 2000). Another attribute related to the risk for alcohol abuse or dependence (alcoholism) is a low level of response (LR) to alcohol, a phenomenon that is genetically influenced in both animals (Baldwin et al., 1991; Li, 2000; Moore et al., 1998) and humans (Heath and Martin, 1992; Madden et al., 1995); a comparison in twins generates an estimated heritability of between 0.4 and 0.5 (Martin, 1988). Most evaluations of LR were determined through the demonstration of a lower effect of alcohol at a given blood level on an alcohol challenge, but a recent self-report measure has been developed that records a low LR as the requirement for more alcohol to have a specific effect (Schuckit, 1998; Schuckit et al., 1997b).

The need for relatively high doses of alcohol to produce an effect from early in a person's drinking career (i.e., a low LR) seems to characterize approximately 40% of sons and daughters of alcoholics but only 10% of family history negative controls (Erblich and Earleywine, 1999; Pollock, 1992; Schuckit and Smith, 1996, 2000; Schuckit et al., 1996, 2000). An 8.2 year follow-up of 450 out of 453 sons of alcoholics and controls reported that a low LR as measured by an alcohol challenge is a powerful predictor of later

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The Collaborative Study on the Genetics of Alcoholism (COGA) (H. Begleiter, SUNY HSCB Principal Investigator, T. Reich, Washington University, Co-Principal Investigator) includes nine different centers where data collection, analysis, and/or storage takes place. The nine sites and principal investigators and co-investigators are Indiana University (T.-K. Li, J. Nurnberger Jr., P.M. Conneally, H. Edenberg); University of Iowa (R. Crowe, S. Kuperman); University of California at San Diego (M. Schuckit); University of Connecticut (V. Hesselbrock); State University of New York, Health Sciences Center at Brooklyn (B. Porjesz, H. Begleiter); Washington University in St. Louis (T. Reich, C.R. Cloninger, J. Rice, A. Goate); Howard University (R. Taylor); Rutgers University (J. Tischfield); and Southwest Foundation (L. Almasy).

alcoholism and explains most of the relationship between a person's family history and later alcohol abuse or dependence, with the predictive ability of LR also noted in several other studies (Rodriguez et al., 1993; Schuckit and Smith, 1996; Volavka et al., 1996). Efforts are now underway to identify genes that contribute to LR, and thus an enhanced alcoholism risk, which include evaluations of specific genes by using the case-control paradigm in family history positive and family history negative men as part of a prospective study (Schuckit et al., 1999).

The "gold standard" of LR evaluations, the alcohol challenge, involves a series of half-day sessions that include laboratory acclimation, exposure to alcohol, and placebo controls. Thus, gathering data from as few as 100 pairs of high-risk and low-risk subjects (200 individuals) requires 600 testing days, representing several years of work. As a result, it can be costly to gather a large enough sample of subjects to have sufficient power for a genome-wide linkage study. Because of these restrictions, the Collaborative Study on Genetics of Alcoholism (COGA) helped develop a 12 item self-administered instrument that measured LR, termed the Self-Rating of the Effects of Alcohol (SRE) questionnaire, where subjects are asked to estimate the number of drinks required for each of four effects of alcohol at three different periods in their lives (Schuckit et al., 1997a,b).

It is worthwhile to briefly review some of the attributes of the SRE. The 1 year retest reliability is 0.8, and there is internal consistency where higher scores are reported for more intense effects and periods of heaviest drinking, whereas the lowest values are noted for the first five times alcohol is consumed (FIRST 5; Schuckit et al., 1997a,b). SRE values correctly identify up to 80% of subjects who had the lowest LR to alcohol in the challenge laboratory, with the correlation between the entire range of SRE scores and the full range of alcohol challenge results as high as 0.4 to 0.6, even when data on the two measures were gathered 15 years apart (Schuckit et al., 1997a,b). The relationship between alcohol challenge and SRE values remains robust even after age and years of drinking are controlled for, and results seem to apply to white, Hispanic, and African American subjects (Daeppen et al., 2000; Schuckit et al., 1997a,b; Wall et al., 1999).

