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No Association of the $GABA_A$ Receptor Genes on Chromosome 5 With Alcoholism in the Collaborative Study on the Genetics of Alcoholism Sample

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A substantial body of literature suggests that γ-aminobutyric acid (GABA) may be involved in the neurochemical pathways contributing to alcohol use and related disorders. Chromosome 5 contains a cluster of $GABA_A$ receptor genes, *GABRA1*, *GABRA6*, *GABRB2*, and *GABRG2*, which have been among the most extensively studied in relation to alcohol use. These studies have yielded mixed results. Using data from large, multiplex alcoholic families collected as part of the Collaborative Study on the Genetics of Alcoholism (COGA), we sought to provide more conclusive evidence regarding the role of the $GABA_A$ receptor genes on chromosome 5. Multiple single nucleotide polymorphisms (SNPs) were tested in each of the four chromosome 5q $GABA_A$ receptor genes, and we conducted both classic trio-based association analyzes and extended pedigree analyzes. We found no consistent evidence of association with alcohol dependence or alcohol dependence comorbid with antisocial personality disorder (ASPD) for any of the regions tested in the chromosome 5 $GABA_A$ receptor genes. These analyses suggest that the $GABA_A$ receptor genes on chromosome 5 do not play a strong role in alcohol dependence. Future studies are planned to test whether these genes are more important in influencing behavioral endophenotypes related to the risk of alcohol dependence.

KEY WORDS: GABA receptor genes; chromosome 5; alcohol dependence; antisocial personality disorder; association

INTRODUCTION

A substantial body of evidence, from animal, human, and in vitro cell models, suggests that γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the human central nervous system, is involved in many of the neurochemical pathways contributing to alcohol use and related disorders. $GABA_A$ receptor agonists tend to potentiate the behavioral effects of alcohol, while $GABA_A$ receptor antagonists attenuate these effects. GABA involvement has been demonstrated in several of the behavioral effects of alcohol, including motor incoordination, anxiolysis, sedation, withdrawal signs, and ethanol preference [Buck, 1996; Grobin et al., 1998]. Additionally, $GABA_A$ receptors have also been implicated in ethanol tolerance and dependence [Grobin et al., 1998]. The precise mechanisms by which GABA receptors are involved in these actions of ethanol remain unknown [Grobin et al., 1998].

Chromosome 5 contains a cluster of four $GABA_A$ receptor genes: *GABRA1*, *GABRA6*, *GABRB2*, and *GABRG2* (NCBI LocusLink). Studies of the relation of these genes to alcoholism have yielded mixed results. Positive linkage [Radel et al., 1999] and association [Loh and Ball, 2000; Loh et al., 2000] have been reported with GABRG2, while other studies have found no evidence of association with the gene [Hsu et al., 1998; Sander et al., 1999]. Similarly, for GABRA6, several studies have reported positive evidence of association [Loh et al., 1999; Sander et al., 1999; Schuckit et al., 1999], while others using similar methods have been negative [Loh and Ball, 2000; Song et al., 2003]. All association studies of GABRA1, thus far, have been negative [Parsian and Cloninger, 1997; Loh and Ball, 2000; Song et al., 2003]. A summary of human and animal studies of these $GABA_A$ receptor genes on chromosome 5 is provided in supplemental materials available online at http://www.interscience.wiley.com/jpages/0148-7299:1/suppmat/index.html.

Here, we report family-based association analyzes of the $GABA_A$ receptor genes on chromosome 5 using a large sample of multiplex alcoholic families collected as part of the Collaborative Study on the Genetics of Alcoholism (COGA) study. Our study has several strengths that build upon the existent literature. We used a large family-based association design that avoids potential problems with population stratification introduced by case-control studies. Many of the existent studies of the chromosome 5 $GABA_A$ receptor genes have employed case-control designs, some of which have used relatively small samples. Additionally, we made use of multiple

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analytic methods, both analyzing extended families and classic TDT parent–child trios to test for consistency across analytic method. We tested multiple single nucleotide polymorphisms (SNPs) in each gene and looked for consistent trends across SNPs within the gene. Many previous studies have tested only one or two genetic variants in the gene under study. This can lead to difficulty in interpreting the results because a negative finding could occur simply because that particular marker is not in linkage disequilibrium (LD) with the disease producing mutation. This could lead to an incorrect conclusion that the gene is not involved in the outcome under study. Alternatively, a positive association could result if that particular marker is in high LD with a disease mutation in a nearby gene. Although the signal would be real, the actual gene involved would not be the one in which the marker resides, leading to the potential for erroneous interpretation. These incorrect conclusions are due to the lack of a simple linear relationship between LD and the physical distance between SNPs [Abecasis et al., 2001]. To ensure accurate interpretation of our study results, we also analyzed LD between all genotyped SNPs, both within and between the $GABA_A$ receptor genes, and used this information to interpret the results of association analyzes. By designing the study in this manner and taking these steps to ensure data quality and consistency, we aimed to provide more conclusive evidence regarding the role of the $GABA_A$ receptor genes on chromosomes 5.

