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Associations of *ALDH2* and *ADH1B* Genotypes With Alcohol-Related Phenotypes in Asian Young Adults

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Abstract

Background—Associations of *ALDH2* and *ADH1B* genotypes with alcohol use have been evaluated largely using case–control studies, which typically focus on adult samples and dichotomous diagnostic outcomes. Relatively fewer studies have evaluated *ALDH2* and *ADH1B* in relation to continuous drinking outcomes or at different developmental stages. This study examined additive and interactive effects of *ALDH2* and *ADH1B* genotypes on drinking behavior in a mixed-gender sample of Asian young adults, focusing on continuous phenotypes (e.g., heavy episodic and hazardous drinking, alcohol sensitivity, drinking consequences) whose expression is expected to precede the onset of alcohol use disorders.

Methods—The sample included 182 Chinese- and Korean-American young adults ages 18 years and older (mean age = 20 years). Effects of *ALDH2*, *ADH1B* and ethnicity were estimated using generalized linear modeling.

Results—The *ALDH2**2 allele predicted lower reported rates of alcohol use and drinking consequences as well as greater reported sensitivity to alcohol. There were significant ethnic group differences in drinking outcomes, such that Korean ethnicity predicted higher drinking rates and lower alcohol sensitivity. *ADH1B* status was not significantly related to drinking outcomes.

Conclusions—Ethnicity and *ALDH2* status, but not *ADH1B* status, consistently explained significant variance in alcohol consumption in this relatively young sample. Results extend previous work by showing an association of *ALDH2* genotype with drinking consequences. Findings are

discussed in the context of possible developmental and population differences in the influence of *ALDH2* and *ADH1B* variations on alcohol-related phenotypes.

Keywords

Alcohol Dehydrogenase; Aldehyde Dehydrogenase; Alcohol Use; Asian-Americans; Generalized Linear Modeling

Twin and adoption Studies have convincingly established that a substantial proportion of variance in the risk for alcohol use and dependence is attributable to additive genetic influences (for reviews see Heath, 1995; McGue, 1999). However, the identification of genes explaining unique variance in alcohol-related behavior has proven difficult, largely because alcohol use and dependence reflect complex, multigenic behaviors that are heterogeneous across individuals and subject to environmental as well as genetic influence (Dick and Foroud, 2003; Li, 2000; Schuckit, 2000). Instances in which individual genes predict significant variability in the risk for alcohol dependence can provide unique opportunities to evaluate how specific genetic factors act additively or interactively with other genetic or environmental factors to influence alcohol-related behavior (Heath et al., 2001; Li et al., 2001).

The 2 genes with the strongest associations with alcohol use and dependence are *ALDH2* (12q24) and *ADH1B* (4q22). These genes encode the major enzymes involved in alcohol metabolism and have functional variations that are protective against alcohol dependence (Edenberg, 2007; Wall, 2005). The major pathway of alcohol elimination involves conversion of ethanol to acetaldehyde by alcohol dehydrogenase (ADH) enzymes, followed by oxidation of acetaldehyde to acetate via mitochondrial aldehyde dehydrogenase (ALDH) (Edenberg, 2007; Thomasson and Li, 1993). The *ADH1B**2 allele encodes an ADH enzyme subunit whose catalytic properties lead to more rapid conversion of ethanol to acetaldehyde, whereas the *ALDH2**2 allele encodes an ALDH enzyme subunit that is functionally inactive, impairing the conversion of acetaldehyde to acetate (for reviews see Li, 2000; Thomasson and Li, 1993; Wall, 2005). Theoretically, these variants protect against the risk for alcohol dependence by promoting increased transient acetaldehyde during alcohol metabolism and, in turn, decreased consumption (Edenberg, 2007; Wall, 2005).

The *ALDH2**2 allele, found exclusively among individuals of northeast Asian heritage (Chinese, Koreans, and Japanese; Goedde et al., 1992), shows the strongest association with drinking behavior. Individuals with *ALDH2**2 show significantly lower rates of alcohol use, heavy drinking and alcohol dependence compared to those without this variant (Chen et al., 1996; Higuchi et al., 1996; Luczak et al., 2001, 2004; Takeshita and Morimoto, 1999; Thomasson and Li, 1993; Thomasson et al., 1991; Wall et al., 2001). A meta-analysis comprising 15 case-control studies and over 4,500 participants showed that *ALDH2**2 heterozygotes have approximately one-fourth the risk for alcohol dependence compared to *ALDH2**1 homozygotes (Luczak et al., 2006), and case-control and population studies have found only 3 individuals homozygous for *ALDH2**2 who were classified as alcohol-dependent (Chen et al., 1999; Luczak et al., 2004). *ALDH2**2 is associated with heightened blood acetaldehyde and cardiovascular responses following alcohol ingestion (Peng et al., 1999, 2007; Wall et al., 1997), as well as greater self-reported sensitivity to alcohol (Duranceaux et al., 2008), lending support for a protective mechanism involving increased acetaldehyde levels and alcohol sensitivity among those with *ALDH2**2.

