Biomedical Genetics and Genomics

Research Article

ISSN: 2398-5399

Associations of $GABA_A$ receptor gene variations with alcohol use disorder and conduct disorder phenotypes in Korean-, Chinese-, and European-American college students

Daria Orlowska[1], Mimy Y. Eng[2], Susan E. Luczak[3], Howard J. Edenberg[4] and Tamara L. Wall[1,2,5*]

[1]Department of Psychiatry, University of California, San Diego, USA

[2]Veterans Medical Research Foundation, San Diego, USA

[3]Department of Psychology, University of Southern California, Los Angeles, USA

[4]Departments of Biochemistry and Molecular Biology, Indiana University, School of Medicine, Indianapolis, USA

[5]VA San Diego Healthcare System, San Diego, USA

Abstract

Aims: This study aimed to determine whether gamma-aminobutyric acid (GABAA) receptor gene variations differed across individuals of Korean, Chinese, and European ancestry and to test for genes associations with four phenotypes: alcohol dependence diagnosis, alcohol use disorder (AUD; alcohol abuse and dependence) symptom count, conduct disorder diagnosis, and conduct disorder symptom count.

Methods: Male and female college students (n=1,310) were genotyped for ALDH2, ADH1B, and 21 SNPs spanning four GABAA receptor genes, GABRA2, GABRA4, GABRA1, and GABRG3. Phenotypes were assessed using DSM-IV criteria. Complete genotypic and phenotypic data were available for 1,154 participants.

Results: There were significant differences in the allele frequencies of ALDH2, ADH1B, and all 21 GABAA receptor gene SNPs across individuals of Korean, Chinese, and European ancestry. Four GABRA2 SNPs were significantly associated with lifetime AUD symptoms in Korean-American men. Three GABRG3 SNPs were significantly associated with conduct disorder diagnosis in Korean-American men.

Conclusion: Results suggest significant variation across ancestry in GABAA receptor genes and that there may be varied associations with phenotypes in different ancestral groups. These findings highlight the need for replication and increased understanding of the mechanism underlying putative associations of GABAA receptor gene variation with AUD and conduct disorder phenotypes.

Introduction

The etiology of alcohol use disorders (AUDs; alcohol abuse and dependence) includes genetic and environmental influences. Twin studies using samples of primarily European ancestry indicate 50-60% of the variability in alcohol dependence is explained by the combined effects of multiple genes [1,2]. However, rates of AUDs differ substantially by sex and in different populations [3]. In particular, Asians in the U.S. have lower rates of AUDs than Whites, Blacks, Native Americans, and Hispanics [3,4]. Two genetic variants, *ALDH2*2* (rs671) and *ADH1B*2* (rs1229984), are found predominantly in Asian populations and associated with lower rates of alcohol dependence [5-7]. The hypothesized mechanism underlying the associations of *ALDH2*2* and *ADH1B*2* with alcohol dependence is that the isoenzymes encoded by these alleles lead to increased acetaldhyde and enhanced reactions to alcohol, which then reduces heavy drinking and AUDs [8].

As an aggregated group, Asians in the U.S. have lower rates of AUDs [3], but there are substantial differences across subgroups [9,10]. In a large cross-national study, the lifetime rate of alcohol abuse and dependence was 23% for South Koreans (43% of men, 3% of women) and 7% for Taiwanese (13% of men, 0.7% for women) compared with 17% for Americans (29% of men, 4% of women) [9]. This large difference in lifetime AUD rates between South Koreans and Taiwanese is similar, but more pronounced, to rates found in more recent epidemiologic studies in Asia and the U.S. [10-12]. Consistent with epidemiologic data, a study from our laboratory found Chinese-American college students had lower rates of alcohol dependence (8% of men, 2% of women) than Korean-American (18% of men, 8% of women) and European-American (22% of men, 12% of women) college students [13].