MATERIALS AND METHODS

Sample

The COGA is a multi-site project, in which families were collected at six centers across the United States: Indiana University, State University of New York Health Science Center, University of Connecticut, University of Iowa, University of California/San Diego, and Washington University, St. Louis. Probands identified through inpatient or outpatient alcohol treatment programs at these six sites were invited to participate if they had a sufficiently large family (usually sibships >3 with parents available) with two or more members in a COGA catchment area [Reich, 1996]. The institutional review boards of all participating institutions approved the study. A total of 1,227 families of alcohol dependent probands were recruited for the first stage of the study. Additionally, a sample of control families, obtained through random sources such as driver's license registries and dental clinics, was assessed. These families consisted of two parents and at least three children over the age of 14. All individuals were administered the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview [Bucholz et al., 1994; Hesselbrock et al., 1999]. Multiplex alcoholic families that were not bilineal and had at least two affected first degree relatives in addition to the proband were invited to participate in the more intensive stage of the study, which included obtaining blood for genetic analyzes. Second and third degree relatives in the families were assessed when they were considered to be informative for the genetic linkage studies. A total of 987 adult individuals from 105 extended families were included in the initial genotyped data set [Reich et al., 1998]. A replication sample was ascertained and genotyped following identical procedures; it consisted of 1,295 individuals from 157 extended families [Foroud et al., 2000]. Thus, a total of 2,282 individuals from 262 multiplex alcoholic families were available for genetic analyzes. An additional 1,254 individuals from 227 control families were included in analyzes of LD between markers.

Phenotypes

Individuals were diagnosed with alcohol dependence using DSM-IV criteria [American Psychiatric Association, 1994]. Additionally, because previous studies have found evidence of association to the chromosome 5 $GABA_A$ receptor genes with alcoholism comorbid with antisocial personality disorder (ASPD), we also examined the evidence of association with alcohol dependence comorbid with ASPD. ASPD was diagnosed using DSM-IIIR criteria in the version of the SSAGA administered to these participants. Individuals meeting criteria for both DSM-IV alcohol dependence and ASPD were considered affected in these analyzes; individuals meeting criteria for neither disorder were considered unaffected; individuals who met criteria for only one of the disorders were considered unknown and were omitted from analyzes of the comorbid phenotype.[1]

DNA Analyzes

SNPs were chosen across each candidate gene from public databases; we did not restrict ourselves to SNPs in coding regions or exons, since allele frequencies for such SNPs are often low. Locations of the SNPs were in most cases determined from the annotations in the NCBI human genome assembly. In some cases, position was determined by BLASTing the sequence against the human genome assembly. Allele frequencies are not usually available for public SNPs, so SNPs were genotyped on approximately 80 unrelated individuals from the Coriell Caucasian and African-American samples to determine approximate allele frequencies; we preferentially chose SNPs with high heterozygosities. Genotyping was done using a modified single nucleotide extension reaction, with allele detection by mass spectrometry (Sequenom MassArray system; Sequenom, San Diego, CA). A total of 3,536 individuals from the COGA families were genotyped. All genotypic data were checked for Mendelian inheritance of marker alleles with the USERM13 [Boehnke, 1991] option of the MENDEL linkage computer programs, which was then used to estimate marker allele frequencies. Due to constant position changes in the NCBI database, and the failure of some SNPs in initial tests, it was not always possible to have even coverage of SNPs across each of the genes. Twenty-nine SNPs were genotyped in the chromosome 5 $GABA_A$ receptor gene cluster: 7 SNPs in *GABRB2*, 5 SNPs in *GABRA6*, 6 SNPs in *GABRA1*, and 11 SNPs in *GABRG2*. The average heterozygosity across the chromosome 5 SNPs was 0.38. These SNPs, the gene in which they are located, their chromosomal positions, and heterozygosity are shown in Table I.

