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ORIGINAL ARTICLE

ALDH2*2 and peer drinking in East Asian college students

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ABSTRACT

Background: The *ALDH2*2* allele (A-allele) at rs671 is more commonly carried by Asians and is associated with alcohol-related flushing, a strong adverse reaction to alcohol that is protective against drinking. Social factors, such as having friends who binge drink, also contribute to drinking in Asian youth. *Objectives*: This study examined the interplay between *ALDH2*2*, peer drinking, and alcohol consumption in college students. We hypothesized that the relationship between *ALDH2*2* and standard grams of ethanol per month would vary based on the level of peer drinking. *Methods*: Subjects (*N* = 318, 63.25% female) were East Asian college students in the United States who reported drinking alcohol. Data were from the freshman year of a university survey that included a saliva DNA sample. *ALDH2*2* status was coded *ALDH2*2*(+) (A/G and A/A genotypes) and *ALDH2*2*(−) (G/G genotype). Peer drinking was students' perception of how many of their friends "got drunk". *Results*: Main effects of *ALDH2*2*(−) and having more friends who got drunk were associated with greater alcohol consumption. The *ALDH2*2* × peer drunkenness interaction showed a stronger positive association with alcohol consumption for *ALDH2*2*(−) versus *ALDH2*2*(+) at increasing levels of peer drunkenness. Follow-up comparisons within each peer drunkenness level identified significantly higher alcohol consumption for *ALDH2*2*(−) compared to *ALDH2*2*(+) at the all friends got drunk level.
Conclusion: There was evidence of a stronger effect for *ALDH2*2*(−) compared to *ALDH2*2*(+) with greater alcohol use when students were more exposed to peer drinking. Findings contribute to a growing literature on the interrelationships between genetic influences and more permissive environments for alcohol consumption.

Introduction

Asian-American college students are five times less likely to engage in heavy drinking as compared to white college students (1,2). This is due in part to an allele (i.e., *ALDH2*2* or A-allele at rs671) more commonly carried by northeast Asians (30–50%) and rare in non-Asians (3). The *ALDH2*2* allele is linked to alcohol-related flushing, an adverse reaction to the metabolism of alcohol that includes reddening of the face, headaches, nausea, drowsiness, and abnormal heart beats (4,5). Alcohol-related flushing occurs when a deficient enzyme, for metabolizing acetaldehyde, the primary metabolite of alcohol, to acetate, results in a buildup of acetaldehyde in the body (6). Studies show that individuals who carry *ALDH2*2* drink less frequently, consume smaller quantities of alcohol, and have a reduced risk for alcohol dependence (2,7,8).

Various social factors, such as friends' alcohol use, also contribute to greater drinking in Asians (9,10). Dick and Kendler (11) suggest that having more friends who drink is an indicator for greater access to alcohol or reduced social controls against drinking. Hahm et al. (12) found that Asian-American youth who have more friends who binge drink are at increased risk of binge drinking. Similarly, Kim et al. (13) found, in a sample of Hong Kong university students, that binge drinking was positively correlated with having friends who frequently drink. Peer drinking has also been shown to moderate the relationship between genetic influences and alcohol use (11). Gou et al. (14) reported that genetic contributions for alcohol use were stronger when friends' drinking increased and weaker when it decreased in adolescent twins. Kendler et al. (15) and Dick et al. (16) showed that genetic effects on alcohol

use increased in more permissive environments, with more deviant peers and friends who use alcohol.

The current study, to our knowledge, is the first to examine the interrelationship between level of peer alcohol use and ALDH2*2 in association with East Asian college student drinking. Previous molecular genetic studies show that alcohol use by peers and family members can moderate the relationships between genetic effects and various alcohol-related phenotypes. Examining a different alcohol metabolism gene, Olfson et al. (17) showed that having most or all best friends who drink greatly attenuated the effect of the protective allele at ADH1B rs1229984 in predicting age of first intoxication and alcohol use disorder symptom in European Americans and African Americans. Relevant to our study of ALDH2*2, Irons et al. (18) showed that parental and older sibling (adoptive) alcohol problems moderated the relationship between this variant and a drinking outcome for Korean adoptees. They reported, for example, that more parental alcohol problems were associated with a reduced protective effect for ALDH2*2. However, peer deviance did not moderate this relationship. It could be that adopted family drinking problems provided a more direct measure of access and exposure to alcohol when compared to the study's broader measure of peer deviance (18). Peer influences for the current study were defined according to students' reports of how many of their friends got drunk.