The *ADH1B**2 allele is highly prevalent among northeast Asians and moderately prevalent in Caucasians, in particular those of Jewish and Russian ancestry (Goedde et al., 1992; Hasin et al., 2002). *ADH1B**2 is associated with a decreased risk of alcohol dependence in both Asian and Caucasian populations (e.g., Chen et al., 1999; Higuchi, 1994; Luczak et al., 2006;

Thomasson et al., 1991; Whitfield et al., 1998). In Asian samples, significant protective effects of *ADH1B**2 have been observed after controlling for *ALDH2* status in some (Chen et al., 1999; Thomasson et al., 1991) but not all studies (e.g., Luczak et al., 2004, 2006; Peng et al., 2002). The aforementioned meta-analysis showed that the protective effects of *ADH1B**2 were somewhat greater for individuals who also had the *ALDH2**2 allele (Luczak et al., 2006), suggesting possible interactive effects between these genes. *ADH1B**2 has not been associated with measured acetaldehyde levels *in vivo* (e.g., Peng et al., 2007), but is associated with increased sensitivity to alcohol as measured by skin flushing, self-reported physiologic symptoms and post-intoxication body sway (Chen et al., 1998; Cook et al., 2005; Duranceaux et al., 2006; Takeshita et al., 1996; Wall et al., 2005). In some research, effects of *ADH1B**2 on alcohol sensitivity are limited to individuals with *ALDH2**2 (Cook et al., 2005; Takeshita et al., 2001), again suggesting the possibility of interactive effects.

Much of the research on *ALDH2* and *ADH1B* has utilized case-control studies that rely predominantly on adult, male participants and focus on dichotomous diagnostic outcomes. Research with younger populations may be important given evidence of possible age differences in the effects of *ALDH2* and *ADH1B* on drinking behavior (Carr et al., 2002; Doran et al., 2007; Hendershot et al., 2005), consistent with increasing genetic influences on alcohol use during the transition from adolescence to adulthood (e.g., Koopmans and Boomsma, 1996; Pagan et al., 2006). It has also been suggested that the examination of multiple, continuous phenotypes is preferable to a focus on dichotomous diagnostic variables (e.g., Dick et al., 2008; Hutchison et al., 2004). For example, in samples with relatively lower rates of alcohol dependence, restricted variability in diagnostic outcomes may obscure genetic effects, whereas examination of subclinical phenotypes may reveal these effects (e.g., Irons et al., 2007).

This study evaluated additive and interactive effects of *ALDH2* and *ADH1B* genotypes on alcohol-related outcomes in a mixed-gender sample of Chinese and Korean young adults. Whereas most studies of Asian-American young adults have included participants at or above legal drinking age, this study included participants 18 years and older, most of whom were under age 21. This study also emphasized evaluation of continuous phenotypes, including heavy episodic drinking, alcohol sensitivity, hazardous drinking, and alcohol-related consequences. Genetic effects were estimated using generalized linear models while controlling for ethnicity, thus allowing estimation of unique contributions of cultural and genetic influences on drinking behavior.

Materials And Methods

Participants

Participants were undergraduates enrolled in a prospective study of genetic and environmental influences on drinking behavior. Individuals were recruited after they completed a web-based survey on alcohol-related norms and behavior that was sent to 4,000 randomly selected undergraduates as part of a different study. Students who completed this survey, reported 100% Chinese, Korean, or Japanese heritage, and consented to follow-up contact ($n = 292$) were eligible for the current study. All eligible students received e-mail and phone notification about the study. Recruitment continued until a target sample of 200 was obtained. Efforts to establish contact were unsuccessful for 44 students and 48 students declined participation. Participants were 46.5% male and reported a mean age of 20.2 years ($SD = 1.54$). In terms of ethnic background the sample was 56.5% Chinese, 33.5% Korean, and 9% Japanese. Because one aim of the study was to examine ethnic group differences in drinking, participants reporting Japanese backgrounds were not included in the present analyses given the small sample size, resulting in a sample of 182 participants (58 Chinese men, 57 Chinese women, 28 Korean men, and 39 Korean women).

Procedures

All participants attended a brief laboratory visit at which they completed informed consent procedures and provided a fingertip-puncture blood sample for DNA analysis. Following the lab visit participants received an e-mail with a link to complete a web-based survey assessing alcohol use and related behaviors. Participants logged onto a secure server using a randomly generated identification number to complete the survey, which typically lasted 25 to 30 minutes. Of the 182 Chinese and Korean participants, 176 (97%) completed the survey. Participants received monetary compensation both for providing the blood sample and for completing the online survey.