The relationship between SRE scores and a diagnosis of alcoholism has been evaluated in several populations. First, a recent study of almost 300 Swiss men and women at an average age of 43 years reported a relative risk of alcohol dependence that was 4.4 times higher among subjects whose FIRST 5 SRE scores fell into the lowest third compared with those whose scores were in the upper third (Daeppen et al., 2000). Second, a follow-up of almost 100 young adult subjects in the United States demonstrated a correlation of approximately 0.4 for various measures on the SRE and the diagnosis of alcohol dependence, with correlations as high as 0.6 in a more heterogeneous sample of more than 500 men and women from a wide range of ages (Schuckit et al., 1997a). Finally, SRE scores also correlated with alcohol metabolizing enzyme patterns in the predicted direction among Asian men and women, with lower LRs among individuals with the more efficient aldehyde dehydrogenase isoenzyme pattern known to be associated with a higher alcoholism risk through more intense and possibly more aversive reactions to alcohol (Wall et al., 1999). In these studies, the correlations between the dependent variables and the SRE remained significant even after researchers controlled for recent drinking patterns of alcohol consumption, age, and sex.

The purpose of this investigation was to address the possibility that a genetic influence contributes to the SRE results. The data include an evaluation of the familial nature of this LR measure, along with the results of a genome-wide analysis performed in the COGA sample.

METHODS

As described in greater detail elsewhere (Begleiter et al., 1998; Bucholz et al., 1994), by using written informed consent approved by an institutional review board, alcohol-dependent men and women who entered inpatient or outpatient treatment programs were invited to participate in the six center-wide COGA protocol if they came from families with multiple alcoholics and where multiple members of sibships along with parents were available for evaluation (Reich et al., 1998). Based on identical criteria used across the centers, original subjects (probands) were excluded only if they did not speak English, had a current, severe, life-threatening physical condition, or had a recent history of extensive intravenous drug use, or if a current level of dementia or psychosis jeopardized informed consent. To optimize family collection for future genetic studies, relatives were systematically ascertained and extended through alcohol-dependent first-degree relatives.

Members of genetically informative families then participated in a protocol that included a standardized semistructured interview that established 17 diagnoses, including DSM-III-R (American Psychiatric Association, 1987) substance abuse and dependence (Bucholz et al., 1994). They also took part in additional protocols that evaluated brain event-related potentials, cognitive functioning, personality characteristics, and potential neurochemical markers associated with alcoholism. Subjects gave a blood sample for extraction of DNA.

The current data were gathered from the phase II, or follow-up, evaluation of these subjects. Here, all individuals from potentially genetically informative families were recontacted 3 to 5 years after their initial participation. Approximately 75% of participants agreed to take part in a protocol that was similar to their initial COGA evaluation but which now included filling out additional instruments such as the SRE. By using this measure, subjects were requested to estimate the number of standard drinks (12 oz of beer, 4 oz of wine, or 1.5 oz of 80 proof beverage) required to produce each of four potential effects that included an initial feeling of intoxication, slurred speech, stumbling gait, or passing out (Schuckit et al., 1997a,b). Answers were originally generated for three time periods: the first five times of drinking (i.e., FIRST 5), the period of heaviest drinking in their lives, and the most recent 3 months.

The analyses here focus on the FIRST 5 measure for several reasons. Even though SRE scores have been reported to be useful for subjects over a relatively wide age range (Schuckit et al., 1997a,b), selection of data from the earliest drinking time period increases the probability that subjects refer more uniformly to a similar period in their lives. Second, it was important to avoid type I errors that might occur if all possible SRE values were analyzed. The scores reported here were computed by using self-reports of the number of drinks required for each effect the first five times of drinking, adding up all the drinks reported to be required for effects

during that time frame, and dividing this figure by the number of effects endorsed (e.g., the first feelings of intoxication, slurred speech, etc.). Prior analyses have demonstrated that the relationship of these SRE scores to various dependent variables (e.g., alcohol challenge results) remains statistically significant even after controlling for the number of effects of alcohol endorsed by the subjects (Schuckit et al., 1997a,b).