Statistical Analyzes

Multiplex alcoholic families were used in tests of association between each of the SNPs and both of the phenotypes studied: alcohol dependence and alcohol dependence comorbid with ASPD. The Pedigree Disequilibrium Test (PDT) [Martin et al., 2000] was used to test for association in the extended pedigrees. The PDT utilizes data from all available trios in a family, as well as discordant sibships. It produces two statistics: the "PDT-avg," which averages the association statistic across all families, and the "PDT-sum," which gives greater weightage to families with a larger number of informative trios and discordant sibships [Martin et al., 2001]. Because the COGA sample consists of several very large families that might overly

[1]In addition, we analyzed the phenotype "alcohol dependence or ASPD" under the assumption that these disorders could be alternative manifestations of the same underlying genetic predisposition. However, very few individuals met the criteria for ASPD without also meeting the criteria for alcohol dependence. Thus, the results for these analyzes were very similar to those for alcohol dependence alone and are not presented here. They are available from the authors upon request.

TABLE I. Association Between Single Nucleotide Polymorphisms (SNPs) in the Chromosome 5 γ-Aminobutyric Acid ($GABA_A$) Receptor Gene Cluster and (1) DSM-IV Alcohol Dependence (AD) and (2) Comorbid Alcohol Dependence and Antisocial Personality Disorder (ASPD)

				AD		AD + ASPD	
Marker	Gene	Position	Heterozygosity	PDT	TRANSMIT	PDT	TRANSMIT
rs1592752	*GABRB2*	159,883,537	0.50	0.76	0.43	0.15	0.40
rs253041	*GABRB2*	160,659,541	0.22	0.33	0.22	0.88	0.42
rs252957	*GABRB2*	160,675,386	0.49	0.77	0.77	0.24	0.33
rs252944	*GABRB2*	160,693,880	0.24	0.11	**0.05**	0.08	0.95
rs194072	*GABRB2*	160,694,198	0.25	0.07	**0.04**	0.07	0.26
rs967771	*GABRB2*	160,697,717	0.33	0.87	0.29	0.44	0.11
rs2303055	*GABRB2*	160,699,159	0.06	0.90	0.76	0.60	0.08
rs1992646	*GABRA6*	161,046,804	0.50	0.93	0.66	0.67	0.09
rs3811995	*GABRA6*	161,048,236	0.50	0.92	0.50	0.68	0.13
rs3811992	*GABRA6*	161,052,485	0.50	0.67	0.44	0.83	0.22
rs3811991	*GABRA6*	161,063,952	0.47	0.34	0.72	0.78	0.28
rs3219151	*GABRA6*	161,064,457	0.49	0.93	0.44	0.97	0.11
rs1026447	*GABRA1*	161,253,313	0.33	0.58	0.98	0.24	0.18
rs980791	*GABRA1*	161,253,979	0.46	0.42	1.00	0.91	0.64
rs1157122	*GABRA1*	161,254,857	0.24	0.27	**0.02**	0.27	0.62
rs2279020	*GABRA1*	161,258,432	0.46	0.87	0.72	0.98	0.54
rs2290732	*GABRA1*	161,260,441	0.47	0.96	0.28	0.68	0.33
rs998754	*GABRA1*	161,261,477	0.47	0.72	0.42	0.64	0.16
rs2268583	*GABRG2*	161,431,395	0.16	0.88	0.41	0.99	0.94
rs2268582	*GABRG2*	161,450,758	0.24	0.52	0.59	0.54	0.23
rs211017	*GABRG2*	161,458,498	0.28	0.90	0.23	0.77	0.31
rs211037	*GABRG2*	161,463,823	0.39	0.58	0.49	0.79	0.66
rs210991	*GABRG2*	161,468,991	0.31	0.85	0.97	0.77	0.61
rs210983	*GABRG2*	161,474,677	0.42	0.80	0.58	0.95	0.74
rs989694	*GABRG2*	161,500,024	0.50	0.40	**0.03**	0.43	0.98
rs211015	*GABRG2*	161,511,196	0.48	0.71	0.39	0.64	0.82
rs211014	*GABRG2*	161,511,961	0.38	0.79	1.00	0.58	0.95
rs211013	*GABRG2*	161,514,984	0.50	0.24	**0.04**	0.29	0.61
rs418210	*GABRG2*	161,516,526	0.39	0.74	0.80	0.39	0.86

P values are shown for both the PDT and TRANSMIT analyzes. *P* values ≤ 0.05 are shown in bold; *P* values are not corrected for multiple tests.

influence the PDT-sum statistic, we report the values from the PDT-avg statistic. For the phenotype of alcohol dependence, an average of 345 trios (range 265–388) and 1,043 discordant sibships (range 921–1,122) were available for analysis. For the comorbid phenotype requiring a diagnosis of ASPD in addition to alcoholism, an average of 78 trios (range 58–88) and 219 discordant sibships (range 185–240) were used in analyzes. We also conducted classic TDT trio-based analyzes by selecting one trio from each COGA family. We used the program TRANSMIT for these analyzes [Clayton, 1999]. On average, 113 independent, informative trios were available for analysis of alcoholism (range 15–151) and 45 trios were available for the comorbid phenotype (range 8–61).