Genotyping

Blood samples were analyzed at the Alcohol Research Center at Indiana University. DNA was isolated using the "HotSHOT" method (Truett et al., 2000). Following this, TaqMan probes were used for allelic discrimination (Applied Biosystems, Foster City, CA). The allelic discrimination assay is a multiplexed (one primer pair and two probes per reaction), endpoint (data are collected at the end of the PCR process) assay. The allelic discrimination assay is a multiplexed (more than 1 primer/probe pair per reaction), endpoint (data are collected at the end of the PCR process) assay. Each assay mix contains 2 different TaqMan probes, labeled with VIC or FAM fluorescent reporter dye, which bind preferentially to 1 of the alleles. The genotype of each sample is determined by the fluorescence levels of the reporter dyes and is clustered on a graph with other samples of the same genotype. Each reaction contains 5 μ l of 2 $\times$ TaqMan Universal PCR Mastermix, No AmpErase UNG, 3.75 μ l of water, 0.25 μ l of 40 $\times$ Assay Mix, and 1 μ l of DNA sample. Eight or 11 controls are included on each 96-well plate: 2 no template controls, 2 or 3 heterozygous samples and 2 or 3 of each of the homozygous samples. As genotyping is done by endpoint reading, the thermo-cycling is carried out in MJ Research PTC-200 thermocyclers (MJ Research, Inc., Waltham, MA). The PCR products are then analyzed in an ABI PRISM[®] 7300 Sequence Detection System (SDS) instrument (Applied Biosystems, Inc., Foster City, CA). SDS Software 1.3.1 converts the raw data to pure dye components and plots the results of the allelic discrimination on a scatter plot of Allele X versus Allele Y; each genotype appears on the graph as a cluster of points.

Measures

Alcohol Use Disorders Identification Test—The Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001) is a 10-item measure assessing hazardous drinking. Items cover quantity/frequency of drinking (3 items), alcohol dependence (3 items), and alcohol-related consequences (4 items). Its psychometric properties have been evaluated in several studies (Babor et al., 2001). Previous research supports the utility of the AUDIT for college populations and indicates that the measure has good psychometric properties as a measure of high-risk drinking in this population (Kokotailo et al., 2004). For the current study, a 3-month reference frame was used.

Daily Drinking Questionnaire—Recent drinking behavior was assessed with the Daily Drinking Questionnaire (DDQ) (Collins et al., 1985). This measure includes questions about drinking frequency/quantity over the past month and a calendar assessing average drinks consumed on each day of the week over the past 3 months. Dependent measures examined in the present analyses were number of drinks per week and hours spent drinking per week in the past 3 months, maximum number of drinks consumed on 1 occasion in the past month and estimated peak BAC in the past month (estimates were calculated based on gender and body weight for those who reported a drinking episode in the past month).

Heavy Episodic Drinking and Maximum Lifetime Consumption—Recent heavy episodic drinking and peak lifetime consumption were assessed using items based on the National Institute on Alcohol Abuse and Alcoholism (NIAAA) alcohol use question set (National Institute on Alcohol Abuse and Alcoholism, 2003). Participants reported the number of days in the past month on which they had a heavy drinking episode, defined in accordance with NIAAA criteria (consumption of at least 4 drinks for women/5 drinks for men within a 2-hour period). Participants also answered questions assessing lifetime alcohol use and lifetime regular (weekly) drinking.

Rutgers Alcohol Problem Index—Alcohol-related problems were measured using the Rutgers Alcohol Problem Index (RAPI) (White and Labouvie, 1989). Respondents rate the frequency with which they experienced various indicators of problem drinking (e.g., tolerance/withdrawal symptoms, social/interpersonal consequences) on a scale of 0 (*Never*) to 4 (*More than 10 times*). In the current study the past 3 months were used as the reference frame.

Self-Rating of the Effects of Alcohol Form—The Self-Rating of the Effects of Alcohol (SRE) form (Schuckit et al., 1997) assesses sensitivity to the effects of alcohol by asking about the number of drinks needed to notice each of 4 effects (feeling different, dizziness/slurred speech, stumbling/loss of coordination, involuntary sleeping/passing out) for 3 different drinking periods (first 5 drinking occasions, most recent 3-month period of regular drinking, period of heaviest drinking). SRE score is calculated as the total number of drinks reported across all items divided by the number of items endorsed. Higher scores indicate more drinks needed to achieve these effects and therefore a lower response to alcohol. Previous studies have used the SRE for examining genetic influences on alcohol sensitivity in Asian samples (Duranceaux et al., 2008; Wall et al., 1999).

Demographic Questions—Participants also completed questions assessing demographic factors. Items used for the present study were self-reported ethnicity and body weight for estimating peak blood alcohol concentration (BAC).

Preliminary Analyses and Data Analytic Plan—Preliminary analyses were conducted to evaluate distributional properties of the dependent variables. Normality tests and examination of histograms and probability plots showed that the distributions for the continuous alcohol use variables were considerably positively skewed. To account for non-normal distributions we used a Generalized Linear Modeling (GzLM) framework for these analyses (Hardin and Hilbe, 2001; Neal and Simons, 2007). Whereas traditional ANOVA or regression approaches based on ordinary least squares assume normally distributed data with constant variance, GzLM allows for the use of probability density functions assuming non-normal distributions, including the negative binomial, gamma, and Poisson distributions. The negative binomial distribution, which assumes positive skewness and non-negative integer values, is appropriate for modeling drinking outcomes based on count/integer data. The gamma distribution is appropriate for modeling BAC data because it assumes a skewed distribution with continuous, non-negative values (Hardin and Hilbe, 2001; Neal and Simons, 2007). Variables that are scored dichotomously can also be modeled in a GzLM framework using binary logistic models. For the present analyses all count variables were analyzed using the negative binomial distribution and the log link function. Continuous data for estimated peak BAC were analyzed using the gamma distribution and the log link function. The only dichotomous variable, lifetime regular drinking, was analyzed using binary logistic models. SRE scores were not significantly skewed and were evaluated using the Gaussian distribution.

