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Effects of *ALDH2*2* on Alcohol Problem Trajectories of Asian American College Students

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Abstract

The variant aldehyde dehydrogenase allele, *ALDH2*2*, consistently has been associated with protection against alcohol dependence, but the mechanism underlying this process is not known. This study examined growth trajectories of alcohol consumption (frequency, average quantity, binge drinking, maximum drinks) and problems over the college years and then tested whether the *ALDH2* genotype mediated or moderated the relationship between alcohol consumption and problems. Asian American college students (N = 433) reported on their drinking behavior in their first year of college and then annually for 3 consecutive years. Alcohol consumption and problems increased over the college years for both those with and without *ALDH2*2*, but having an *ALDH2*2* allele was associated with less of an increase in problems over time. A mediation model was supported, with *ALDH2*2* group differences in problems fully accounted for by differences in frequency of binge drinking. Findings also supported a moderation hypothesis: All four alcohol consumption variables were significant predictors of subsequent alcohol problems, but these relationships were not as strong in those with *ALDH2*2* as in those without *ALDH2*2*. Our findings suggest that the interplay between *ALDH2*2* and drinking-related problems is complex, involving both mediation and moderation processes that reduce the likelihood of developing

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problems via reduction of heavy drinking as well as by altering the relationship between alcohol consumption and problems. Results of this longitudinal study provide evidence that what seems like a relatively straightforward effect of a diminished ability to metabolize alcohol on drinking behavior is actually dependent on behavior and developmental stage.

Keywords

ALDH2; Asian American college students; growth models; mediation; moderation

In the United States, alcohol use typically begins in mid-adolescence, with consumption increasing throughout the teenage years and peaking in the early 20s (Faden, 2006; Moore et al., 2005; Sher, Grekin, & Williams, 2005). Twin studies have found both genetic and environmental factors contribute to differences in alcohol consumption patterns and risk of developing drinking problems (see Dick, Prescott, & McGue, 2009, and Young-Wolff, Enoch, & Prescott, 2011, for reviews). The influence of genetic factors on alcohol involvement also has been shown for specific genetic variants, with the association of genes and alcohol involvement becoming stronger over the course of adolescence and young adulthood as alcohol consumption increases (e.g., Dick et al., 2006; Doran, Myers, Luczak, Carr, & Wall, 2007; Irons, Iacono, Oetting, & McGue, 2012). Differences in the strength of the relationship between genetic factors and alcohol involvement across adolescence and young adulthood highlight the importance of studying genetic risk factors within a developmental framework (see Rose, 1998).

One of the three major theoretical models for the development of alcohol dependence is the pharmacological vulnerability model (see Sher, 1991). The pharmacological vulnerability model posits that there are individual differences in sensitivity to the reinforcing and punishing effects of alcohol that ultimately lead to differences in alcohol problems and dependence. This model arose out of findings from twin studies that level of response to alcohol is genetically influenced (see Heath et al., 1999), as well as findings that children of alcoholics are generally less sensitive to the effects of alcohol than children of non-alcoholics (see Schuckit et al., 2005).

There has been considerable research aimed toward identifying genes that underlie pharmacological vulnerability for alcohol problems, including those that affect the alcohol metabolizing enzymes (Schuckit et al., 2005). The *ALDH2* gene (*rs671*), located on chromosome 12 (12q24.2), consistently has been associated with differential risk for alcohol dependence (Li, 2000; Luczak, Glatt, & Wall, 2006). *ALDH2* is polymorphic with two allele types, the common wild type allele *ALDH2*1* (**Glu487*), and the variant *ALDH2*2* (**Lys487*). *ALDH2*2* is present in about one third to one half of individuals of northeast Asian origin, but is extremely rare among individuals of non-Asian heritage (Goedde et al., 1992; see Eng, Luczak, & Wall, 2007, for review in Asians). Although this genetic variant is largely limited to Asian populations, it is estimated that there are at least 540 million individuals in the world (8% of the population) with an *ALDH2*2* allele (Brooks, Enoch, Goldman, Li, & Yokoyama, 2009).

The *ALDH2*2* allele encodes a deficient protein subunit of the ALDH2 enzyme; this enzyme is primarily responsible for the conversion of acetaldehyde into acetate during alcohol metabolism. Alcohol challenge studies consistently have demonstrated that *ALDH2*2* produces elevated levels of acetaldehyde during alcohol metabolism (Enomoto, Takase, Yasuhara, & Takada, 1991; Peng et al., 1999; Wall et al., 1997), which has been associated with stronger subjective and objective responses to alcohol (Luu et al., 1995; Shibuya, Yasunami, & Yoshida, 1989;Wall et al., 1997). Because of these heightened reactions to alcohol, individuals with *ALDH2*2* are expected to have lower levels of alcohol consumption and reduced likelihood of heavy drinking compared with individuals without *ALDH2*2*, which in turn is thought to lower the likelihood of developing alcohol problems and disorders (see Wall, 2005).

Results from previous cross-sectional studies indicate possession of an *ALDH2*2* allele is associated with lower likelihood of being a regular drinker, lower quantity and frequency of alcohol use, less frequent heavy episodic (binge) drinking, and lower maximum number of drinks consumed in a 24-hr period in both men and women (Higuchi, Matsushita, Muramatsu, Murayama, & Hayashida, 1996; Luczak, Wall, Shea, Byun, & Carr, 2001; Takeshita & Morimoto, 1999; Wall, Shea, Chan, & Carr, 2001). Possession of an *ALDH2*2* allele also has been associated with lower levels of self-reported alcohol-related problems (Hendershot et al., 2009; Luczak, Shea, et al., 2006) and alcohol dependence (Luczak, Glatt, et al., 2006). Individuals with *ALDH2*2*, however, expect to have more severe hangover symptoms from the same amount of alcohol and are more likely to report hangovers after consuming lower amounts, suggesting that lower doses of alcohol may lead to negative drinking consequences in those with *ALDH2*2* (Wall, Horn, Johnson, Smith, & Carr, 2000; Yokoyama et al., 2005). Consistent with this idea, there is evidence that individuals with *ALDH2*2* who develop alcohol dependence do so at lower levels of alcohol intake (Iwahashi, Matsuo, Suwaki, Nakamura, & Ichikawa, 1995). Reports of three cases with *ALDH2*2/*2* genotype indicate these individuals each developed alcohol dependence through a low-quantity, high-frequency pattern of consumption (Chen et al., 1999; Luczak, Wall, Cook, Shea, & Carr, 2004).