For the sake of completeness, the FIRST 5 value was used in the linkage studies both as a continuous score (a quantitative variable) and as a qualitative variable with LR values in the lowest third of the distribution used to identify individuals as "affected." In presenting the data, we placed a higher emphasis on a clearly low level of response (i.e., lower third of SRE scores) for several reasons. Prior evaluations of the alcohol challenge results have demonstrated the most robust relationship between LR and alcoholic outcome among those who fell in the low end of the distribution, where LR explained approximately half of the relationship between family history and alcoholic outcome (Schuckit and Smith, 1996, 2000). In addition, the highest correlation between SRE and alcohol challenge scores was observed when data from those clearly high and low on SREs were evaluated (Schuckit et al., 1997b). In viewing results it is important to remember that a low LR on alcohol challenge involves a less intense reaction at a given blood alcohol concentration, whereas the similar result on the SRE reflects the need for a higher number of drinks to obtain a particular effect from alcohol.

A genome screen was performed by using 336 markers distributed throughout the genome, with an average intermarker distance of 10.5 cM. Markers had an average heterozygosity of 0.74 and were primarily tri- or tetra-nucleotide repeat polymorphisms. Genotyping was completed by using radioactive and fluorescence-based detection methods as described in Reich et al. (1998). Previous analyses (Foroud et al., 1998; Reich et al., 1998) reported results of a genome screen by using 291 markers in the COGA families. The analyses reported herein include an additional 45 markers, as well as new marker maps that represent a significant improvement over the marker maps developed in the initial data (Foroud et al., 1998; Reich et al., 1998).

All data were checked for Mendelian inheritance of marker alleles with the program CRIMAP (Green et al., 1990) and the USERM13 option of the MENDEL suite of linkage programs (Boehnke, 1991). Maximum likelihood estimates of marker allele frequencies were obtained by using the USERM13 program. Marker order and distance were estimated from the data by using CRIMAP.

We determined Pearson correlations across SRE scores for the more than 2095 subjects with SREs; for those with genetic material, the statistical methods reported here used the genotypical data from parents and their offspring as well as population marker allele frequencies to estimate the proportion of alleles shared identical by descent (ibd) by a sib-pair. For the analysis of qualitative variables (i.e., scores that fall into the lowest third on FIRST 5), the multipoint sib-pair analysis method implemented in ASPEX programs, termed Sib Phase, was used to evaluate evidence of linkage. Only those sib-pairs who were both in the lower third of the LR distribution were used in the estimation of marker allele sharing and, hence, in the linkage calculations. Analyses were performed initially by using all possible affected sib-pairs ($n = 103$), and results were then confirmed by using the more conservative method of analyzing only independent sib-pairs ($n = 76$).

Quantitative, or continuous, SRE data were analyzed by using the multipoint maximum likelihood variance method implemented in the program Mapmaker/Sibs (Kruglyak and Lander, 1995). Unlike the qualitative linkage analyses that were limited to sib-pairs both of whom were in the lower third of the LR distribution, the quantitative linkage analyses used all sib-pairs with both genome scans and FIRST 5 data, regardless of its value. Analyses were performed by using both all possible combinations of sib-pairs ($n = 745$) as well as the more conservative method of weighing the contribution of each sibship that contained more than two sibs to that of an equivalent number of independent ($n - 1$) sib-pairs ($n = 373$).

Table 1. Correlation of SRE Among Relatives in COGA Families and Among Unrelated Individuals

	SRE score FIRST 5
First-degree relatives	
Mother/daughter ($n = 561$)	0.18*
Sisters ($n = 518$)	0.21*
Total female/female ($n = 1079$)	0.20*
Father/son ($n = 449$)	0.22*
Brothers ($n = 467$)	0.12**
Total male/male ($n = 916$)	0.16*
Second-degree relatives	
Female/female ($n = 99$)	0.16
Male/male ($n = 55$)	0.09
Unrelated subjects	
Female/female ($n = 410$)	0.02
Male/male ($n = 369$)	0.03

* $p < 0.001$; ** $p < 0.01$.