LD between markers was evaluated using the program GOLD [Abecasis and Cookson, 2000] with both multiplex alcoholic family data and control family data. This program uses haplotype input from Simwalk2 [Sobel and Lange, 1996], and produces pair-wise disequilibrium measures for all markers entered into the analysis. We ran LD across all 29 SNPs in the region. Families that had more than one individual with four or more recombination events across the region were dropped from subsequent analyzes; thus, allowance was made for one possible recombination between each gene cluster and one recombination within a gene before the family was considered problematic. The extent of LD was measured using Lewontin's standardized disequilibrium coefficient (D′). D′ is a commonly used measure of LD that varies between 0 (no disequilibrium) and 1 (maximum disequilibrium).

P values are not corrected for multiple testing, because the SNPs are not independent. Thus, we conservatively interpret our results by (1) requiring consistency across analytic methods and (2) requiring consistency between the pattern of association results and the pattern of LD across the region.

RESULTS

The *P* values from the tests of association with both alcohol dependence and alcohol dependence comorbid with ASPD, using both the PDT and TRANSMIT, are presented in Table I. There was no consistent evidence of association across any of the genes tested in the chromosome 5 GABA receptor cluster. Two adjacent SNPs in *GABRB2* yielded *P* values ≤ 0.05 using trio-based analyzes (TRANSMIT). There was a trend toward significance with these two SNPs using the PDT as well. These two SNPs also showed trends toward significance with the PDT for the comorbid phenotype; however, analyzes of independent trios from each family using TRANSMIT yielded no evidence of association for alcohol dependence comorbid with ASPD. Furthermore, inspection of the transmissions observed in the PDT and TRANSMIT suggests that the evidence of association is very modest (supplemental material available on-line). Allele 1 of rs252944 was over transmitted to affected individuals using both the extended family analysis of the PDT and the independent trios analyzed with TRANSMIT; however, the discordant sibling pairs did not show the expected effect: allele 1 was not over transmitted to the affected siblings as compared to the unaffected siblings. Furthermore, the deviation from the expected transmission pattern was modest. The marker rs194072 showed an identical pattern: allele 1 was over transmitted in both all possible trios from the PDT and independent trios from TRANSMIT, but the discordant sibling pairs did not provide evidence consistent with the

findings from the trios. Deviation from the expected transmission pattern was again modest.

One SNP in *GABRA1* and two nonadjacent SNPs in *GABRG2* provided some evidence of association ($P < 0.05$) using trio-based methods (TRANSMIT); however, there was no evidence of association using the PDT. No SNPs yielded significant evidence of association for the comorbid phenotype, alcohol dependence with ASPD. Although several SNPs approached the trend level using TRANSMIT, these results should be interpreted very cautiously due to the smaller sample sizes used in these analyzes and the lack of consistency with the PDT.

LD was high within each gene and low between genes (details shown in the supplemental material on the web). The first SNP in *GABRB2*, rs1592752, had lower levels of LD with the other SNPs in the gene (average D′ with the six other *GABRB2* SNPs = 0.18); this is not entirely surprising since the other SNPs were more closely clustered in the gene. The other six SNPs in the gene generally had higher levels of LD (average D′ between SNPs omitting rs1592752 = 0.81). For the purpose of interpreting the association results, it is important to point out that rs252944 and rs194072, the two SNPs showing significant association with alcohol dependence were in high LD not only with each other, but also with several other surrounding SNPs that showed no evidence of association. The average LD for SNPs in *GABRA6* was D′ = 0.88. The average LD for SNPs in *GABRA1* was D′ = 0.84. LD was somewhat more variable across *GABRG2*; average D′ = 0.60.