Based on the findings reviewed above, we hypothesized that ALDH2*2 status, from now on ALDH2*2/*2 and ALDH2*1/*2 are referred to as ALHD2*2 (+) and ALDH2*1/*1 as ALDH2*2(−), and friends' drinking would be associated with alcohol use in our sample, and also that friends' drinking would change the association between ALDH2*2 and alcohol use. In the context of having few friends who got drunk, the ALDH2*2(+) allele would be associated with less drinking compared to the ALDH2*2(−) genotype, but the protective effect of ALDH2*2(+) would be weakened at higher levels of friends' drinking. While we have predicted a reduced protective effect for ALDH2*2(+), this hypothesis is somewhat complicated by mixed evidence from other studies of environmental exposures and alcohol metabolism-related genetic effects. For example, two studies by Meyers et al. (19) and Sartor et al. (20) examined the relationship between ADH1B rs1229984 and childhood adversity. Both studies reported a significant interaction effect, but in the presence of adverse childhood events Sartor et al. (20) identified a reduced effect for the protective variant and Meyers et al. (19) found an increased effect for the risk variant. Chartier et al. (21) also showed that risk variants associated with several alcohol dehydrogenase genetic markers were strengthened under conditions of low religious involvement. Both relationships (i.e., reduced protective effect and strengthened risk effect) under more permissive or adverse conditions are plausible. There is more support for a reduced protective genetic effect from studies of ALDH2*2(+) [i.e., (18,22)].

Methods

Subjects and procedures

Subjects were a subsample from an ongoing study, addressing a range of topics pertaining to emotional and behavioral health, of students attending a public university described in Dick et al. (22). All study protocols were approved by the university's Institutional Review Board. Students consented to complete an online survey, administered through the Research Electronic Data Capture (REDCap) (23), and to provide a saliva DNA sample. A 4 ml saliva DNA sample was collected per subject in Oragene collection tubes and genotyped on the Affymetrix Biobank Version 2 Array. Alcohol use and peer drinking data for the current analysis were collected in the freshman year spring semester. Some students have completed follow-up surveys in the later years of their undergraduate studies. The year 1, spring survey time point was chosen to maximize the sample size for the analysis.

The sample ($N = 318$) was limited to subjects, ages 18–20, of East Asian ancestry who self-identified as Asian and reported consuming at least one drink in their lifetime. One hundred and ten subjects who did not meet criteria for lifetime drinking were excluded, recognizing that alcohol exposure is required to assess genetic risk or protection for alcohol use. Excluded and included subjects were not significantly different based on ALDH2*2 status, $\chi^2(1,428) = .172$, $p = .678$, age, $t(426) = −.406$, $p = .685$, or gender, $\chi^2(1, 428) = .239$, $p = .625$, but excluded students did have fewer friends who got drunk $\chi^2(4, 420) = 69.80$, $p < .001$. For example, 42.1% of those excluded from the study reported none of their friends got drunk compared to 10.9% of lifetime drinkers. Self-identified race was based on U.S. census categories, which have limited utility in genetic studies of Asians. Genetic ancestry analysis was performed using SmartPCA (Eigenstrat) and matched each DNA sample to the best fitting 1000 Genomes reference population using minimum Mahalanobis distance (24). East Asian subjects were matched with reference populations from China, Japan, or Vietnam. Individuals of South Asian descent (matched with populations from India, Pakistan, or Bangladesh) were excluded from the sample due to the limited number who carried the ALDH2*2(+) allele (< 5%; $n = 8$).