In most cultures, men have higher rates of AUDs than women, but the sex discrepancy is particularly pronounced in many Asian groups [3,9] and may be due, in part, to societal, familial, and peer pressures on women not to drink. In support of this hypothesis, the male-to-female AUD ratio in South Korea and China has decreased as Westernization has occurred [14,15]. These findings suggest the possibility that the

Correspondence to: Tamara L. Wall, Ph.D., VA San Diego Healthcare System, Psychology Service (116B), 3350 La Jolla Village Drive, San Diego, CA 92161. Tel.: 858-552-8585, **E-mail:** twall@ucsd.edu

Received: June 12, 2016; **Accepted:** July 28, 2016; **Published:** August 02, 2016

relative influence of genetics on AUDs in Asian men and women may differ from that found in studies of predominantly European men and women [2] and could vary over time.

In our prior study of Korean-, Chinese-, and European-American college students, analyses indicated that the relationship of ancestry with alcohol dependence was mediated by *ALDH2* gene status and conduct disorder, although Chinese ancestry remained significant [13]. *ADH1B* gene status was not related to alcohol dependence with *ALDH2* included in the analyses and no interactions were significant. These results suggest that different rates of risk (e.g., conduct disorder) and protective (e.g., *ALDH2* status) factors account for some the variability in rates of alcohol dependence between Korean, Chinese, and European Americans.

One set of genes that might contribute to differences in rates of AUDs and conduct disorder observed between Koreans, Chinese, and Europeans are the gamma-aminobutyric acid ($GABA_A$) receptor genes. Multiple reports have identified associations between single nucleotide polymorphisms (SNPs) of the $GABA_A$ receptor genes with AUD and/or conduct disorder phenotypes. For the current study, we selected 21 SNPs spanning four $GABA_A$ receptor genes, *GABRA2 (*chromosome 4), *GABRA4 (*chromosome 4), *GABRA1* (chromosome 5), and *GABRG3* (chromosome 15) based on prior significant associations with either AUD phenotypes [16-36] or conduct disorder phenotypes [20,34,36-38]. It is important to note that the majority of these reports were case-control studies, which have greater power to detect significant associations than general population studies. In addition, few, if any, participants of Asian descent were included in these prior investigations and not all studies examining the same SNPs have reported consistent associations [23,27,29,31,34,39,40].

To date, no functional variants have been identified that account for the associations of the $GABA_A$ receptor genes with AUDs and/or conduct disorder, and the mechanism of action of these gene associations is unknown. Some investigators have hypothesized that *GABRA2* SNPs may exert their effect on alcohol dependence via differences in levels of response to alcohol [32,33]. Roh and colleagues [33] assessed a Japanese sample and stratified by *ALDH2* genotype. Individuals heterozygous and homozygous for several *GABRA2* variants were more sensitive to the effects of alcohol irrespective of their *ALDH2* genotype. This finding suggests that *GABRA2* variation, similar to *ALDH2* variation, may contribute to individual variability in response to alcohol. Other investigators have hypothesized *GABRA2* variants might relate to alcohol dependence and conduct disorder via general externalizing pathways given associations of several SNPs not only with alcohol phenotypes, but also with conduct disorder, antisocial personality disorder, and other (non-alcohol) drug dependencies [20,31,37,39].

To extend our prior research [13], we genotyped for *ALDH2*, *ADH1B*, and 21 SNPs spanning four $GABA_A$ receptor genes, *GABRA2, GABRA4, GABRA1* and *GABRG3* and tested for associations with both AUD and conduct disorder phenotypes in a larger sample of Korean-, Chinese-, and European-American college students. We hypothesized that there would be differences in the allele frequencies of $GABA_A$ receptor genes across ancestry but not across sex. Given that genetic and environmental influences may differ across groups and across phenotypes, we conducted analyses separately by ancestry and sex and analyzed both dichotomous (*i.e.,* diagnosis) and continuous (*i.e.,* symptom count) outcomes [41]. Based on prior investigations, we hypothesized that there would be significant associations between $GABA_A$ receptor gene SNPs and two AUD phenotypes (alcohol dependence diagnosis, AUD symptom count) controlling for variation in the *ALDH2* and *ADH1B* genes. We also hypothesized that there would be significant associations between $GABA_A$ receptor gene SNPs and two conduct disorder phenotypes (diagnosis and symptom count).