RESULTS

Table 1 presents the Pearson correlations for the FIRST 5 SRE scores across same-sex relatives and unrelated individuals among those COGA subjects who had experience with alcohol and completed the SRE. In these subjects, the correlation between SRE scores and body weight for men and for women was 0.01 to 0.03, and, thus, the data are not corrected for weight. Among first-degree relatives, all of the correlations were significant, with most around 0.20, whereas the correlations among unrelated subjects were 0.03 or less. Although the sample of available cousins (second-degree relatives) with SREs was relatively small, the correlations for females (0.16, $p = 0.12$) and for males (0.09, not significant) were between those noted for first-degree relatives and unrelated individuals.

Data for the genome scan (i.e., SREs plus genotyping) were available from subjects in 411 nuclear families with at least two sibs with completed SREs. After we excluded individuals who were greater then 2.5 SD from the mean on LR measures, 745 sib-pairs had sufficient SRE data and genotyping information to be appropriate for the quantitative analyses, whereas 103 affected sib-pairs (i.e., both sibs in the lower third on LR) had similar available data for the qualitative evaluations.

The subjects included in the analyses were an average of 39.4 ± 14.67 years old, similar to those used in several other SRE analyses (Daeppen et al., 2000; Schuckit et al., 1997a,b). They had an average of 12.8 ± 2.35 years of education, and 55.1% were women. Because recent data indicate that both sons and daughters of alcoholics tend to have LR values in the lower third of the distribution (Schuckit et al., 2000), analyses were carried out for the two sexes combined. In this dataset, 51.1% individuals met criteria for alcohol dependence at sometime in their lives. At the time of study, 63.0% were married, 19.2% separated or divorced, and 17.7% single. The racial distribution across these subjects included 76.6% white, 21.2% African American, and 2.2% other.

As shown in Table 2, there were 10 chromosomal regions

Table 2. Chromosomal Regions With Multipoint Lod Scores ≥2.0 for the FIRST 5 SRE Value

Chromosome	Qualitative or quantitative analysis[a]	Marker(s) in proximity to maximum lod score	Maximum lod score	Max. allele sharing (IBD)[b]
1	Qualitative	D1S1588, D1S1631	2.0	64.1%
2	Quantitative	D2S425, D2S434, D2S424, D2S1323, D2S1333	2.4	NA
5	Quantitative	D5S807	2.2	NA
9	Quantitative	D9S304, D9S301	2.2	NA
10	Quantitative	D10S544, D10S610	2.1	NA
11	Quantitative	D11S1977, D11S2002[c]	4.0	NA
13	Quantitative	D13S787, D13S765[c]	3.1	NA
20	Quantitative	D20S94	3.0	NA
21	Quantitative	GR1K1	2.6	NA
21	Qualitative	D21S1809, D21S1446	4.0	75.2%

[a] Qualitative uses sibling pairs in lower third of the SRE distribution, and quantitative uses all siblings with SRE data; [b] Identical by descent (IBD) allele sharing at the position of the maximum lod score; [c] Peak lod score does not occur within 15 cM of flanking markers.

with multipoint lod scores ≥2.0 by using either the qualitative Sib Phase or the quantitative Mapmaker/Sibs linkage phenotypes for the FIRST 5 SRE measure. The most interesting data were in four regions on chromosomes 1, 2, 9, and 21, where a marker that flanked the peak linkage result had a lod score of at least 2.0. Two of these are highlighted in Figs. 1 and 2. These findings were selected because, as explained previously, a qualitative approach that emphasizes the importance of the extreme lower third of the LR distribution might be more reliable than a continuous score across all SRE values. Where appropriate, information about the quantitative results also is provided.