Measures

ALDH2*2 status

Due to the infrequency of carrying the homozygous ALDH2*2/*2 genotype ($n = 11$ in the current sample) and congruent with previous ALDH2*2 alcohol studies (25), variants at rs671 were coded to compare subjects who carried the ALDH2*2/*2 or ALDH2*1/*2 (A/A or A/G) genotypes with those who carried the ALDH2*1/*1 (G/G) genotype. As described in the introduction, we refer to these two groups, respectively, as ALDH2*2(+) ($n = 103$; coded 0) and ALDH2*2(−) ($n = 215$; coded 1).

Alcohol consumption

Standard grams of ethanol consumed per month measures alcohol consumption, calculated from students' reported frequency and quantity of drinking. Subjects reported how often they have a drink containing alcohol using the following categories: 0 = never; 1 = monthly or less; 2 = 2 to 4 times a month; 3 = 2 to 3 times a week; and 4 = 4 or more times a week. Subsequently, they reported how many drinks containing alcohol they have on a typical day when drinking, from: 0 = 0 drinks; 1 = 1–2; 3 = 3–4; 4 = 5–6; 5 = 7–9; and 6 = 10 or more drinks. Midpoints were set for each frequency and quantity category and multiplied by 14 (i.e., Frequency × Quantity × 14) (26). One drink was equivalent to 14 grams of ethanol consumed (27). The frequency midpoints (shown in parenthesis), based on a month with 30 days, were never (0), monthly or less (0.5), 2 to 4 times a month (3), 2 to 3 times a week (10.7), and 4 or more times a week (23.54). The quantity midpoints (shown in parentheses) were 1–2 (1.5), 3–4 (3.5), 5–6 (5.5), 7–9 (8), and 10 or more (15.5) (27).

Peer drunkenness

Drinking in each subject's peer group was assessed over the last 12 months by asking "how many of your friends", and friends were defined as those "you have seen regularly and spent time within school or outside of school", have "got drunk" (0 = none; 1 = a few; 2 = some; 3 = most; and 4 = all). Observations of drunken behavior by peers can be vivid and easy to remember and, moreover, can have significant influence on the perceived permissive of drinking norms among college students (28).

Analysis

All analyses were conducted using SPSS 23. Descriptive analyses included bivariate comparisons for ALDH2*2 status with age, gender, alcohol consumption, and peer drunkenness, using the chi-square statistic or t-test, respectively, for categorical and continuous variables.

Multivariate models were tested using a general linear model (GLM) approach, and because the assumption of equal variances was not met, bootstrapping with replacement for 1000 samples was used to derive robust estimates of standard errors and p-values. Interaction effects are susceptible to distributional problems in the data and unequal error variance (29).

We first tested the main effects of ALDH2*2 status and peer drunkenness, controlling for gender and age. The interaction model included these same variables, plus the cross-product term for ALDH2*2 status × peer drunkenness. The interaction was tested for a significant departure from additivity. To assess the robustness of the hypothesized interaction effect, the interaction model was rerun to control all other relevant interactions, i.e., age × ALDH2 status; gender × ALDH2 status; age × peer drunkenness; and gender × peer drunkenness (30). Plots of raw data were constructed to assist in the interpretation of the ALDH2*2 status × peer drunkenness interaction. Post hoc comparisons, using GLM with bootstrapping, evaluated mean differences for alcohol consumption by ALDH2*2 status within each level of peer drunkenness.

Results

Sample characteristics

In this sample of East Asian college students, subjects were majority female (63.25%) and on average $M = 19.01$ ($SD = .421$) years old. The bivariate associations between ALDH2*2 status and other study variables are presented in Table 1. There were no associations with subject age, $t(316) = -0.12$, $p = .906$, or gender, $\chi^2(1, 318) = 0.89$, $p = .902$. Subjects who carried the ALDH2*2(+) allele drank less alcohol, $t(281.28) = -3.94$, $p < .001$, than those who carried the ALDH2*2(−) genotype. There was no relationship between ALDH2*2 status and peer drunkenness, $\chi^2(4, 313) = 6.65$, $p = .155$. About 44% of subjects reported that most or all of their friends got drunk. Because ALDH2*2/*2 carriers are more sensitive to alcohol (31,32), differences between ALDH2*2/*2 and ALDH2*1/*2 were also evaluated. The two genotypes were similar ($p > .05$) on all study variables, including alcohol consumption, $t(97) = -1.04$, $p = .300$, and number of friends who got drunk, $\chi^2(4, 100) = 1.81$, $p = .771$.