Methods

Participants were 21 to 26 year old college students recruited from the University of California, San Diego (UCSD). All individuals reported that they were of entirely Korean (n=379), Chinese/Taiwanese (n=406), or European (n=525) heritage. The sample included 1,310 individuals (56% female) with a mean age of 22.0 (SD=1.34) years. A prior report included a subsample of these participants, n=604 (50% female) [13].

Potential participants were recruited based on self-reported ancestry via advertisements on campus for a paid research project. Respondents were initially screened by telephone and then rescreened in person to assure they met inclusion criteria. Europeans who reported any known African, Hispanic, Native American, Asian, or Jewish ancestry were excluded from participation. Asians who reported all grandparents were entirely of Chinese/Taiwanese or entirely Korean ancestry was included in the study. The research protocol was approved by the human research protection program at UCSD. All study participants provided written informed consent for clinical and genetic studies.

Each participant completed an individual assessment with a trained research interviewer. To increase the likelihood of accurate reporting, we explained our procedures for protecting confidentiality. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) was used to assess lifetime symptoms and diagnoses of alcohol abuse, alcohol dependence, and conduct disorder (prior to age 18 years) based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [42]. The SSAGA has shown good reliability and validity for these disorders [43,44] and was designed to assess psychiatric symptomatology independent of substance abuse. Thus, no symptom of conduct disorder was the result of substance use.

A blood sample was collected from each participant via fingertip puncture. Genotyping for *ALDH2*, *ADH1B*, and 21 SNPs spanning *GABRA2*, *GABRA4*, *GABRA1* and *GABRG3* was conducted using methods described previously [23,45,46]. Complete genotype data were not available for 156 participants.

Genotype distributions in each ancestry group were examined for significant deviation ($p < .05$) from Hardy-Weinberg equilibrium. Chi-square tests of association were conducted to determine if allele frequencies differed significantly across ancestry and sex. For comparisons of allele frequencies as well as rates of diagnoses and levels of symptoms among the three ancestry groups, we used planned, pair-wise tests, controlling the Type I error-rate by considering significant a p-value less than .0167 (.05/3).

Phenotypic analyses were conducted separately by ancestry and sex. Each SNP was coded 0, 1, or 2 for the major allele and treated as an ordinal relationship when examining relationships between genotypes and phenotypes. Chi-square tests of association were used to examine associations with dichotomous phenotypes. Regression analyses were used to examine associations with continuous phenotypes. For AUD phenotypes, multiple regression analyses also were conducted to control for the effects of *ALDH2* and *ADH1B* as they are related to alcohol dependence and other alcohol phenotypes.

We expected that the four phenotypes would be related. Alcohol dependence and AUD symptoms, as well as conduct disorder and conduct disorder symptoms were expected to be highly correlated; AUD and conduct disorder phenotypes also were expected to be correlated [47]. Due to their close proximity, we expected some SNPs within the same gene to be correlated. We did not make corrections for multiple phenotypic comparisons because it would increase the likelihood of a Type II error due to low phenotype rates in the sample and because predictions were expected to be similar across the set of correlated outcome measures. Multiple comparisons are less critical when tests are correlated [48], *i.e.,* comparisons for related outcome measures and for alleles in linkage disequilibrium do not each provide an independent opportunity for a Type I error.

Results

Complete genotypic and phenotypic data were available for 1,154 participants. The final sample included 337 Korean- (53% female), 350 Chinese- (49% female), and 467 European-American (49% female) college students. Table 1 displays the allele frequencies across ancestry for *ALDH2*, *ADH1B*, and $GABA_A$ receptor gene SNPs. All genotype distributions were in Hardy-Weinberg equilibrium ($p > .05$) except for four correlated *GABRA2* SNPs (rs1442059, rs279826, rs279828, rs279836) in Chinese Americans and one *GABRA2* SNP (rs1442059) in Korean Americans (Table 1), and likely are due to chance. There were no significant sex differences, but there were significant ancestry differences in allele frequencies of *ALDH2*, *ADH1B*, and all 21 $GABA_A$ receptor gene SNPs. Planned pair-wise tests (p-values < .0167) revealed significant differences between the Korean-, Chinese-, and European-American groups as shown in Table 1.