Four nested models were evaluated across dependent measures. Given the modest sample size, Chinese and Korean participants were examined together and ethnicity was entered as a covariate. Model 1 included ethnicity as the only predictor. Model 2 included ethnicity and

ALDH2 status. In Model 3, *ADH1B* was added to evaluate the effect of each gene while controlling for the influence of the other. In Model 4, the *ALDH2* × *ADH1B* interaction was added. Subsequent models were compared to the previous model using likelihood ratio tests and chi-square fit statistics to evaluate whether predictive ability improved across models. Models evaluating SRE score included gender and body weight as covariates to control for these influences on alcohol sensitivity. Because each set of nested models were tested across 10 different dependent variables, which could lead to alpha inflation, omnibus model *ps* were adjusted using a modified Bonferroni procedure (Jaccard and Wan, 1996).

Within each model the effects of *ALDH2* and *ADH1B* genotypes on drinking outcomes were evaluated using 2 dummy-coded contrasts. Individuals with no variant alleles (**1/*1* genotype) were designated as the reference group (coded 0) and compared to those with the **1/*2* and **2/*2* genotypes (each coded 1). Individual comparisons of the **1/*2* and **2/*2* groups to the **1/*1* group were obtained from model parameter estimates. Subsequently, models were re-run designating the **2/*2* group as the reference category to allow comparison of this group with the **1/*2* group (i.e., to evaluate the influence of having 2 variant alleles vs. 1). Note that this additional step does not introduce any changes to the overall model statistics or increase the number of comparisons, but simply provides parameter estimates for the **1/*2* - **2/*2* contrast, thus allowing comparison of all group combinations (Aiken and West, 1991).

Results

Genotyping results for the 182 participants showed that 95 (52.2%) had the *ALDH2*1/*1* genotype, 66 (36.3%) had the *ALDH2*1/*2* genotype, and 21 (11.5%) had the *ALDH2*2/*2* genotype. With regard to *ADH1B*, 16 (8.8%) were *ADH1B*1/*1*, 67 (36.8%) were *ADH1B*1/*2*, and 98 (53.8%) were *ADH1B*2/*2*. One person had missing data for *ADH1B* status. Chi-square analyses did not indicate a significant association between *ALDH2* and *ADH1B* genotype frequencies [$\chi^2(4, n = 181) = 1.32, p = 0.86$] and genotype distributions did not deviate from Hardy–Weinberg Equilibrium. Consistent with established population differences, *ALDH2*2* allele frequency was significantly higher among Chinese (0.36) compared to Koreans (0.19) [$\chi^2(1) = 12.33, p < 0.01$] but did not differ significantly by gender. *ADH1B*2* allele frequency did not differ significantly by ethnicity or gender. Genotype frequencies are presented in Table 1.

Of the 176 Chinese and Korean participants who completed the web-based assessment after enrolling in the study, 19 reported never having consumed alcohol. These participants were omitted from subsequent analyses because the putative mechanism by which *ALDH2* and *ADH1B* influence drinking behavior assumes alcohol exposure (Wall, 2005). Those reporting no lifetime alcohol use did not differ significantly from the remainder of the sample on gender or ethnicity, but they were significantly younger, on average ($M = 19.0$ years, $SD = 1.13$) than lifetime drinkers ($M = 20.3$ years, $SD = 1.56$); $F(1, 174) = 14.37, p < 0.001$. Table 2 presents raw means for drinking variables, stratified by genotype, for the 157 lifetime drinkers included in the primary analyses.

Effects of Ethnicity, *ALDH2*, and *ADH1B* on Drinking

Four successive models were tested for each dependent measure to evaluate incremental effects of the 3 predictor variables (ethnicity, *ALDH2*, and *ADH1B*), as well as possible gene–gene interactions, on alcohol-related outcomes. Results for Model 1 (with ethnicity as the sole predictor) indicated that Korean participants reported significantly higher scores on all consumption variables than Chinese, as well as significantly higher AUDIT scores and significantly higher SRE scores (i.e., significantly lower alcohol sensitivity) (see Table 3).

Model 2 evaluated *ALDH2* effects, controlling for ethnicity. For all outcomes, overall model effects were significant and the likelihood ratio test indicated that Model 2 explained significantly more variance than Model 1 (Table 4). Contrasts showed that *ALDH2**2 homozygotes reported significantly lower alcohol use and alcohol-related problems, as well as increased alcohol sensitivity, compared to *ALDH2**1 homozygotes. *ALDH2**2 heterozygotes reported significantly lower scores on several drinking outcomes, as well as significantly lower RAPI scores and significantly higher alcohol sensitivity, compared to *ALDH2**1 homozygotes. In general, exponentiated regression coefficients (i.e., incident rate ratios, odds ratios) ranged from 0.2 to 0.5 for the *2/*2 contrast and 0.5 to 0.7 for the *1/*2 contrast, consistent with an additional protective effect for 2 *2 alleles versus 1 *2 allele. Upon adjusting omnibus *ps* for Models 1 and 2 using a modified Bonferroni procedure (Jaccard and Wan, 1996), all significant effects remained significant at an alpha level of 0.05.