It is also important to note that individuals with *ALDH2*2* are more vulnerable to certain alcohol-related pathologies, including head and neck cancers and alcoholic liver disease (Brennan et al., 2004; Zintzaras, Stefanidis, Santos, & Vidal, 2006). Thus, the influence of *ALDH2*2* may vary across progression of alcohol involvement and be protective at one stage of alcohol use (e.g., the progression to heavy drinking), but be a risk factor at another stage (e.g., the progression to alcohol-related medical problems).

In addition to *ALDH2*2* being differentially associated with various alcohol outcome measures over developmental periods, the effect of *ALDH2*2* has also been shown to vary for the same alcohol measure across contexts. This was first demonstrated by Higuchi et al. (1994), who reported that the percentage of Japanese individuals in treatment for alcohol dependence who had an *ALDH2*2* allele increased from 3% in 1979 to 8% in 1986 to 13% in 1992. During this time period, the rates of per capita alcohol consumption in Japan also increased. The authors concluded that the increased cultural acceptance of alcohol

consumption coupled with increased social pressure for men to drink after work reduced the protective effect of the *ALDH2*2* allele over this period of time.

These findings suggest that environmental factors, in addition to developmental factors, can moderate the effects of *ALDH2*2* on alcohol involvement. In this way, *ALDH2* provides a model system for examining the nature of gene-environment interplay over development (Irons et al., 2012). The current study prospectively follows college students in a high-risk environment (i.e., college; Slutske et al., 2004) during the age range in the United States when regular drinking typically begins through when it typically peaks. Evidence from this developmental period can help provide a more complete understanding of the influence of *ALDH2* on the emergence and progression of drinking behavior. More broadly, through mediational and moderational models of gene and environment effects, it can shed light on how variation in a specific gene gives rise to differential progression of a complex, genetically-influenced behavior.

The goal of the current study is to examine the relationships of *ALDH2*2* with alcohol consumption and alcohol-related problems, two intermediate phenotypes in the hypothesized mechanistic pathway between *ALDH2*2* and decreased likelihood of alcohol dependence. Our two previous studies of the current sample focused on binge drinking during the first 2 years of college (Doran et al., 2007; Hendershot, MacPherson, Myers, Carr, & Wall, 2005). In the first year of college, we found that *ALDH2*2* was not associated with onset of drinking or with rates of binge drinking (Hendershot et al., 2005). Individuals with *ALDH2*2*, however, were less likely to progress to binge drinking in their second year of college than those without *ALDH2*2* (Doran et al., 2007).

The current study was designed to extend these findings by examining the influence of *ALDH2*2* on longitudinal trajectories of alcohol consumption and drinking-related problems over 4 years of college. We first present longitudinal models that individually examine trajectories of four different aspects of consumption (drinking frequency, average quantity, frequency of binge drinking, and maximum number of drinks in a 24-hr period) and a composite measure of alcohol-related problems. We examine how *ALDH2*2* relates to each of these alcohol outcomes across the 4 years of college. We expect the different binge drinking trajectories associated with *ALDH2*2* that emerged in the second year of college (Doran et al., 2007) to continue to diverge over 4 years of college. We further hypothesize that larger differences will be found across *ALDH2*2* groups on measures of heavy consumption (e.g., binge drinking, maximum drinks consumed in 24 hrs) than on measures of drinking frequency and average quantity, which should be less affected by rate of metabolizing alcohol.

We then test models for different mechanisms explaining the associations among alcohol consumption, *ALDH2*2*, and alcohol-related problems. We test a mediation hypothesis: that *ALDH2*2* leads to lower levels of problems because it reduces alcohol consumption; i.e., the primary effect of *ALDH2*2* is on alcohol consumption levels, which in turn leads to lower alcohol problems. We also test a moderation hypothesis: that *ALDH2*2* alters the relationship of alcohol consumption with alcohol problems; i.e., the same level of

consumption is related to greater problems in those with *ALDH2*2* alleles. These processes are not mutually exclusive, so it is possible that both occur.

Method

Participants

Data were from a sample of 433 Chinese- and Korean-American undergraduates attending a public university in California who were recruited for participation during their first year in college. Participants were recruited by fliers on campus and advertisements in the school newspaper; to reduce bias, these materials did not state the study focused on substance use. Individuals were screened for being 18 or 19 years old and for having all four grandparents of full Chinese or Korean heritage. Participants provided written informed consent at the initial interview for participating in a longitudinal study of risk and protective factors for substance use.

In the analyses, we excluded 18 individuals (8 Chinese Americans and 10 Korean Americans) who did not report having consumed alcohol by the end of their participation in the study. We also removed one participant whose genotype was not determined. This resulted in a sample of 414 participants, which consisted of 107 Chinese American females, 108 Chinese American males, 103 Korean American females, and 96 Korean American males. At initial enrollment, 352 (85%) of the participants were 18 years old and 62 (15%) were 19 years old. Of these 414 participants, we assessed 97% at Time 2, 84% at Time 3, and 82% at Time 4. Analyses indicated that the 13% attrition from Time 2 to Time 3 was not related to genotype or any of the alcohol consumption or problem variables; instead, this attrition was more likely due to students studying abroad in their latter years of college.

Procedure

Data for the present study are from four assessment occasions. The first assessment was conducted during the beginning of the first year in college; the other three assessments were conducted at the end of the second, third, and fourth school years, resulting in the first two assessments being on average 17 months apart and subsequent assessments being on average 12 months apart. Trained research assistants conducted all interviews and participants completed self-report questionnaires on computers. At baseline, participants also provided blood samples via fingertip puncture for determination of *ALDH2* genotypes.