Table 2 presents frequencies for alcohol dependence and conduct disorder diagnoses, and means and SDs for AUD symptoms and conduct disorder symptoms, according to ancestry and sex. For all analyses, square root transformations were used to adjust for the positive skew found for both AUD symptoms and conduct disorder symptoms, but untransformed data are shown to facilitate interpretability.

In the total sample, 4.6% of participants met criteria for a lifetime diagnosis of alcohol dependence using DSM-IV criteria. Significantly more men (7.1%) than women (2.1%) were alcohol dependent, χ^2=16.63, $p < .001$. Ancestry group differences also were significant, χ^2=17.22, $p < .001$. Chinese Americans (1.1%) were significantly less likely to be diagnosed with alcohol dependence than Korean (4.4%) and European (7.2%) Americans, χ^2=16.99, $p < .001$, but the rate did not significantly differ between Korean and European Americans, χ^2=2.74, p=.098. A similar pattern of significance emerged for AUD symptoms (Table 2). Men had significantly more lifetime AUD symptoms than women F (1, 1,153)=12.05, $p < .001$; Chinese Americans had significantly fewer lifetime AUD symptoms than Korean F (1, 685)=42.19, $p < .001$) and European F (1, 815)=279.07, $p < .001$) Americans.

In the total sample, 6.6% of participants had a diagnosis of conduct disorder. Rates of conduct disorder differed across sex, χ^2=29.8, $p < .001$, and ancestry, χ^2=9.54, $p < .001$. Significantly more men (10.6%) than women (2.6%) met lifetime criteria for conduct disorder. Korean Americans were significantly more likely to be diagnosed with conduct disorder (9.8%) than European (6.2%) and Chinese (4%) Americans, (χ^2=9.04, $p < .003$), but the rate did not significantly differ between European and Chinese Americans (χ^2=1.96, p=.162). A similar pattern of significance emerged for conduct disorder symptoms (Table 2). Men had significantly more lifetime conduct disorder symptoms than women F (1, 1,153)=113.21, $p < .001$; Chinese Americans had significantly fewer conduct disorder symptoms than Korean F (1, 685)=13.01, $p < .001$ and European F (1, 815)=11.28, $p < .01$ Americans.

Table 1. Allele Frequencies for *ALDH2*, *ADH1B* and $GABA_A$ Receptor Gene SNPs in Korean, Chinese, and European Americans.

Gene	SNP	NT	Korean American (*n*=337)	Chinese American (*n*=350)	European American (*n*=467)	Ancestry differences
ALDH2	rs671	A/G	.17/.83	.27/.73	0/1.0	a,b,c
ADH1B	rs1229984	A/G	.73/.27	.72/.28	.03/.97	b,c
GABRA2	rs1442059	C/T	.53/.47	.60/.40 *	.42/.58	a,b,c
GABRA2	rs279826	A/G	.47/.53	.40/.60 *	.56/.45	a,b,c
GABRA2	rs279827	A/G	.48/.53	.41/.59	.56/.45	b,c
GABRA2	rs279828	A/C	.47/.53	.40/.60 *	.56/.45	a,b,c
GABRA2	rs279836	A/T	.53/.47 *	.60/.40 *	.42/.58	a,b,c
GABRA2	rs279845	A/T	.53/.47	.59/.41	.45/.56	b,c
GABRA2	rs279858	A/G	.51/.49	.47/.53	.57/.43	b,c
GABRA2	rs279871	A/G	.51/.49	.47/.53	.57/.43	c
GABRA2	rs490434	A/G	.40/.60	.49/.51	.41/.59	c
GABRA2	rs495818	A/G	.61/.39	.52/.48	.58/.42	a,c
GABRA2	rs531460	A/G	.39/.61	.49/.51	.41/.60	c
GABRA2	rs572227	A/G	.39/.61	.48/.52	.42/.58	a
GABRA4	rs2036943	A/T	.60/.40	.69/.31	.31/.69	a,b
GABRA1	rs4263535	A/G	.51/.49	.55/.45	.82/.18	b,c
GABRA1	rs4478357	A/C	.30/.70	.31/.69	.54/.46	b,c
GABRG3	rs3097490	C/T	.21/.79	.30/.70	.50/.51	a,b,c
GABRG3	rs3097493	C/G	.25/.75	.32/.68	.49/.51	a,b,c
GABRG3	rs3101636	A/G	.75/.25	.68/.32	.51/.49	a,b,c
GABRG3	rs3101639	A/G	.75/.25	.68/.32	.51/.49	a,b,c
GABRG3	rs140679	C/T	.27/.73	.33/.67	.49/.51	a,b,c
GABRG3	rs2303879	A/G	.79/.21	.70/.30	.51/.50	a,b,c