As shown in Fig. 1, on chromosome 1, for the qualitative linkage approach for FIRST 5 a maximum lod score of 2.0 was obtained near the markers D1S1588 and D1S1631 when all possible sib-pairs in the lowest third of the distribution were analyzed. Lod scores greater than 1.5 were observed across a 23 cM interval. Evidence of linkage with a lod score of 1.5 also was observed by using the smaller sample of independent sib-pairs. Although not shown in Table 2, linkage analyses of FIRST 5 revealed another local maximum lod score at marker D1S224 for all subjects, but this score was only 1.9. It is interesting that this local maximum is within 20 cM of the region identified by Reich et al. (1998) as potentially related to alcohol dependence.

Even stronger findings were observed for the qualitative linkage analyses approach on chromosome 21 between the markers D21S1809 and D21S1446, as shown in Fig. 2. By using those sib-pairs both of whom had FIRST 5 scores in the lower third of the distribution, a maximum lod score of 4.0 was observed when all possible pairs were analyzed. At the adjacent markers, D21S1809 and D21S1446, which are 25 cM apart, the lod score was 2.7. When only independent sib-pairs were analyzed, the maximum lod score (3.5) was in the same position, with the adjacent markers having lod scores of 1.9 and 2.4, respectively.

Table 2 relates additional, potentially interesting, quantitative linkage analyses results. These include chromosome 2, where FIRST 5 produced a lod score of 2.4 near marker D2S434 when all sib-pairs were used, which decreased to 1.1 when sibs were weighted to an equivalent number of independent pairs; chromosome 9, where a maximum lod score of 2.2 for all pairs was noted near markers D9S304 and D9S301, a score that decreased to 1.0 for independent pairs; and chromosome 21, where FIRST 5 when using all pairs revealed a lod score of 2.6 near the marker GR1K1. This finding decreased to 1.2 when the sibs were weighted to an equivalent number of independent pairs.

DISCUSSION

The ultimate goal of the current series of studies is to find genes that contribute to the low LR to alcohol and, thus, impact alcoholism risk. A low LR as measured by an alcohol challenge has been shown to have a heritability of approximately 0.4 and to predict alcoholism 10 and 15 years later, which explains the majority of the relationship between family history and the development of alcohol abuse or dependence (Martin, 1988; Schuckit and Smith, 1996, 2000). A candidate gene study of a small sample of individuals who had received alcohol challenge and follow-up identified several genetic markers that might relate to both a low LR and alcoholism (Schuckit et al., 1999).

With the preponderance of data that relate to alcohol challenges, the ideal approach for sib-pair analyses that search for genes that contribute to a low LR would use alcohol challenge results. However, it was not clear whether the amount of effort and money required to gather a large enough sample of sib-pairs who are both genotyped and have experienced an alcohol challenge was justified. The current study addresses that question. These data used a simple paper-and-pencil test that measured LR through self-reports of the number of drinks required for an effect. This instrument has a 1 year retest reliability of 0.8 and, depending on the cutoff score used, has been reported to successfully identify up to 80% of the individuals who demonstrated the lowest intensity of response to alcohol on alcohol challenges (Schuckit et al., 1997b). Thus, the ease of administration of this measure and the availability of a moderately sized sample for whom both SRE data and genome scan results were available made this a logical focus of the present analyses.

Similar to the results of an earlier alcohol challenge study in twins (Martin, 1988), the approximate 0.2 correlation