Measures

At each assessment point, we used the Time-Line Follow-Back procedure (TLFB; Sobell & Sobell, 1992) to assess alcohol use over the previous 90 days. This measure has been shown to have good reliability and validity when applied to college student drinking (Sobell, Sobell, Leo, & Cancilla, 1988). From this measure, we coded four commonly used alcohol consumption variables for the past 90 days: frequency of drinking days (Frequency); average number of standard drinks (e.g., 12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits) consumed per drinking episode (Quantity); frequency of heavy drinking episodes, defined as four or more drinks for women and five or more drinks for men in a 24-hr period (Binge; Wechsler, Dowdall, Davenport, & Rimm, 1995); and maximum number of drinks

consumed in a 24-hr period (Max24). We used data from 1,507 TLFBs in our analyses; 28 TLFBs (1.8%) were incomplete and thus were excluded from the analyses.

Participants also completed the Young Adult Alcohol Problems Screening Test (YAAPST; Hurlbut & Sher, 1992), a 27-item self-report measure of alcohol problems that was developed in a college setting. The YAAPST has been shown to possess good reliability and satisfactory validity (Hurlbut & Sher, 1992) and was scored using the standard weighted scoring system for past-year problem severity (Problems). Eight relatively common consequences (e.g., hangover, problems at work or school) were scored using nine categories from 0 times to 40+ times in the past year; 12 less typical problems (e.g., others complained about your drinking, arrested for drunk driving) were rated using four categories from 0 to 3+ times in the past year; and seven items indicative of greater problem severity (e.g., ever felt dependent on alcohol, attended AA meeting) were rated dichotomously for having occurred in the past year.

The YAAPST was completed by lifetime drinkers (i.e., those who had ever consumed more than a sip of alcohol) at each assessment time, resulting in a total of 1,518 usable scores; of these, 20 had one missing item and two had two missing items, which were replaced with the mean of the other items. Nineteen additional YAAPST measures that had three or more missing items were excluded from the analyses. Internal consistency of the YAAPST was good in our sample, with Cronbach's alphas of .84, .87, .87, and .86 at the four assessments. Consistent with previous studies, factor analyses and scree plots of our data indicated the YAAPST measured a single construct.

ALDH2 genotyping was conducted at the Alcohol Research Center at Indiana University using polymerase chain reaction and allele-specific oligonucleotide probes (Crabb, Edenberg, Bosron, & Li, 1989). *ALDH2* genotype was determined to be *ALDH2*1/*1* for 113 (51%) Chinese and 141 (68%) Koreans, *ALDH2*1/*2* for 95 (43%) Chinese and 65 (31%) Koreans, and *ALDH2*2/*2* for 15 (7%) Chinese and 3 (1%) Koreans. These genotype distributions were in Hardy-Weinberg equilibrium ($\chi^2 = 0.70$, $p = .40$ for Chinese, $\chi^2 = 2.21$, $p = .14$ for Koreans), indicating that there was no sample-selection bias for the *ALDH2* gene.

Analyses

Variables used in the models—Given the infrequency of possessing two *ALDH2*2* alleles ($n = 17$) and consistent with prior studies of the effects of *ALDH2*2* on alcohol behavior, we combined individuals with one or two *ALDH2*2* alleles into one group, referred to as *ALDH2*2*(+). The remaining individuals without an *ALDH2*2* allele are referred to as *ALDH2*2*(−). The correlations between consumption variables and Problems were very similar whether those with two *ALDH2*2* alleles were included or excluded from the *ALDH2*2*(+) group (i.e., no correlation differed more than .02 with and without these individuals in the group).

As is common in studies of alcohol consumption, all measures had substantial positive skew, so were square-root transformed prior to analysis. After these transformations, skew statistics were less than |1.5| and kurtosis statistics were less than |2.5| for all consumption variables. We also tested whether the consumption variables could be combined into a single

latent construct that would represent drinking over time. Recognizing that Frequency is distinct from the other consumption variables, which are more specific to heavy drinking, we tested for invariance of a three-indicator factor (excluding Frequency) over time in each *ALDH2*2* group. Measurement invariance over time was supported in the *ALDH2*2*(−) group, $\chi^2(6, 244) = 7.8$, $p = .26$, but not in the *ALDH2*2*(+) group, $\chi^2(6, 171) = 35.7$, $p < .001$. Because of these differences in the interrelationships of the consumption variables over time in the *ALDH2*2*(+) group, our models include each consumption variable separately rather than as part of a factor.

Trajectories of alcohol consumption and Problems over time—We estimated trajectories of each alcohol involvement variable across *ALDH2*2* groups using latent growth models (LGMs). The LGM framework allowed us to estimate each parameter separately in *ALDH2*2* groups, providing flexibility for testing hypotheses about group differences. These models included a latent intercept factor and a linear slope factor. (We also estimated quadratic change models, but found near-0 means and variances for the quadratic growth factors for all outcomes, so we present results from the linear growth models only.) The loadings for the linear growth factor were fixed to be proportional to the intervals at which data were collected (0, 17, 29, 41 months). As is standard, the groups were allowed to vary on remaining parameters, including variation in level, variation in slope, level-slope correlation, and residual variance.

Multilevel models using alcohol consumption to predict Problems—We utilized multilevel structural equation models (MSEMs) to examine the effects of *ALDH2*2* on the relationship between alcohol consumption and Problems (Preacher, Wichman, MacCallum, & Briggs, 2008; Preacher, Zyphur, & Zhang, 2010). The MSEM approach enabled us to model individual differences and *ALDH2*2* group differences in the average level of each variable, variation across time, and in the consumption-Problems regression. MSEM makes it possible not only to model random slope (which is also possible in traditional multilevel modeling), but also to allow random slope to covary with other parameters or differ across groups in the model, which is not possible in traditional multilevel modeling. We took advantage of this benefit of MSEM to investigate how the within-person association between alcohol consumption and Problems differed among persons in each *ALDH2*2* group. Our MSEM models had two levels: Level 1 included repeated measures of consumption and Problems, which were nested within individuals (Level 2). This version of MSEM does not explicitly structure growth; the repeated observations are simply time points nested within persons. Thus, we additionally used time dummy variables to capture systematic effects of time on level of consumption and Problems.

Because alcohol consumption and Problems were assessed simultaneously, we used the previous time point (*t*-1) of consumption to predict Problems; for example, consumption reported at Time 1 was used to predict Problems at Time 2. Thus, our analyses used consumption data at Times 1, 2, and 3 and Problems data at Times 2, 3, and 4. The analyses excluded Time 1 Problems data because Time 1 lagged consumption data were not available, and excluded Time 4 consumption data because Time 5 Problems data were not available.