Notes.
* Hardy-Weinberg equilibrium violated, $p < .05$
a - Korean Americans significantly different from Chinese Americans, $p <$. 0167
b - Korean Americans significantly different from European Americans, $p < .0167$
c - Chinese Americans significantly different from European Americans, $p < .0167$

Table 2. Diagnoses (Percentages) and Symptom Counts (Means and SDs) by Ancestry and Sex.

	Korean Americans		Chinese American		European Americans	
	Men (*n*=159)	Women (*n*=178)	Men (*n*=179)	Women (*n*=171)	Men (*n*=239)	Women (*n*=228)
Alcohol dependence	6.3%	2.8%	1.7%	0.6%	11.7%	2.6%
AUD symptoms	1.1 (1.8)	0.6 (1.3)	0.4 (1.0)	0.2 (0.5)	1.4 (2.0)	0.6 (1.2)
Conduct disorder	17.6%	2.8%	5.6%	2.3 %	9.6%	2.6%
Conduct disorder symptoms	1.8 (1.78)	0.4 (0.8)	0.9 (1.3)	0.4 (0.8)	1.2 (1.3)	0.6 (0.9)

Four *GABRA2* SNPs (rs490434, rs495818, rs531460, rs572227) were significantly associated with AUD symptoms in Korean-American men. These four SNPs were significantly correlated in this sample *r*s=.57-.94, p-values < .05). In univariate analyses, Korean-American men whose genotype was homozygous for the minor allele: AA for rs490434, GG for rs495818, AA for rs531460, and AA for rs572227 had, on average, a significantly higher number of lifetime AUD symptoms (mean ranged from 1.87–2.08) than Korean-American men whose genotype was heterozygous (mean ranged from 1.15–1.25) or whose genotype was homozygous for the major allele (mean ranged from 0.77–0.78).

Table 3 shows results of multiple regression analyses for each of these four *GABRA2* SNPs and *ALDH2* and *ADH1B* on the number of

Table 3. Summary of Separate Multiple Regression Analyses for Four Adjacent *GABRA2* SNPs, *ALDH2*, and *ADH1B*, with AUD Symptoms in Korean-American men (*n*=156).

***GABRA2* SNP**	**Variable**	***F*-value df=2, 152**	***p*-value**
rs490434	*ALDH2*2*	5.38	0.006
	*ADH1B*2*	0.43	0.651
	A allele	6.01	0.003
rs495818	*ALDH2*2*	5.51	0.005
	*ADH1B*2*	0.38	0.684
	G allele	4.29	0.015
rs531460	*ALDH2*2*	5.36	0.006
	*ADH1B*2*	0.44	0.644
	A allele	6.09	0.003
rs572227	*ALDH2*2*	5.51	0.005
	*ADH1B*2*	0.38	0.684
	A allele	4.29	0.015

lifetime AUD symptoms in Korean-American men. *ALDH2* but not *ADH1B* was significantly associated with AUD symptoms, and each *GABRA2* SNP remained significant. To test for the possibility of a gene x gene interaction, an interaction term of *ALDH2* with rs490434, rs495818, rs531460, or rs572227 was added to each respective model. None of the interactions were significant (*p*-values > .05; data not shown).