To allow follow-up comparisons between the *ALDH2**1/*2 and *ALDH2**2/*2 groups, models were re-run with *ALDH2**2 homozygotes as the reference category. Parameter estimates suggested that the difference between these groups was significant for 2 variables, despite low power due to the small size of the *ALDH2**2/*2 group: *ALDH2**1/*2 individuals reported significantly more drinks per week [IRR = 2.55, 95% CI = 1.25–5.17; Wald $\chi^2(1) = 6.66, p = 0.01$] and significantly higher SRE scores (and thus lower sensitivity to alcohol) [IRR = 5.85, 95% CI = 3.15–10.86, Wald $\chi^2(1) = 31.31, p < 0.001$] compared with *ALDH2**2/*2 individuals. In Model 3, the effects of *ADH1B* status were evaluated while controlling for effects of ethnicity and *ALDH2* status. As shown in Table 5, likelihood ratio tests indicated that Model 3 explained significantly more variance than Model 2 for some variables; however, parameter effects showed no instance in which the *ADH1B* was a significant predictor of the drinking variables. On the other hand, *ALDH2* effects observed in Model 3 were virtually identical to those observed in Model 2, indicating that these effects remained consistent and robust when accounting for *ADH1B*.

Model 4 added the *ALDH2* $\times$ *ADH1B* interaction as an additional predictor. Results did not suggest a significant influence of gene–gene interactions on drinking. Likelihood ratio tests showed 2 instances in which Model 4 accounted for significantly more variance than Model 3 (heavy drinking episodes and RAPI score). However, the interaction terms did not approach statistical significance (all *ps* > 0.5), suggesting no interactive effects of *ALDH2* and *ADH1B*. The logistic model for lifetime regular drinking failed to converge upon including the interaction term because there was no variability on this outcome within some of the 9 cells comprising the *ALDH2* $\times$ *ADH1B* interaction. Therefore, this model was re-run with both genotypes coded dichotomously, based on the absence (0) or presence (1) of a variant (*2) allele. Again, there was no evidence of a significant *ALDH2*–*ADH1B* interaction.

Discussion

Effects of *ALDH2* and *ADH1B* variations on drinking behavior have often been evaluated in the context of case–control studies focusing primarily on adult, male samples and dichotomous outcomes (i.e., the diagnosis of alcohol dependence). In this study, we evaluated these genetic influences in a relatively young sample, focusing on continuous phenotypes whose expression is expected to precede the onset of alcohol use disorders. *ALDH2**2 predicted lower rates of alcohol use (including frequency of consumption, heavy drinking episodes, and peak consumption levels), lower scores on an index of hazardous drinking (the AUDIT) and a decreased likelihood of transitioning from drinking initiation to regular use. *ALDH2**2 also predicted a lower frequency of alcohol-related problems as measured by the RAPI, suggesting that *ALDH2* may predict social/interpersonal consequences of drinking in addition to actual consumption.

ALDH2 effects were robust while accounting for significant influences of ethnicity on drinking outcomes. Similar to previous research with college students (Hendershot et al., 2005; Luczak et al., 2001, 2004), Korean (vs. Chinese) ethnicity was a risk factor for alcohol use in the present sample. To the extent that ethnicity is a proxy for cultural influences, these results support that both genetic and cultural factors are important predictors of drinking behavior in Asian young adults. In addition, Korean participants reported lower sensitivity to alcohol as measured by the SRE, consistent with another recent study (Duranceaux et al., 2008). Further research is necessary to determine whether these ethnic group differences in alcohol sensitivity are attributable to additional genetic influences, aspects of drinking history, or both.

Although the genetic model of influence for *ALDH2* is undefined, findings from observational and laboratory studies are consistent with a partial dominant model, such that the effect of 2 *2 alleles is greater than—but not double than—that of 1 *2 allele (for review see Luczak et al., 2006). The current findings are mostly consistent with this model of influence. Both the *2/*2 and *1/*2 genotypes conferred protection against alcohol use, with the *2/*2 genotype showing the strongest effects. We also found that heavy drinking and estimated peak BAC did not differ significantly between the *1/*1 and *1/*2 groups, suggesting that 1 *2 allele does not necessarily protect against heavy drinking and the risk for alcohol dependence. Differences between the *1/*2 and *2/*2 groups were significant for just 2 variables (drinks per week and SRE score). As was expected, however, the number of *ALDH2* *2/*2 participants was low, which decreased power for this comparison.