We assessed relative goodness of fit of non-nested MSEMs using Akaike Information Criterion (AIC) fit statistics, for which a smaller number reflects a better fit. For nested models, we utilized the Wald test, which produces a chi-square statistic associated with restricting parameters in the model. The Wald test can be useful when the estimation method (here, maximum likelihood with robust standard errors) precludes the assumption of a normally-distributed traditional chi-square test (Muthén & Muthén, 1998-2012). In our models, a significant Wald statistic reflected significant reduction in model fit due to constraining parameters across *ALDH2*2* groups.

Mediation—We tested mediation of the relationship between *ALDH2*2* and Problems by consumption using a series of 2-1-1 MSEM models (Preacher et al., 2008; 2010). The 2-1-1 model indicates that the structure operates from a Level-2, or person-level variable (*ALDH2*2* group), to a Level-1 variable measured at multiple time points for each person (consumption) to another Level-1 variable measured at multiple time points for each person (Problems). In these models, person-level averages of consumption and Problems are modeled explicitly as between effects. Because the predictor in the chain of effects (*ALDH2*2*) varies at the person level only, any variance in Problems that is explained through the association of *ALDH2*2* with consumption in these models is contained entirely at the person level.

The mediation of *ALDH2*2* and Problems by consumption was assessed for each consumption variable separately to reveal unique effects and avoid issues of multicolinearity. For each variable, we first tested whether there was significant variance of the slope between the consumption variable and Problems across persons. For the consumption variables for which we did not find significant variance of the slope across persons (Quantity, Max24), no random slope parameter was included in subsequent models. For the consumption variables for which we did find significant variance of the slope across persons (Frequency, Binge), a random slope parameter was included. In the two models with a random slope parameter, we regressed this random slope parameter on *ALDH2*2* group to examine how the heterogeneity of this slope depended on *ALDH2*2* group.

Mediation was indicated by 1) a significant drop in the direct effect of *ALDH2*2* on Problems (the *c* path) at the person level when the consumption mediator was added to the model, and 2) a significant *a*b* indirect path. In these models, *a* is the effect of *ALDH2*2* on the person-specific average consumption score across time points, and *b* is the effect of consumption on Problems at the between-person level. In the models with constant slopes, *b* is simply the effect of consumption on Problems as modeled at the between level. In the models with random slopes, *b* is the sum of the effect of consumption on Problems as modeled at the between level (as in the constant slopes models) plus the mean random slope between consumption and Problems.

Because the standard error for an indirect effect can be biased if its sampling distribution is not symmetric (Preacher et al., 2010), we simulated the sampling distribution for the indirect effect and constructed a 95% confidence interval (CI) for the effect using a web-based utility for nonparametric bootstrapping (Selig & Preacher, 2008). We employed ranges of 5,000 to

20,000 iterations and obtained similar results, so present the CIs from the 20,000 iteration bootstrap.

Moderation—We examined whether *ALDH2*2* moderated the relationship of consumption on Problems in another series of MSEMs. Moderation of the effect of consumption on Problems by *ALDH2*2* group was tested separately at the between-person level (between people within each *ALDH2*2* group) and at the within-person level (across observations within persons in each group). Moderation was tested as follows: Between-person level moderation was tested by constraining the unstandardized beta for consumption on Problems at the between level to be equal across *ALDH2*2* groups. For within-person level moderation when the consumption-Problem slopes were held constant (Quantity, Max24), moderation was tested by equating the within-level unstandardized beta for the effect of consumption on Problems across *ALDH2*2* groups. When the consumption-Problems slopes were allowed to vary across persons (Frequency, Binge), within-level moderation was tested by equating the mean random slopes of the *ALDH2*2* groups. For all models, moderation was indicated by a significant Wald test, meaning that constraining the parameter to be equal across *ALDH2*2* groups resulted in a significantly poorer overall fit than when the parameter was free across *ALDH2*2* groups.

To incorporate time into the moderation models, we modeled the within-person levels of consumption and Problems as being directly affected by Year3 and Year4 effect-coded dummy variables. Year3 was coded 0 for the second year and 1 for the third and fourth years to represent a contrast against second-year levels; Year4 was coded 0 for the second and third years and 1 for the fourth year to represent additional change relative to that seen by the third year.

As a final step, we examined whether the moderation results were modified by inclusion of gender (female = 0, male = 1) and ethnicity (Chinese = 0, Korean = 1) dummy-coded covariates at the between-person level.

Results

Table 1 shows the intercorrelations between the four consumption variables (square-root transformed) and Problems at each time point, with *ALDH2*2*(−) above the diagonal and *ALDH2*2*(+) below the diagonal. In addition to correlations between consumption and Problems at each time point, we provide correlations between consumption and *t*+1 Problems, as modeled in the MSEMs. The *ALDH2*2* groups had significantly different correlations for Binge-Frequency at Year 1 and for consumption variables with Problems at Year 2 (all *p*s < .05). Means and standard deviations of the alcohol variables by *ALDH2*2* group are also presented in Table 1, using raw (rather than transformed) values for ease of interpretation. When group differences existed in mean levels of consumption and Problems, scores were consistently higher for the *ALDH2*2*(−) group.

Trajectories of Alcohol Consumption and Problems Over Time

Figure 1 displays the raw mean levels of Frequency, Quantity, Binge, and Max24 over time by *ALDH2*2* group. Neither intercepts (*p*s > .22) nor slopes (*p*s > .50) of the consumption

variables significantly differed across *ALDH2*2* groups. Figure 2 displays the mean levels of Problems over time by *ALDH2*2* group. The groups did not differ on initial levels of Problems ($p = .32$), but the slopes differed, with the *ALDH2*2*(−) group having a steeper slope for Problems over time than the *ALDH2*2*(+) group, $\Delta\chi^2(1, 414) = 13.75$, $p < .001$. In addition, only for the *ALDH2*2*(+) group was there a significant negative correlation between intercept and slope for Binge, Quantity, and Problems (ps < .01), indicating that within this group, those who started with higher levels had less increase over time than those who started with lower levels.