Three adjacent *GABRG3* SNPs (rs3097493, rs3101636, rs3101639) were significantly associated with conduct disorder diagnosis in Korean-American men: rs3097493 χ^2 (2, *N*=159)=7.67, *p*=.022; rs3101636 χ^2 (2, *N*=159)=7.33, *p*=.026; rs3101639, χ^2 (2, *N*=159)=7.67, *p*=.022. These three SNPs were significantly correlated in this sample (*r*s=.721-.985, *p*-values < .05). Results indicated Korean-American men whose genotype was homozygous for the major allele: AA for rs3101639, AA for rs3101636, and GG for rs3097493 had a higher frequency of conduct disorder (range 23-24%) than Korean-American men whose genotype was heterozygous (range 8-9%) or whose genotype was homozygous for the minor allele (0%).

Discussion

The aim of this study was to extend prior research and explore associations between $GABA_A$ receptor gene SNPs with AUD and conduct disorder phenotypes in samples of Korean-, Chinese-, and European-American college students. Specifically, we determined if there were sex or ancestry differences in the allele frequencies of 21 SNPs spanning four genes, *GABRA2, GABRA4, GABRA1* and *GABRG3*, and tested for associations with alcohol dependence, AUD symptom count, conduct disorder, and conduct disorder symptom count.

The $GABA_A$ receptor gene variants were chosen based on prior associations with AUD and/or conduct disorder phenotypes from predominantly case-control studies that included few, if any, participants of Asian descent. As hypothesized, results showed no significant sex differences, but significant ancestry differences for all 21 SNPs, with many (*n*=10) showing significant differences between all three ancestral groups. Some prior investigations have reported varied associations of $GABA_A$ receptor gene variants with AUD or conduct disorder phenotypes in different racial and ethnic groups, primarily African Americans or Hispanics compared with non-Hispanic Caucasians [16,34,38], but have not reported if allele frequencies differed significantly across ancestry. Given the potential for population stratification, it is important to determine if there are ancestry differences in the allele frequencies of candidate genes. Results from the current study suggest there is considerable variation in $GABA_A$ receptor gene variants across the Korean-, Chinese- and European-American college students that were sampled in this study.

As expected, there were significant sex differences and significant ancestry differences for the four AUD and conduct disorder phenotypes that were evaluated. Because of phenotypic differences and the potential for population stratification, gene association analyses were conducted stratifying by ancestry and sex. We identified two clusters of $GABA_A$ receptor gene SNPs that related significantly to different phenotypes in Korean-American men. One cluster of correlated SNPs (rs490434, rs495818, rs531460, rs572227) located on *GABRA2* was significantly associated with AUD symptoms, and the associations remained significant in analyses that included *ALDH2* and *ADH1B*. In previous studies, these four SNPs have been associated with alcohol dependence [16,23,39]. Edenberg and colleagues [23] found multiple *GABRA2* SNPs, including rs490434, rs495818, rs531460, and rs572227, were significantly associated with DSM-IV alcohol dependence using data from the Collaborative Study on the Genetics of Alcoholism (COGA) sample, a large study of families in which at least three individuals met diagnostic criteria for alcohol dependence. Agrawal and colleagues [39] replicated the association of these four and other *GABRA2* SNPs with alcohol dependence using the COGA sample. However, when individuals with comorbid drug dependence were excluded from analyses, the relationship for many of the SNPs including rs490434, rs495818, rs531460, and rs572227, were no longer significant. Bierut and colleagues [16] examined only one of these four SNPs, rs572227, in a sample of European-American and African-Americans and also replicated a significant association with alcohol dependence. Another study, however, did not corroborate these findings; Philibert and colleagues [31] found that rs495818, rs531460, and rs572227, but not rs490434, were associated with alcohol dependence symptoms. However, the findings were in the opposite direction; they reported that the risk allele for each of these SNPs was A for rs495818, G for rs531460, and G for rs572227.