*ADH1B**2 had no protective effect on drinking outcomes. Mean drinking rates were actually lower, though not significantly so, in the *ADH1B**1/*1 group compared to those with 1 or 2 *ADH1B**2 alleles. The direction of this effect was anomalous given the established protective effect of *ADH1B**2 on the risk for alcohol dependence (Luczak et al., 2006). It should be noted that the *ADH1B**1/*1 group was not only small in size but also had a high proportion of female participants, which may explain the relatively low mean levels of consumption in this group. To date, studies of *ADH1B* in young adults have yielded mixed findings. One study of Asian and White college students found evidence suggesting that *ADH1B* was related to alcohol dependence, but this effect appeared attributable to population stratification in that White students had proportionally higher rates of dependence, as well as lower prevalence of *ADH1B**2, than Asians (Luczak et al., 2004). Studies of Jewish college students have found that *ADH1B**2 was unrelated to drinking (Carr et al., 2002) or related to only one of several phenotypes (Shea et al., 2001). Conversely, a study of White, non-Jewish college students found protective effects *ADH1B**2 as measured by rates of alcohol use disorders and related phenotypes (Wall et al., 2005). Overall, protective effects of *ADH1B**2 appear somewhat more consistent in studies using relatively older samples (e.g., Chen et al., 1999; Luczak et al., 2006; Thomasson et al., 1991; Whitfield, 1997). Many of these studies have focused on treatment populations, which is potentially important because protective effects of *ADH1B**2 may be more evident in groups with relatively greater drinking rates (Heath et al., 2001; Neumark et al., 1998). Our focus on a young sample with relatively low drinking rates may explain the lack of association between *ADH1B* and alcohol-related outcomes.

There are several limitations to this study. First, cross-sectional studies of *ALDH2* and *ADH1B* at different ages can provide only limited insight about genetic influences across development; longitudinal studies are needed to clarify how *ALDH2* and *ADH1B* influence changes in alcohol involvement over time (Wall et al., 2007). Second, the power to detect significant associations was in some cases limited by the small size of *ALDH2**2/*2 and *ADH1B**1/*1 groups. Although the sizes of these groups were anticipated, a larger sample would decrease the risk of Type II error. A third limitation is that this study focused mainly on genetic predictors. The use of ethnicity as a covariate controlled for differences in allele frequencies while also allowing estimation of cultural influences on drinking. However, other

environmental variables are shown to influence drinking behavior in Asian adolescents (e.g., Hahm et al., 2003). Another limitation is our focus on 2 single nucleotide polymorphisms (SNPs) implicated in alcohol dependence. Molecular genetic research has increasingly examined numerous SNPs across the ADH and ALDH genes (e.g., Edenberg et al., 2006; Kuo et al., 2008; Luo et al., 2007). These studies have implicated additional SNPs in the etiology of alcohol dependence; for instance, the *ADH4* (Edenberg et al., 2006; Luo et al., 2005) and *ADH7* (Luo et al., 2006) loci have emerged as regions of interest. Another study found evidence for a qualitative trait locus on chromosome 4, independent of *ADH1B*, that accounted for 64% of the observed genetic influence on *in vivo* alcohol metabolism (Birley et al., 2005). These findings illustrate that additional loci in the ADH and ALDH regions are involved in alcohol response and drinking behavior.

The current results support that the protective effects of *ALDH2*2* on the risk for alcohol use disorders are presaged by differences in alcohol-related phenotypes during late adolescence and early adulthood. Associations between *ADH1B*2* and drinking were not evident; it is possible these associations manifest at relatively later developmental periods or in the context of heavier drinking. As relationships between genetic variations and drinking behavior are continually identified, an important goal is to identify mechanisms that give rise to these effects. Because *ALDH2* and *ADH1B* variations and their associated phenotypes are relatively well characterized, these genes may serve as a good starting point for these investigations (Heath et al., 2001; Li et al., 2001; Wall et al., 2005). Also critical is the use of prospective studies evaluating both measured genes and measured environmental variables in the context of theory-based hypotheses about how these variables interact (e.g., Moffitt et al., 2005). As was the goal in this study, examining intermediate phenotypes at different developmental stages should extend knowledge about how genetic differences ultimately lead to variability in behavioral outcomes.

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Table 1

Genotype Combinations and Participant Ethnicity/Gender Within Genotype

	<i>ALDH2*1/*1</i> (<i>n</i> = 95)	<i>ALDH2*1/*2</i> (<i>n</i> = 66)	<i>ALDH2*2/*2</i> (<i>n</i> = 21)	Female	Chinese
<i>ADH1B*1/*1</i> (<i>n</i> = 16)	8	5	3	12 (75)	10 (63)
<i>ADH1B*1/*2</i> (<i>n</i> = 67)	36	25	6	35 (52)	45 (67)
<i>ADH1B*2/*2</i> (<i>n</i> = 98)	51	35	12	49 (50)	59 (60)
Female	47 (50)	39 (59)	10 (48)		
Chinese	50 (53)	47 (71)	18 (86)		

Includes all Chinese and Korean participants (*n* = 182). Parenthesized values indicate percentages. *ADH1B* status was undetermined for 1 participant.