Multilevel Models Using Alcohol Consumption to Predict Problems

Mediation—Table 2 shows the results of the MSEMs for testing mediation of *ALDH2*2* group differences in Problems by differences in consumption. The first column shows the baseline model, which is compared with subsequent models. As seen in the LGM analyses, the *ALDH2*2*(+) group has significantly lower scores on Problems than the *ALDH2*2*(−) group ($b = -2.76$, $p < .001$).

The second through fifth columns of Table 2 show results from four separate models that estimate the extent to which group differences in consumption during Years 1 to 3 mediate the *ALDH2*2* group difference in Problems reported at Years 2 to 4. The *a* path from *ALDH2*2* to consumption was significant only for Binge ($b = -.28$, $p < .05$), indicating that on average, individuals with *ALDH2*2* have lower person-level Binge scores across Years 2 to 4 than those without *ALDH2*2*.

The *b* path was significant in all four models (all ps < .001), indicating that higher consumption levels were predictive of higher Problems levels. The effect of *ALDH2*2* group on the random slope was significant for both Frequency ($b = -.72$, $p < .05$) and Binge ($b = -1.62$, $p < .01$), indicating that the relationship of each of these variables with Problems was more varied over time among individuals in the *ALDH2*2*(−) group than in the *ALDH2*2*(+) group.

For the *c* path, the relationship of *ALDH2*2* group with person-level scores for Problems (the *c* path) was significantly reduced only in the Binge model (from $b = -2.76$ to $b = 0.22$, $p = .82$; the drop was significant at $t = -2.28$, $p < .05$). The *c* paths in the other consumption models were not significantly reduced (ps > .12). Consistent with this, the total indirect effect (the *a*b* path) also was significant only in the Binge model ($b = -2.72$, $p < .05$).

Moderation—Table 3 shows the results of MSEM analyses testing whether the *ALDH2*2* groups differed in the strength of the association between consumption and Problems. For all four consumption variables, this person-level association was stronger in the *ALDH2*2*(−) group than in the *ALDH2*2*(+) group ($p < .01$ for Frequency and Binge; $p < .05$ for Quantity and Max24).

At the within-person level, we did not find significant moderation, meaning that how the consumption-Problems association varied across time points was not moderated by *ALDH2*2* group. There was some suggestion of moderation of the within-person Frequency-Problems relationship ($p = .08$), which we probed in single-level regression

models estimated for each time point. These regression models indicated that the strength of the association between Frequency and Problems did not significantly differ between the *ALDH2*2* groups at Year 2, but was stronger in the *ALDH2*2*(−) group than in the *ALDH2*2*(+) group by Years 3 and 4 (both *p*s < .05). These results, however, should be interpreted with caution, given the differences between the single-level models used in probing these differences and the MSEMs used in the rest of the mediation and moderation analyses.

Next, Year3 and Year4 time dummy variables were added to the model to examine how the levels of consumption and Problems relation varied over time, as well as to examine the effects of this variation on our moderation results. Level of consumption increased at each year in both *ALDH2*2* groups for all consumption variables except Quantity; level of Problems decreased in the final year for the *ALDH2*2*(+) group only. The moderation effects of *ALDH2*2* at the person level, however, were not significantly altered by the inclusion of the time dummy variables.

Last, we examined whether the findings about *ALDH2*2* group differences in the consumption-Problems relationships held when gender and ethnicity were included in the model. In the *ALDH2*2*(+) group, women had lower Quantity ($p < .01$) and Max24 ($p = .001$) levels than men. No significant differences were found across ethnic groups. Moderation effects of *ALDH2*2* on the person level were never altered by the inclusion of these covariates.

In sum, these final two sets of analyses, which included time, gender, and ethnicity, indicate that there are effects of these variables on *levels* of consumption and Problems, but accounting for these variables did not alter the *process* by which consumption affects Problems on the between-person level with regard to *ALDH2*2*. In all models, the moderation of the consumption-Problems association by *ALDH2*2* group remained significant, highlighting the robust and consistent role of *ALDH2*2* on the consumption-Problems associations over the college years in this sample.

Discussion

The aim of this study was to better understand the underlying mechanism for how possession of an *ALDH2*2* allele leads to lower levels of alcohol-related problems. Specifically, we sought to understand differences in the progression of alcohol consumption and problems, and the relationship between alcohol consumption and problems, during 4 years of college in individuals with and without an *ALDH2*2* allele. The *ALDH2* gene, with its well-established effect on alcohol metabolism, its strong association with risk for alcohol dependence, and its prevalence in an estimated 540 million people worldwide, provides a unique opportunity to test genetic and environmental influences in conjunction on the development of alcohol problems.

Consistent with our prediction, we found in the multilevel models that possessing an *ALDH2*2* allele was associated with lower levels of binge drinking among drinkers. This significant difference in binge drinking across *ALDH2*2* groups was not seen in the

traditional growth models, which showed that initial levels of binge drinking and linear growth over the next 3 years of college did not significantly differ between *ALDH2*2* groups. The multilevel models were able to differentiate between person level and within-person level effects, did not force a model of linear change, and included only the first 3 years of binge drinking as predictors of alcohol-related problems in subsequent years. Thus, these models are each informative in different ways, and indicate that *ALDH2*2* group differences for binge drinking emerge as significant when the between-person level is parceled out in the model.

We hypothesized that larger differences would emerge across *ALDH2*2* groups on measures of heavy consumption than on measures of drinking frequency and average quantity, and in our sample, frequency of binge drinking was the only consumption variable that significantly differed across *ALDH2*2* groups in any of the models. Previous cross-sectional studies, however, have linked *ALDH2*2* to lower levels of all four of the alcohol-consumption variables examined in the current study (e.g., Higuchi, et al., 1996; Luczak, et al., 2001; Takeshita & Morimoto, 1999; Wall et al., 2001). In Figure 1, all four consumption variables were lower in the *ALDH2*2*(+) group than in the *ALDH2*2*(−) group, but there was substantial variation within each group so that these differences were not significant. It is also of interest to note that the intercorrelations among the consumption variables changed over time only in those with an *ALDH2*2* allele, as indicated by a lack of invariance of an alcohol consumption construct over the college years in the *ALDH2*2*(+) group. Taken together, these findings indicate that possession of an *ALDH2*2* allele is more strongly associated with frequency of heavy drinking than with other measures of alcohol consumption over the college years, and is also associated with the relationships among consumption variables changing over this period of time.