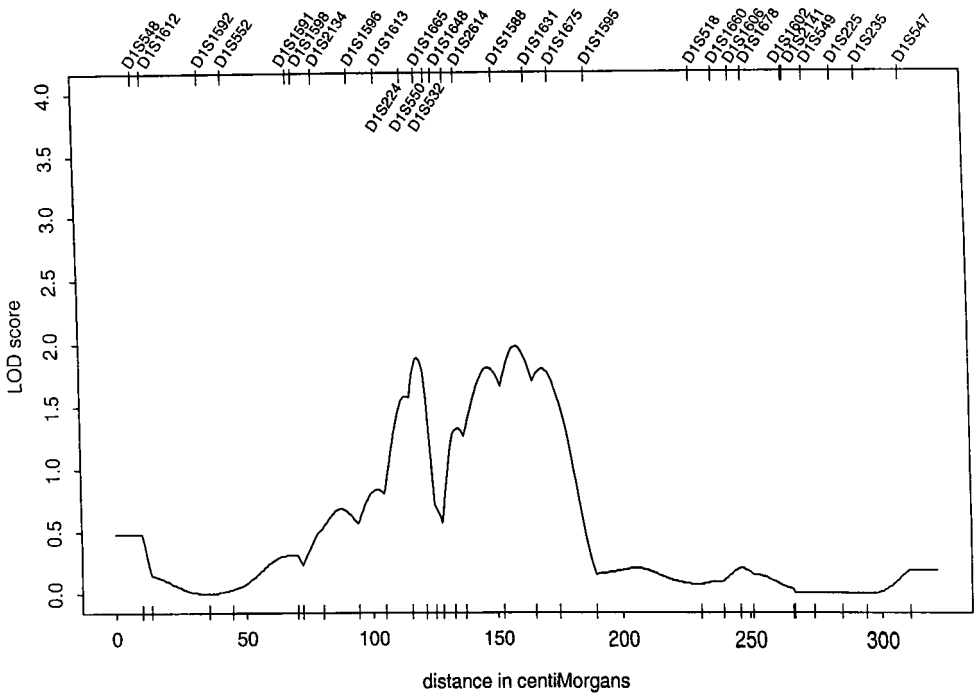

Fig. 1. Multipoint sib-pair linkage analysis performed on chromosome 1 by using Sib Phase with all possible pairs of sibs both of whom were in the lower third of the FIRST 5 distribution.

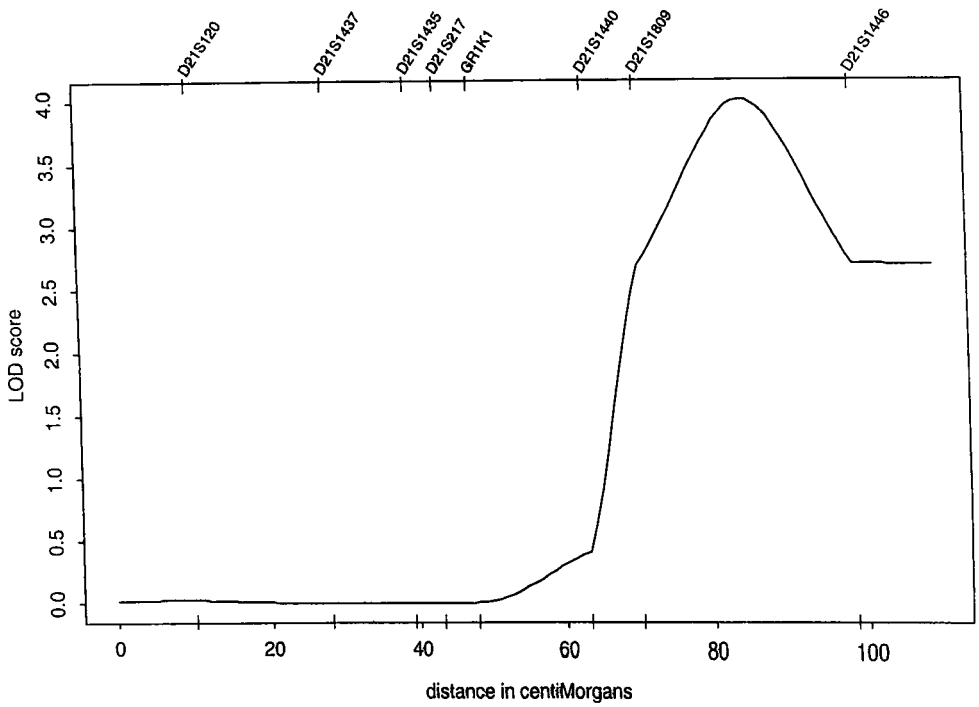

Fig. 2. Multipoint sib-pair linkage analysis performed on chromosome 21 by using Sib Phase with all possible pairs of sibs both of whom were in the lower third of the FIRST 5 distribution.

among first-degree relatives as compared with 0.03 correlations among unrelated individuals is consistent with a possible heritability for the SRE results that approaches 0.4. However, the current data do not exclude the possibility that environmental factors or expectations of the effects of alcohol might have contributed to the correlations among more closely related individuals.