Tests of main effects for ALDH2*2 status and peer drunkenness

Table 2 shows the results of the main effects and interaction models for predicting standard grams of ethanol per month, controlling for age and gender. In the main effect model, ALDH2*2(+) was statistically significant

Table 1. Describing the sample of East Asian college student drinkers.

		Genotypes		
	Total M (SD) or %	ALDH2*2(+) M (SD) or %	ALDH2*2(−) M (SD) or %	
	N = 318	n = 103	n = 215	p
Age	19.06 (0.421)	19.01 (0.373)	19.02 (0.444)	.906
Gender (female)	63.52	64.08	63.26	.887
Standard grams of ethanol per month	153.38 (325.83)	71.96 (153.06)	194.71 (378.69)	**<.001***
Peers who got drunk				.155
None	10.86	15.00	08.92	
A few	22.36	20.00	23.47	
Some	26.20	32.00	23.47	
Most	31.63	26.00	34.27	
All	08.95	07.00	09.86	

Notes: Statistics are mean (standard deviation) or percentage; *t statistic not assuming equal variances was computed; significant p-values <.05 appear in **bold**.

Table 2. Main effects and interaction models* predicting standard grams of ethanol per month.

	Main effects model		Interaction model	
	B (SE)	p	B (SE)	p
ALDH2*2(+)	−102.46 (28.96)	**.005**	131.92 (68.15)	.066
Peers who got drunk	98.46 (17.86)	**.001**	124.78 (24.34)	**.001**
Peers × ALDH2*2	–	–	−78.63 (27.42)	**.012**

Notes: All models controlled for age and gender; *bootstrapping procedures were used to obtain robust standard errors and p-values; significant p-values <.05 appear in **bold**.

and predicted reduced alcohol use ($B = -102.46$, $SE = 28.96$, and $p = .005$), while having more friends who got drunk was associated with increased use ($B = 98.46$, $SE = 17.86$, and $p = .001$).

Tests of the ALDH2*2 × peer drunkenness interaction

The interaction term for ALDH2*2 status and peer drunkenness was statistically significant ($B = -78.63$, $SE = 27.42$, and $p = .012$) (see Table 2). Moreover, this interaction was robust and remained significant after all other interactions were controlled for in the model ($B = -85.77$, $SE = 28.12$, and $p = .004$). Figure 1 presents mean standard grams of ethanol per month by ALDH2*2 status and peer drunkenness. The plot shows a positive association between peer drunkenness and alcohol use for both ALDH2*2(−) and ALDH2*2 (+). However, the slope for this association was significantly steeper for ALDH2*2(−) than for ALDH2*2(+). The plot also appears to show a leveling off of alcohol use for ALDH2*2(+) carriers at the highest or "all" level of peer drunkenness.

Post hoc comparisons, with bootstrap confidence intervals (bCI), showed that ALDH2*2(−) carriers ($M = 73.15$, $SD = 204.85$) drank significantly more alcohol than ALDH2*2(+) carriers ($M = 7.92$, $SD = 109.93$) at the "a few" peers got drunk level, 95% bCI [15.80, 126.62]. The mean difference between ALDH2*2(−) and ALDH2*2(+)

carriers at the "all" peers got drunk level was also significant, but markedly larger (respectively, $M = 538.56$, $SD = 598.30$ and $M = 134.00$, $SD = 192.24$), 95% bCI [106.77, 744.01]. Mean differences at the other levels of peer drunkenness were not significantly different, including "none" (ALDH2*2(−): $M = 8.85$, $SD = 11.21$; ALDH2*2(+): $M = 27.75$, $SD = 88.87$; 95% bCI −75.86, 9.52), "some" (ALDH2*2(−): $M = 112.86$, $SD = 144.70$; ALDH2*2(+) $M = 58.01$, $SD = 104.30$; 95% bCI −4.76, 112.87), and "most" (ALDH2*2(−): $M = 292.41$, $SD = 468.43$; ALDH2*2(+) $M = 152.96$, $SD = 235.24$; 95% bCI −14.26, 287.82).