Also consistent with our hypothesis, having an *ALDH2*2* allele was associated with less increase in problems over the college years. The initial level of alcohol-related problems in the LGM did not differ across *ALDH2*2* groups. This lack of association was not due to restriction of range, as a substantial proportion of our sample did report problems in the first year. Differences in levels of problem drinking emerged by the later years of college. These results are consistent with general reports that genetic influences increase as individuals obtain greater experience with alcohol (Rose, 1998) and with specific reports that the effects of *ALDH2*2* emerge over the course of adolescence and early adulthood (Doran et al., 2007; Irons et al., 2012).

The most novel of our findings offers insight into the potential mechanism by which *ALDH2*2* leads to lower levels of alcohol problems. The hypothesized mediational mechanism that individuals with *ALDH2*2* are protected from developing drinking problems because they have lower alcohol consumption was supported for binge drinking only. In our sample, the lower level of problems in *ALDH2*2*(+) individuals was fully mediated by the addition of binge drinking in the model, but it was not significantly reduced by including any of the other consumption variables. This suggests that it is not how often one drinks, nor is it the typical or highest amount one drinks, but rather, it is the reduced frequency of heavy drinking that leads to the protection afforded by *ALDH2*2* against alcohol problems.

Tests of moderation offered further insight into the protective process of the *ALDH2*2* allele on drinking problems. *ALDH2*2* interacted with each alcohol consumption variable to differentially predict alcohol problems. Greater alcohol consumption was associated with problems in both *ALDH2*2* groups, but among *ALDH2*2*(−) individuals, consumption was more strongly associated with problems. This difference in the strength of the relationship between consumption and problems was found consistently over time.

One interpretation of these findings of moderation is that individuals with an *ALDH2*2* allele adjust their drinking in a way that alters the relationship between alcohol consumption and problems. In the United States, the highest levels of alcohol consumption are seen in individuals in their early 20s (Moore et al., 2005; Sher et al., 2005), and the college environment has been found to further promote heavy drinking (Slutske et al., 2004). Thus, the drinking patterns of college students with *ALDH2*2* may initially be similar to their peers, but given their heightened physical response to alcohol they may learn to regulate or pace their drinking to maintain lower peak blood alcohol levels, thereby avoiding some of the negative consequences typically associated with consumption (see Luczak et al., 2011). In a previous study examining blackouts, we found that Asian American college students with *ALDH2*2* were less likely to experience blackouts than those without *ALDH2*2*, even after adjusting for heavy drinking (based on lifetime maximum drinks in a 24-hr period; Luczak, Shea, et al., 2006). Taken together, these findings suggest that individuals who possess an *ALDH2*2* allele are less likely to binge drink than those without *ALDH2*2* and may also have an altered pattern of alcohol intake that further reduces the likelihood that their consumption leads to problems.

In the current study, the definitions of binge drinking and maximum drinks did not include duration of time to consume these drinks nor did we have measures of frequency of intoxication. Examining variations in pace of drinking and peak alcohol levels associated with genotype may further elucidate the mechanism underlying *ALDH2*2* as a protective factor for alcohol problems. This highlights the importance of examining multiple aspects of alcohol consumption independently as well as in conjunction to gain a clearer picture of how variation in consumption behaviors and patterns uniquely and jointly relate to the development of alcohol-related problems.

Our findings should be viewed within the limitations of the study design. First, this study relied on self-report measures of alcohol consumption and problems. Although there are concerns regarding the validity of self-report data, we do not expect differential response bias on the basis of *ALDH2*2*. Second, this was a college sample so results may not generalize to non-college samples. Third, although we started with a relatively young sample, 81% of our sample had already consumed alcohol prior to enrolling in our study, such that the very initial stages of alcohol experience were not captured for most of our participants. Because of this, we were able to prospectively examine progression from alcohol consumption to problems, but not the very initial stages of drinking. We did, however, find that the effects of *ALDH2*2* on problems emerged over time in this sample, so we were able to capture when *ALDH2*2* began to have a significant association with problems despite not having prospectively collected initial drinking data. Finally, as noted earlier, we did not have detailed measures of rates of consumption, which could have

allowed for better identification of differences in drinking intake patterns associated with *ALDH2*2*.

Despite these limitations, the results of this study offer insight into how *ALDH2*2* relates to the developmental pattern of early alcohol use. This research represents the first study to examine prospectively the effects of *ALDH2*2* on alcohol consumption and problems over the course of college. Our findings suggest that the interplay between *ALDH2*2* and drinking-related problems is complex, involving both mediation and moderation processes that reduce the likelihood of developing problems via reduction of heavy drinking, as well as by altering the relationship between alcohol consumption and problems. The developmentally contingent nature of the *ALDH2*2* effect on problem drinking is an important finding. It extends other research on the developmental moderation of *ALDH2*2* effects and provides further evidence that what seems like a relatively straightforward effect of a diminished ability to metabolize alcohol on drinking behavior is actually dependent on behavior and developmental stage. The identification and characterization of gene modifiers using explicitly measured variables will provide a more comprehensive understanding of the complex interplay of factors and processes involved in the etiology of alcohol involvement. Ultimately, such knowledge can inform not only for whom, but also at what stage in the development of alcohol involvement, intervention efforts might be most useful. Future studies with more detailed data on alcohol consumption patterns and problems, including rates of alcohol intake and peak alcohol levels, will be able to extend our current findings and test additional aspects of alcohol involvement and intermediate phenotypes to further our understanding of how *ALDH2*2* protects against the development of alcohol problems. This research serves as a model for other candidate gene studies where the mechanisms of action between genotype and phenotype are less well understood.