Table 2

Raw Means for Alcohol Variables Among Lifetime Drinkers ($n = 157$)

Drinking outcome	Totals	ALDH2*1/*1 ($n = 82$)	ALDH2*1/*2 ($n = 58$)	ALDH2*2/*2 ($n = 17$)	ADH1B*1/*1 ($n = 14$)	ADH1B*1/*2 ($n = 60$)	ADH1B*2/*2 ($n = 82$)
Drinks per week ^a	4.26 (6.67)	5.66 (8.04)	3.17 (4.74)	1.24 (1.89)	2.43 (3.16)	4.50 (7.45)	4.44 (6.55)
Hours per week ^a	3.67 (4.24)	4.48 (4.56)	2.97 (3.76)	2.18 (3.54)	3.86 (5.32)	3.05 (3.58)	4.12 (4.50)
Maximum drinks ^b	2.99 (3.35)	3.80 (3.80)	2.31 (2.66)	1.41 (1.97)	1.86 (1.92)	3.37 (3.72)	2.94 (3.26)
Estimated peak BAC ^b	0.087 (0.081)	0.105 (0.089)	0.069 (0.058)	0.050 (0.078)	0.050 (0.049)	0.103 (0.085)	0.084 (0.081)
Heavy episodes ^b	0.87 (1.66)	1.15 (1.96)	0.62 (1.23)	0.35 (1.06)	0.93 (2.06)	0.98 (1.75)	0.78 (1.54)
RAP1 score ^c	2.69 (5.32)	3.50 (5.82)	1.98 (5.11)	1.18 (2.10)	1.86 (3.42)	3.32 (6.28)	2.40 (4.84)
Max drinks 24 hrs ^d	7.15 (6.56)	9.11 (7.27)	5.53 (5.20)	3.15 (2.74)	6.21 (5.70)	6.81 (7.46)	7.64 (6.00)
AUDIT score ^e	3.91 (4.00)	4.94 (4.60)	3.02 (2.90)	2.00 (2.62)	2.86 (2.32)	4.12 (4.72)	3.98 (3.66)
Regular drinking (% y) ^d	51	65	40	24	57	45	55
SRE score ^f	4.73 (2.54)	5.56 (2.58)	4.15 (2.18)	2.34 (1.18)	4.00 (3.07)	4.82 (2.88)	4.80 (2.21)

^aFor the past 3 months.^bFor the past month.^cTotal score on the Rutgers Alcohol Problem Index.^dLifetime.^eAUDIT = total score on the Alcohol Use Disorders Identification Test.^fMean score on Self-Rating of the Effects of Alcohol (SRE) form.

Table 3

Model 1: Reduced Model Examining Ethnicity Effects

Drinking outcome	n	Model statistics		Parameter statistics			
		Model χ^2	Exp(B) (95%CI)	B	SE	Wald χ^2	p
Drinks per week	157	10.15**	1.79 (1.24–2.57)	0.581	0.186	9.80**	0.002
Hours per week	157	9.00**	1.74 (1.21–2.52)	0.556	0.188	8.72**	0.003
Maximum drinks	157	8.03**	1.71 (1.17–2.50)	0.538	0.192	7.81**	0.005
Estimated peak BAC [†]	103	5.66*		0.475	0.202	5.51*	0.019
Heavy episodes	157	11.85**	2.27 (1.42–3.65)	0.821	0.241	11.62**	0.001
RAPI score	157	2.89	1.39 (0.95–2.05)	0.332	0.197	2.85	0.091
Max drinks 24 hrs	155	7.61**	1.63 (1.15–2.32)	0.489	0.181	7.34**	0.007
AUDIT score	157	6.16*	1.58 (1.10–2.28)	0.458	0.187	5.99*	0.014
Regular drinking [‡]	157	14.13***	3.74 (1.83–7.64)	1.319	0.365	13.09***	<0.001
SRE score [§]	131	100.58***		1.215	0.180	45.56***	<0.001

In accordance with reporting conventions, exponentiated coefficients are not reported for the Gamma and Gaussian models. Model for SRE score includes gender and body weight as covariates. All omnibus *p*s were also subjected to a modified Bonferroni procedure and all significant effects shown here maintained their significance at $\alpha = 0.05$. All parameters represent ethnicity effects, where 0 = Chinese and 1 = Korean.

Exp(B), exponentiated parameter estimate (odds ratios for logistic model, incident rate ratios for negative binomial models); CI, confidence intervals for exponentiated parameter estimates; SRE, self-rating of the effects of alcohol.

[†] Logistic model,

[‡] Gamma model,

[§] Gaussian (all other models negative binomial).

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$ for model chi-squared test.