A possible reason that we found significant associations between these four *GABRA2* SNPs and AUD symptoms, but not with alcohol dependence, in our sample of Korean-American men may relate to the characteristics of our sample, which was young (21-26 years of age) and non-treatment seeking. Previous studies that have found significant associations of these SNPs with alcohol dependence have used case-control designs [16,23,39]. Because of the relatively low prevalence of alcohol dependence in our college student sample, we also evaluated AUD symptom count as a phenotype, which includes individuals who are experiencing problems that are below diagnostic thresholds and provides greater power to detect significant associations [40].

We also identified a cluster of correlated SNPs (rs3101639, rs3101636, rs3097493) located on *GABRG3* that was significantly associated with conduct disorder in Korean-American men. In the COGA study, these three SNPs were associated with alcohol dependence [18], but they have not been previously tested for an association with conduct disorder. Kramer and colleagues [27] reported that rs3097493 was not associated with problematic alcohol use in a young adult sample (mean age 20.6 years) that was initially ascertained as children in the COGA study, but an association with conduct disorder was not tested. Variation in the *GABRG3* gene has been less well studied than the *GABRA2, GABRA4,* and *GABRA1* genes. The current findings suggest that Korean-American men whose genotype is homozygous for the major allele for each of these SNPs have a higher rate of lifetime conduct disorder (23-24%) than Korean-American men whose genotype is heterozygous (8-9%) or homozygous for the minor

allele (0%). The major allele for these three SNPs is significantly higher in Korean Americans (.75) than in Chinese (.68) and European (.51) Americans and the Korean-American men in this study have a high rate of conduct disorder (17.6%). These results suggest the possibility that *GABRG3* gene variation could contribute to the development of this disorder. Further research is needed to replicate these exploratory findings and to determine the function of the *GABRG3* gene to understand the mechanism by which these SNPs might influence the development of conduct disorder and alcohol dependence [18].

Several factors limit the generalizability of these results. Because of the possibility of varied associations, analyses were stratified by ancestry and sex, which limited our sample sizes and power. In addition, the relatively low prevalence of alcohol dependence and conduct disorder in this young adult sample further limited our power to detect associations with diagnostic phenotypes. It is possible that the relationships between these genotypes and phenotypes may change over time as more of the participants develop AUD symptoms and diagnoses. Larger, as well as older, samples of Korean, Chinese, and European participants may reveal additional associations between these $GABA_A$ receptor gene SNPs and AUD phenotypes.

Despite these limitations, this study also has several strengths. The total sample is relatively large and diverse in their ancestry. Asian participants are typically underrepresented in U.S. studies and subgroups are often aggregated in analyses. This study included two Asian-American groups, Koreans and Chinese, with significantly different rates of AUDs and conduct disorder. We used a reliable and valid instrument for assessing symptoms and diagnoses, and the current phenotypic results show a similar pattern to our previous findings [13] as well as with extant epidemiologic data [9-12]. Our analyses first determined whether allele frequencies differed across ancestry because of the potential for population stratification. Importantly, we found significant ancestry differences in the allele frequencies of all 21 $GABA_A$ receptor gene SNPs that were evaluated. In addition results corroborated findings that *GABRA2* SNPs (rs490434, rs495818, rs531460, rs572227) are associated with AUD phenotypes and is the first study to demonstrate an association of *GABRG3* SNPs (rs3101639, rs3101636, rs3097493) with conduct disorder in Korean-American men. The results suggest there is significant variation across ancestry in the $GABA_A$ receptor genes and that there may be varied associations with phenotypes in different ancestry groups. These findings highlight the need for replication and increased understanding of the mechanism underlying putative associations of $GABA_A$ receptor gene variation with AUD and conduct disorder phenotypes.

Acknowledgement

This work was supported by the National Institutes of Health [R01AA11257, T32AA013525, and P50AA07611].

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