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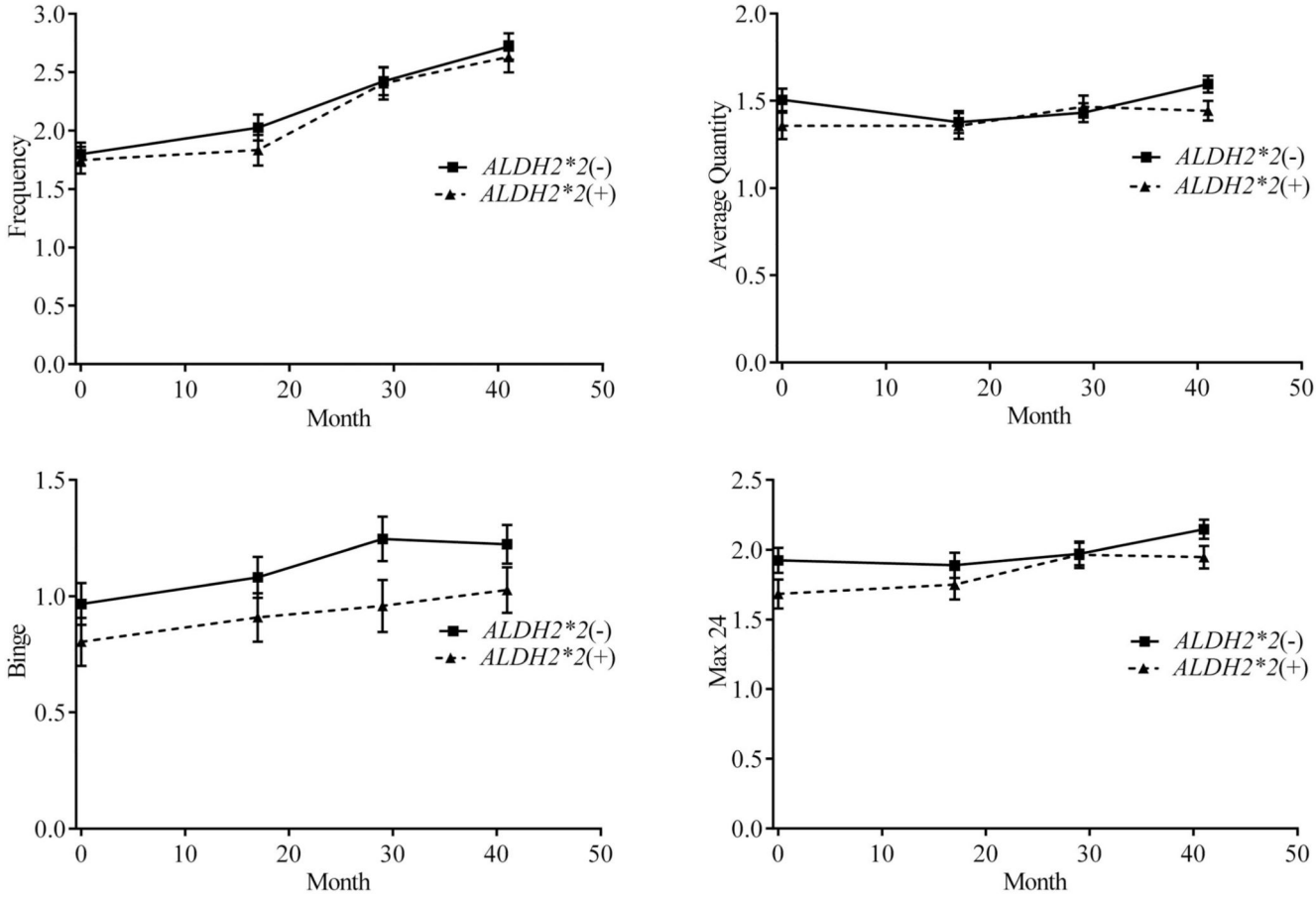

Figure 1.

Mean alcohol consumption and standard errors over time among 414 college students grouped by *ALDH2*2*.

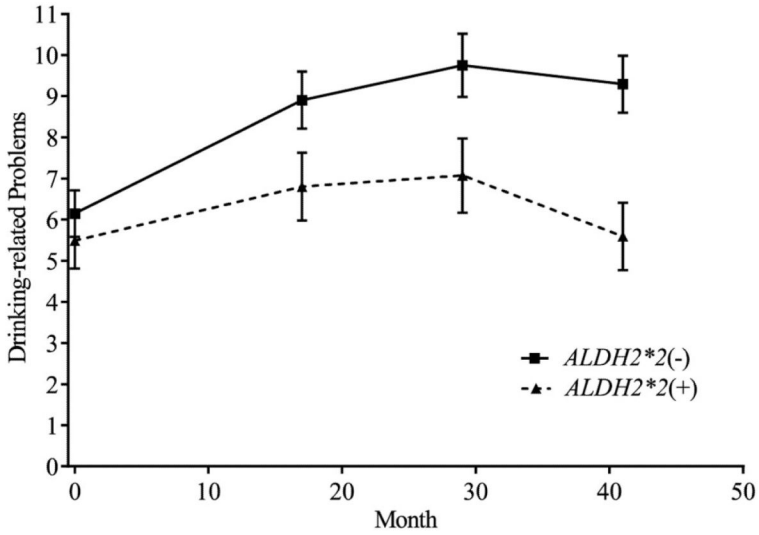

Figure 2.
Mean alcohol problems and standard errors over time grouped by *ALDH2*2*.

Table 1

Correlations, Means, and Standard Deviations for Alcohol Variables in 414 Asian American College Drinkers by ALDH2*2 Group and Year