The results of the genome scan that used the SRE are promising and support the need for additional study. Four chromosomal regions were identified with possible linkage

to the low LR phenotype as measured on the FIRST 5 SRE score, which included two with the potentially more reliable qualitative measures. Of particular interest, the region of chromosome 1 in Fig. 1 was not far from an area previously reported to be linked to alcohol dependence (Reich et al., 1998). Several potential candidates within this relatively wide region include genes that affect opioid binding, prostaglandin receptors, protein kinase activity, and the adenosine A3 receptor. This article also reports possible linkage to several chromosomal regions not identified as part of the study by Reich et al. (1998).

The current data are consistent with the philosophy that one potentially useful approach for finding genetic influences in a complex disorder such as alcoholism is to search for genetically influenced characteristics that, although neither necessary nor sufficient to cause alcoholism, contribute significantly to the probability of developing the problem (Schuckit, 1999). Thus, if the SRE taps on a low LR, this might be a relatively "neutral" trait if a person chooses to be a lifelong abstainer or avoids ever consuming more than two or three drinks in an evening. On the other hand, the same characteristic might impart an enhanced probability of developing heavy drinking and alcohol-related problems in people who live in a heavy drinking environment and who choose to consume alcohol ad libitum without close self-monitoring of amounts imbibed. In most alcohol challenge studies, a low LR to alcohol is related to a family history of alcoholism and predicts a high future risk for alcohol-related life problems, and both 10 and 15 year follow-ups of almost 450 young men report that the low LR explained most of the relationship between family history and alcoholism in a population without antisocial personality disorder (Schuckit and Smith, 1996, 2000).

It is of interest to note that a prior report of a small subgroup of subjects who had received an alcohol challenge tested several candidate genes in a separate population. The results indicated possible relationships between a low LR to alcohol measured by an alcohol challenge and the LL genotype of the serotonin transporter as well as a polymorphism associated with the γ-aminobutyric $\text{acid}_{A\alpha 6}$ gene (Schuckit et al., 1999). These findings will be tested in the COGA population once a large enough sample with both alcohol challenges and relevant genotyping is available.

Of course, the current results require confirmation before conclusions can be drawn. One major caveat involves the nature of the SRE, because retrospective self-reports are not always optimally accurate. The genome scan results will need to be confirmed in analyses that use the alcohol challenge itself, because this test is the measure that has been shown to predict alcohol abuse and dependence. Also, the correlation between the full range of the SRE and the alcohol challenge results is at best only 0.6, and although SRE scores correlate with a diagnosis of alcoholism, the current analyses do not establish definitively that the same genetic material contributes to both LR measures. An additional caveat is the relatively small size in the qualitative SRE analyses that contributed to our decision to emphasize the more clearly defined lower third versus above the median categories for LR, and it is possible that a more accurate measure of LR through the alcohol challenges will facilitate quantitative LR measure analyses as well. A fourth consideration relates to the heterogeneity of the population as a consequence of the decision to include both white and African American subjects to evaluate the largest possible number of people. As the number of subjects increases and as alcohol challenge results can be related to genome scans, the results should be reanalyzed separately in each racial group. A similar caveat should be noted about the wide age range of the current sample, although a prior study reported no significant correlation between FIRST 5 SRE scores and the subject's age (Daeppen et al., 2000). Finally, the chromosomal areas of interest are relatively wide, and further work is required to identify relevant candidate genes.

In summary, these results are consistent with the conclusion that a low LR to alcohol in humans is both heritable and potentially useful as an endophenotype related to the alcoholism risk. Future work will attempt to confirm these results by using the more precise alcohol challenges and will use the genome scan results to facilitate the search for relevant candidate genes.

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