Discussion

This analysis examined the relationships between ALDH2*2 status and peer drunkenness in association with alcohol consumption in East Asian college students. We reported findings consistent with earlier studies in Asian samples that ALDH2*2(−) and greater peer alcohol use were associated with drinking more alcohol (7,12,13). Although, the Luczak et al. (25) study of college-attending Asians found that ALDH2*2(+) and ALDH2*2(−) carriers were not different in terms of their frequency and quantity of drinking, but reported different levels—lower for ALDH2*2(+)—of binge drinking (4 drinks or more for women, 5 drinks or more for men). Our hypothesis for an interaction between ADLH2*2 and friends' drinking, i.e., a reduced protective effect for ALDH2*2(+) with increased peer drunkenness, was not supported. We instead identified a strengthened risk effect for ALDH2*2 (−) with having more friends who got drunk. However, it is notable that some ALDH2*2(+) carriers reported consuming higher amounts of ethanol per month ($M = 152.96$ and 134.00, respectively, at the most and all friends got drunk levels). Even light drinking levels for this group could have the potential for later health consequences because of the association between acetaldehyde (a toxin) and esophageal cancer (33). It is likely, based on earlier studies, that these
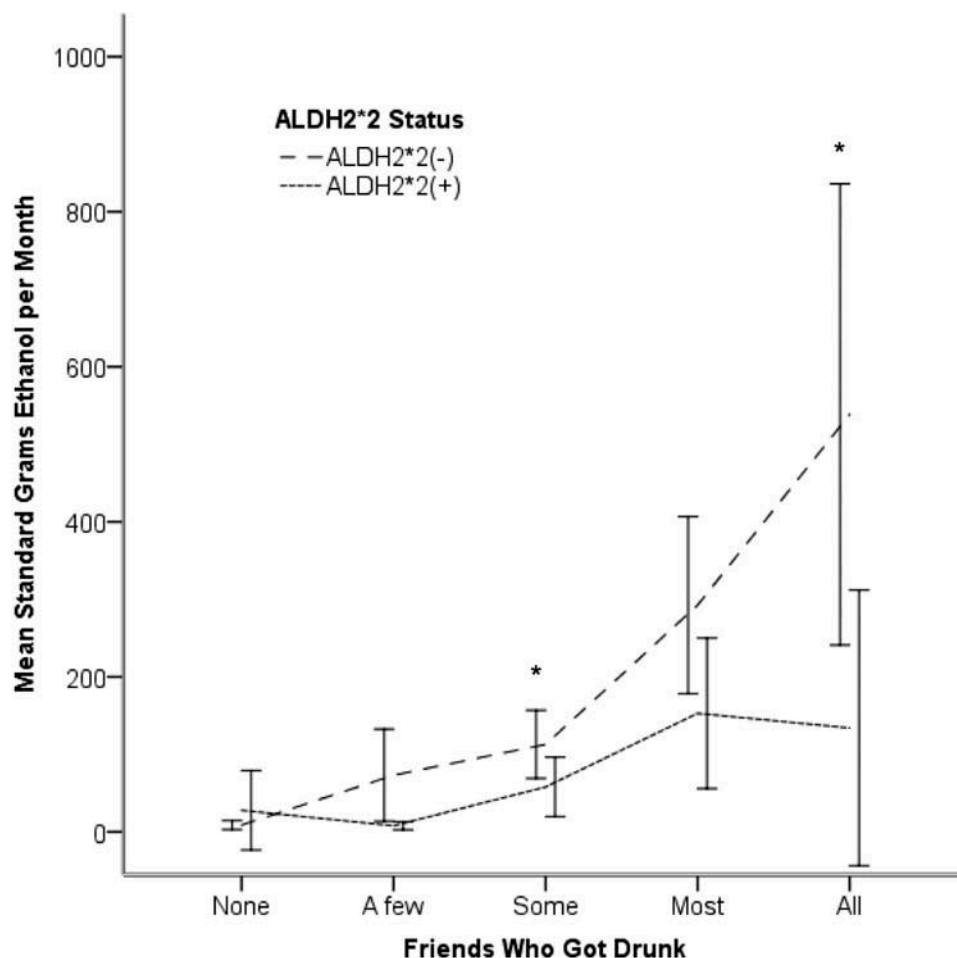
Figure 1 Plots are mean standard grams of ethanol consumed per month and 95% confidence intervals by ALDH2*2 status and number of friends who got drunk. Bootstrap post hoc tests evaluated mean differences within each level of peer drunkenness. Significant differences at p < .05 are marked * with an asterisk