DISCUSSION

We have tested for association between the $GABA_A$ receptor genes on chromosome 5 and DSMIV alcohol dependence, as well as alcohol dependence comorbid with ASPD, using a sample of multiplex alcoholic families. Our strategy employed multiple analytic methods for family-based designs, tested multiple SNPs in each gene, and used patterns of LD across the SNPs to interpret association results and reduce the possibility of false positives. We find no consistent evidence that any of the genes in the $GABA_A$ receptor gene cluster on chromosome 5 are associated with alcohol dependence or alcohol dependence comorbid with antisocial personality. Although two adjacent SNPs in *GABRB2* yielded P values ≤ 0.05 using TRANSMIT, and there was suggestion of association using the PDT ($P \leq 0.11$), we think it is likely that these results are false positives. These SNPs are in high LD with other surrounding SNPs, which show no evidence of association. Thus, the results are not consistent with the pattern of LD observed in the region. Additionally, the deviation from the expected transmission pattern is modest using trios from both the PDT (all possible trios in a family) and TRANSMIT (analyzes using only one independent trio from each family). Furthermore, the allele frequencies observed in the discordant sibling pairs analyzed in the PDT were not consistent with the association observed in trios for either marker. Finally, the P values were uncorrected for multiple testing and would no longer be significant if a Bonferroni correction were applied. Although three other SNPs yielded P values < 0.05 using TRANSMIT, there was no evidence of association using the PDT test for these SNPs. Additionally, they too showed high LD with surrounding SNPs that yielded no evidence of association.

These findings are in contrast to our results from association tests of the chromosome 4 and chromosome 15 $GABA_A$ receptor gene clusters. We used an identical strategy to that employed here to test the association of alcohol dependence to SNPs in these other chromosomal regions using the COGA sample. On chromosome 4, we found that nearly all SNPs in the gene *GABRA2* were in high LD and showed consistent evidence of association, using both classic TDT analyzes and the PDT [Edenberg et al., 2004]; none of the surrounding genes showed consistent evidence of association. Similarly, on chromosome 15, we found evidence of association with SNPs across the *GABRG3* gene that was consistent across analytic methods and with the pattern of LD observed in the region [Dick et al., 2004]. Thus, we believe the strategy we employ is a powerful one for identifying genes potentially involved in alcoholism; however, the results observed for the $GABA_A$ receptor genes on chromosome 5 are not consistent with the expected pattern under association.

The previous studies reporting associations with alcohol dependence comorbid with antisocial personality both reported very modest effects [Sander et al., 1999; Loh et al., 2000]. In the Loh et al. [2000] study, the association with alcohol dependence comorbid with ASPD was not significant after correcting for multiple testing, and in the Sander et al. [1999] study, although the association remained significant after Bonferroni correction, the study population was small (n = 57) and the authors acknowledged the possibility that the finding may be a false positive.

It remains a possibility that variation in the chromosome 5 $GABA_A$ receptor genes may be important in a subgroup of alcoholics yet to be identified. Another possibility is that the chromosome 5 $GABA_A$ receptor genes may play a role in some of the intermediary processes contributing to alcohol use, rather than in alcohol dependence per se. Some of the most compelling evidences for the involvement of the chromosome 5 $GABA_A$ receptor genes in the actions of alcohol have come from the animal literature, in which the phenotype of alcohol dependence has not been studied. In these animal models, evidence of association was observed with a variety of alcohol-related behavioral traits such as ethanol consumption, ethanol sleep time, and locomotor activation [Buck, 1996]. In the COGA sample, no linkage was observed to the phenotype of alcohol dependence on chromosome 5 [Reich et al., 1998], but there was linkage in this region to an alcohol-related electrophysiological endophenotype [Ghosh et al., 2003].

It also remains possible that there are genetic variants that are not in LD with the SNPs tested here that may influence alcohol dependence. In this study, it was not possible to test SNPs evenly across all of the genes, due to the constraints mentioned in the "Materials and Methods." In particular, the SNPs tested in *GABRB2* and *GABRA1* were largely concentrated toward the 3′ end of the gene. With the recent completion of human genome project and better annotations in the public database (NCBI) over time, it should be possible to test more genetic variants across the genes in the region.

In conclusion, using data from the largest family-based association study of the $GABA_A$ receptor genes on chromosome 5 reported to date, we did not find compelling evidence of association for *GABRA1*, *GABRA6*, *GABRB2*, or *GABRG2* with alcohol dependence or with alcohol dependence comorbid with ASPD with any of the genetic variants tested. Although some significant sporadic findings were reported for SNPs within the genes, there was no consistency across analytic methods or with the pattern of LD across SNPs within each of the genes. Thus, we find no evidence that the chromosome 5 $GABA_A$ receptor genes play a strong role in alcohol dependence diagnoses in this sample. Future research will concentrate on whether these genes have an impact on behavioral endophenotypes related to the development of alcohol dependence.

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