Measure	1	2	3	4	5	6	*M*	*SD*
				Year 1				
1. Frequency	—	.67	.83*	.77	.68	.54	5.96	8.42
2. Quantity	.73	—	.72	.93	.50	.45	3.35*	2.95
3. Binge	.72*	.69	—	.78	.69	.46	2.93	6.53
4. Max24	.79	.95	.72	—	.61	.49	5.99**	6.43
5. Problems, *t*	.64	.53	.66	.59	—	—	7.82	10.33
6. Problems, *t*+ 1	.50	.34	.43	.39	—	—	9.50*	11.87
M	4.99	2.67*	2.08	4.26**	6.47	7.31*		
SD	5.63	2.40	4.01	3.93	7.51	9.25		
				Year 2				
1. Frequency	—	.70	.83	.79	.72	.70	7.09	9.99
2. Quantity	.65	—	.70	.93	.51	.50	2.81	2.38
3. Binge	.79	.68	—	.75	.74*	.74*	3.14	6.45
4. Max24	.76	.92	.72	—	.60	.59*	5.55	5.58
5. Problems, *t*	.62	.40	.61*	.51	—	—	9.50*	11.87
6. Problems, *t*+ 1	.57	.40	.61*	.42*	—	—	9.93**	12.49
M	6.02	2.75	2.50	4.77	7.31*	6.88**		
SD	8.99	2.73	5.14	4.75	9.25	8.48		
				Year 3				
1. Frequency	—	.67	.77	.77	.68	.59	9.00	11.52
2. Quantity	.60	—	.69	.92	.48	.43	2.70	2.12
3. Binge	.72	.69	—	.73	.74	.59	3.65	7.12
4. Max24	.74	.89	.74	—	.59	.52	5.34	4.74
5. Problems, *t*	.66	.51	.70	.60	—	—	9.93**	12.49
6. Problems, *t*+ 1	.50	.39	.44	.47	—	—	8.77***	11.86
M	7.87	2.65	2.63	4.94	6.88**	5.16***		
SD	8.94	2.01	5.81	4.40	8.48	6.24		
				Year 4				
1. Frequency	—	.43	.60	.61	.56	—	9.83	11.34
2. Quantity	.54	—	.68	.92	.41	—	2.98*	2.27
3. Binge	.66	.69	—	.75	.58	—	2.90	4.67
4. Max24	.70	.94	.77	—	.51	—	5.45*	4.33
5. Problems, *t*	.53	.38	.57	.45	—	—	8.77***	11.86
M	9.38	2.47*	2.27	4.55*	5.16***	—		

Measure	1	2	3	4	5	6	*M*	*SD*
SD	11.13	1.60	3.78	3.19	6.24	—		

Note. Statistics above diagonal are for ALDH2*2(−) (*n* = 243) and below diagonal are for ALDH2*2(+) (*n* = 171) participants. Year 1-4 *n*s, respectively, are 191, 213, 191, and 193 for *ALDH2*2*(−); 145, 156, 140, and 139 for *ALDH2*2*(+). *M*s and *SD*s are presented in raw units; correlations based on square-root transformed scores. Correlations reflect pairwise deletion.

All correlations significant at $p < .001$. Significance of differences between *ALDH2*2* groups:

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 2

Mediation of the Relationship Between ALDH2*2 Group and Problems by Consumption in Multilevel Models

	Baseline	Mediation by			
	No mediator	Frequency	Quantity	Binge	Max24
Effect/Fit	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*
Direct effects (Level 2)					
*ALDH2*2* on consumption (*a*)	—	−.16 (.15)	−.02 (.07)	−.28* (.13)	−.09 (.11)
Consumption on Problems (b_1)	—	6.68*** (.68)	11.17*** (1.08)	8.97*** (.85)	7.90*** (.67)
*ALDH2*2* on consumption-Problems random slope		−.72* (.34)		−1.62** (.58)	
*ALDH2*2* on Problems (*c*)	−2.76** (.91)	−1.03 (.68)	−2.65*** (.81)	.22 (.94)	−2.16** (.74)
Indirect effect (Level 2)					
*ALDH2*2* on Problems	—	−1.08 (1.06)	−.22 (.82)	−2.72* (1.30)	−.74 (.83)
(95% CI)	—	(−3.13, 0.95)	(−1.85, 1.40)	(−5.17, −0.32)	(−2.38, 0.87)
Additional random slope effects					
Variance/Residual variance	—	2.18*** (.32)	—	5.77***(1.56)	—
Mean/Intercept (b_2)	—	.17 (.30)	—	.65 (.56)	—
Model fit (AIC)	7444.9	10774.2	9934.6	10312.1	10530.4

Note. a and *b* refer to components of the *a***b* indirect effect. In models with a random slope, the indirect effect equals $a*(b_1 + b_2)$. In models without a random slope, the indirect effect equals $a*b_1$. Indirect effect confidence intervals determined by bootstrap method (20,000 iterations). Values reported are unstandardized. AIC = Akaike Information Criterion.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 3

Moderation of the Relationship Between Consumption and Alcohol Problems by ALDH2*2 Group (−/+) in Multilevel Models

Consumption-Problems parameterization	Random Slope Models: Between effects *b (SE)*	Random Slope Models: Within effects Mean *RS (SE)*	Random Slope Models: Wald *p*	Constant Slope Models: Between effects *b (SE)*	Constant Slope Models: Within effects *b (SE)*	Constant Slope Models: Wald *p*
	Frequency (−) / (+)			Quantity (−)/(+)		
Free across *ALDH2**2 on both levels	6.71*** (.46)/4.69 (.45)	.29 (.24) /−.41 (.33)	_	13.94*** (1.68)/9.01*** (1.76)	.75 (.44)/.09 (.44)	_
Constrained on between level	5.89*** (.37)	.66 (.36) / .55 (.32)	.001	11.69*** (1.41)	1.15** (.43)/−.43 (.41)	.028
Constrained on within level	6.67*** (.52)/4.33*** (.55)	.25 (.21)	.079	14.21*** (1.54) / 8.31*** (1.49)	.44 (.30)	.296
	Binge (−)/(+)			Max24 (−)/(+)		
Free across ALDH2*2 on both levels	9.51*** (.75)/6.33*** (.82)	.39 (.28) / .07 (.29)		12.00*** (1.76)/7.38*** (1.16)	.15 (.38)/−.22 (.35)	
Constrained on between level	7.91*** (.47)	.55 (.34) / −.09 (.23)	.003	8.19*** (.89)	.98** (.36)/−.52 (.31)	.019
Constrained on within level	9.56*** (.97)/6.28*** (1.26)	.16 (.43)	.412	12.06*** (1.59)/6.98*** (1.10)	−.02 (.27)	.475

Note. The effect of consumption on Problems at the within level is expressed for Binge and Frequency as the mean of the random slope (RS) for the regression of Problems on the consumption variable. The effect of consumption on Problems at the within level is expressed for Quantity and Max24 as an unstandardized beta effect. Variances of between-level variables are not allowed to vary across classes. Wald tests are 1 *df* tests of the fit of the model with the between- or within-level parameter constrained across *ALDH2**2 groups against the freer model without this constraint. Values reported are unstandardized. Free models for Binge and Frequency have 17 estimated parameters. Free models for Quantity and Max24 have 16 estimated parameters. (−) = *ALDH2**2(−) group. (+) = *ALDH2**2(+) group.

* $p < .05$.

** $p < .01$.

*** $p < .001$.