students are not drinking one drink nightly over the month but instead are drinking at higher rates during the weekend or other social engagements (28,34).

Olfson et al. (17) previously reported that having most or all friends who drink was associated with a weakened protective effect at *ADH1B* in predicting two different drinking outcomes. This is partly consistent with our finding; we similarly found that the association between *ALDH2*2* status and alcohol consumption varied with more exposure to peer drinking. An elevated level of peer drinking is apt to enable a more permissible environment for drinking (11). Ham and Hope (34) identified higher perceived drinking norms and increased alcohol availability as factors that facilitate drinking in college settings. Drunken behavior among college students is often memorable and subsequently talked about with friends, which can inflate drinking norms (28). For the current study, students' reporting that all their friends got drunk indicated a particularly high risk drinking environment. It is not clear what about the all peer drunkenness level was different from the most peer drunkenness level. There was a lot of

variability in the amount of ethanol that students reported consuming at the "most" and "all" levels, but the mean difference in consumption between *ALDH2*2(−)* and *ALDH2*2(+)* carriers was larger at the "all" peers level. Relative to white college students, Asian-American students are low risk drinkers (1,2). It is possible that this highly saturated (all peers) drinking environment was needed to weaken important social factors (e.g., sense of family obligation, parental disapproval of drinking, and gender norms) that are protective against drinking (35,36).

However, we observed a different *type* of interaction effect than that reported by Olfson et al. (17). We found that the *ALDH2*2(−)* risk effect was stronger, not that the *ALDH2*2(+)* protective effect was weaker, with higher levels of peer drunkenness. This may not be surprising given the results from gene-by-environment studies of the *ADH1B* rs1229984 marker, showing both weakened protective effects (17,20) and strengthened risk effects (19,21) under more permissive or adverse conditions. Yet, prior evidence from studies of *ALDH2*2* provides more

support for a reduced protective effect under more permissive environmental conditions for drinking or with increased access to alcohol (e.g., when parents or older siblings had alcohol problems there was a reduction in the protective effect for ALDH2*2) (18,37). Our study findings suggest that, like AHD1B, the interrelationships between ALDH2*2 status, alcohol consumption, and environmental exposures may be more complex.

One plausible explanation for the current study's strengthened risk effect, as compared to earlier ALDH2*2 studies' reduced protective effect, may be related to our environmental condition of peer drunkenness. For example, while ALDH2*2(−) carriers may be more susceptible to the permissive norms for drinking associated with higher levels of peer drunkenness in college settings, ALDH2*2(+) carriers may be less so because of the negative consequences of drunken behavior, which can include students vomiting or passing out in public places (28). ADLH2*2(+) carriers may be more deterred by these instances, as the protective effects of ALHD2*2(+) in reducing drinking include such adverse reactions as nausea and drowsiness that can, for some individuals, occur after only 1 to 2 drinks (31,32). Seemingly in support of this, Hendershot et al. (38) found that carriers of ALDH2*2(+) report higher negative alcohol expectancies and physiological expectancies such as dizziness and nausea compared to carriers of ADLH2*2(−). Alternatively, Irons et al. (18) reported developmental changes in the protective effect of ALDH2*2(+), which increased in size between mid-adolescence and early adulthood and reached a moderate effect size at age 22. It could be that the age of our sample (M = 19) limited our ability to detect the expected decrease in the protective effect. Luczak et al. (25) reported increased alcohol consumption and related problems over the college-years for Asian students; larger increases were observed for those with ALDH2*2(−) than with ALDH2*2(+).

Overall, this college student survey provided a strong dataset for the analysis with the availability of genetic, phenotypic, and environmental variables. We selected a genetic marker (ALDH2 rs671) and environmental effect (a measure of peer alcohol use) with strong empirical evidence and, respectively, biological and theoretical relevance (39). In our analyses we attempted to rule out potential confounders, including by controlling for all relevant gene × covariate and environment × covariate interactions (30) and by testing for gene–environment correlation (rGE) (39). Similar to the Irons et al. (18) study, we found no rGE between ALDH2*2 status and our measure of the peer environment. Genetic susceptibility for substance use and peer selection are correlated, but likely attributed to other genes than those for alcohol metabolism (40,41). For example, Chassin et al. (42) and Mrug and

Windle (43), respectively, studied dopamine receptor (DRD4) and μ-opioid receptor M1 (OPRM1) genes in association with alcohol use behaviors and found evidence for both genetically influenced peer selection and gene–environment interaction. These interactions, as with the current study, showed stronger risk allele effects with greater peer influences.

Several limitations for the study should be stated. These results may not generalize to the full Asian-American college population, including non-drinkers who were excluded from the current study. The low frequency of ALDH2*2/*2 (n = 11) precluded us from analyzing differences across genotypes. Individuals with ALDH2*2/*2 can experience a more intense alcohol-related flushing response (31,32), which may deter them more from consuming alcohol than ALHD2*1/*2 carriers. Although in the current sample, students with ALDH2*2/*2 and ALDH2*1/*2 reported similar amounts of ethanol consumed and numbers of peers who got drunk. Additionally, follow-up surveys for the larger study of college students are still ongoing and precluded us from examining the developmental effects of ALDH2*2 status (e.g., Irons et al. (18)) and peer drinking in this Asian subsample. We were also unable to examine some other factors that have been shown to contribute to drinking in Asians, including ethnic subgroup differences in alcohol use. The study data did not measure self-identified race/ethnicity below the major U.S. census categories. Some East Asian ethnic groups such as Japanese and Filipino are more likely to engage in heavy drinking (9). Luczak et al. (44) also reported differences in both drinking and ALDH2*2 frequency counts between Korean and Chinese college students.

Several future areas of research could extend the current study's findings and help identify targets, such as behavioral and cultural mechanisms, for prevention interventions to reduce risky drinking in Asian college students. Asian Americans are generally known to have high rates of abstinence and to be low-risk drinkers (45); however, this study identified two relatively small but risky drinking subgroups. The first included ALDH2*2(−) carriers who were highly exposed to their peers' alcohol use, and the second included ALDH2*2(+) carriers who, while they could be defined as light drinkers, are still at a greater risk for some cancers. The risky drinking level of these ALDH2*2(+) carriers may be related to social media reports about the use of over-the-counter medications to dampen the flushing reaction in order to continue drinking (33), as well as the perception by some Asian college students, especially among males, that the flushing reaction provides no special warning about how much they should drink (46). Risky drinking levels for ALDH2*2(−) carriers may point to a weakening of known cultural protections against drinking for Asian-American youth at this high

level of peer drunkenness (35,36). The use of over-the-counter medications for this purpose, students' perceptions about whether the flushing response means they should stop or slow their drinking, and cultural factors could be examined. Negative alcohol expectancies and physiological consequences could also be evaluated as possible mediators for the observed interaction between *ALDH2**2 status and alcohol consumption (38). This might help explain why *ALDH2**2(−) had a stronger relationship than *ALDH2**2 (+) with alcohol consumption under the condition of having more friends who got drunk.

Conclusion

The current study examined the interrelationships between *ALDH2* rs671, perceptions of friends' drunken behavior, and alcohol use in East Asian college drinkers. We identified a gene-by-environment interaction in predicting alcohol consumption. We showed that the *ALDH2**2(−) risk effect was strengthened compared to the *ALDH2**2(+) protective effect with greater exposure to friends' drinking, particularly at the highest level of peer drunkenness. This interaction was robust to other explanations, including rGE and other interaction effects, but suggests that the relationship between *ALDH2**2 and drinking is more complex than we hypothesized.

Acknowledgments

Declaration of interest

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