Table 4

Model 2: *ALDH2* Effects, Controlling for Ethnicity

Drinking outcome	Model statistics		Parameter statistics				
	<i>n</i>	Model χ^2 ^A	<i>ALDH2</i>	Exp(B) (95%CI)	B	SE	Wald χ^2 <i>p</i>
Drinks per week	157	-20.20***	* ₂ / ₂	0.23 (0.12–0.46)	-1.466	0.350	17.53 <0.001
			* ₁ / ₂	0.59 (0.40–0.86)	-0.532	0.194	7.54 0.006
Hours per week	157	-5.67**	* ₂ / ₂	0.54 (0.29–1.01)	-0.616	0.321	3.68 0.055
			* ₁ / ₂	0.69 (0.47–1.02)	-0.367	0.196	3.50 0.062
Maximum drinks	157	-8.99**	* ₂ / ₂	0.40 (0.20–0.78)	-0.925	0.343	7.27 0.007
			* ₁ / ₂	0.67 (0.45–1.00)	-0.406	0.205	3.94 0.047
Estimated peak BAC [‡]	103	-6.01*	* ₂ / ₂		-0.835	0.346	5.85 0.016
			* ₁ / ₂		-0.311	0.219	2.02 0.155
Heavy episodes	157	-6.99**	* ₂ / ₂	0.34 (0.13–0.90)	-1.091	0.505	4.67 0.031
			* ₁ / ₂	0.62 (0.37–1.05)	-0.473	0.268	3.11 0.078
RAPI score	157	-12.50***	* ₂ / ₂	0.35 (0.17–0.69)	-1.062	0.354	9.01 0.003
			* ₁ / ₂	0.59 (0.39–0.89)	-0.527	0.207	6.48 0.011
Max drinks 24 hrs	155	-10.46**	* ₂ / ₂	0.39 (0.21–0.73)	-0.933	0.313	8.90 0.003
			* ₁ / ₂	0.66 (0.46–0.96)	-0.416	0.190	4.81 0.028
AUDIT score	157	-9.60**	* ₂ / ₂	0.42 (0.22–0.79)	-0.862	0.322	7.15 0.007
			* ₁ / ₂	0.64 (0.44–0.95)	-0.440	0.196	5.03 0.025
Reg. drinking, lifetime [†]	157	-10.10**	* ₂ / ₂	0.22 (0.06–0.76)	-1.511	0.632	5.71 0.017
			* ₁ / ₂	0.40 (0.20–0.82)	-0.918	0.366	6.28 0.012
SRE score [§]	131	-107.41***	* ₂ / ₂		-2.966	0.307	93.21 <0.001
			* ₁ / ₂		-1.199	0.193	38.73 <0.001

ALDH2 was dummy-coded such that listed variables represent the *₂/₂ and *₁/₂ genotypes (coded 1) versus *₁/₁ genotype (coded 0). In accordance with reporting conventions, exponentiated coefficients are not reported for the Gamma or Gaussian models. Model for SRE score includes gender and body weight as covariates. All omnibus *p*s were also subjected to a modified Bonferroni procedure and significant effects shown here maintained their significance at $\alpha = 0.05$.

Exp(B), exponentiated parameter estimate (odds ratios for logistic model, incident rate ratios for negative binomial models); CI, confidence intervals for exponentiated parameter estimates; SRE, self-rating of the effects of alcohol.

[†] Logistic model,

[‡] Gamma model,

[§] Gaussian (all other models negative binomial).

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$ for model chi-squared test.

Table 5

Model 3: *ADH1B* Effects, Controlling for Ethnicity and *ALDH2*

Drinking outcome	Model statistics		Parameter statistics				
	<i>n</i>	Model χ^2_Δ	<i>ADH1B</i>	Exp(B) (95% CI)	B	SE	Wald χ^2 <i>p</i>
Drinks per week	156	-6.16*	$*_2/*_2$	1.86 (0.93–3.72)	0.622	0.353	3.10 0.078
			$*_I/*_2$	1.78 (0.88–3.61)	0.577	0.361	2.56 0.110
Hours per week	156	-6.24*	$*_2/*_2$	1.17 (0.62–2.24)	0.160	0.329	0.24 0.627
			$*_I/*_2$	0.83 (0.43–1.62)	-0.185	0.340	0.30 0.586
Maximum drinks	156	-4.81*	$*_2/*_2$	1.53 (0.74–3.14)	0.424	0.368	1.33 0.249
			$*_I/*_2$	1.67 (0.80–3.48)	0.511	0.376	1.85 0.174
Estimated peak BAC [‡]	102	1.80	$*_2/*_2$		0.549	0.349	2.47 0.116
			$*_I/*_2$		0.726	0.362	4.01 0.045
Heavy episodes	156	-1.45	$*_2/*_2$	0.97 (0.41–2.29)	-0.036	0.441	0.01 0.936
			$*_I/*_2$	1.18 (0.49–2.83)	0.166	0.446	0.14 0.711
RAP1 score	156	-4.08*	$*_2/*_2$	1.28 (0.61–2.67)	0.245	0.377	0.42 0.516
			$*_I/*_2$	1.58 (0.75–3.32)	0.457	0.379	1.46 0.227
Max drinks 24 hrs	154	-5.10*	$*_2/*_2$	1.20 (0.65–2.24)	0.186	0.316	0.35 0.556
			$*_I/*_2$	1.00 (0.53–1.89)	-0.001	0.326	0.00 0.997
AUDIT score	156	-4.06*	$*_2/*_2$	1.37 (0.70–2.67)	0.314	0.341	0.85 0.357
			$*_I/*_2$	1.33 (0.67–2.64)	0.284	0.350	0.66 0.417
Reg. drinking, lifetime [†]	156	-2.91	$*_2/*_2$	0.74 (0.21–2.63)	-0.302	0.647	0.22 0.641
			$*_I/*_2$	0.47 (0.13–1.73)	-0.755	0.666	1.29 0.257
SRE score [§]	131	-94	$*_2/*_2$		0.220	0.323	0.46 0.496
			$*_I/*_2$		0.316	0.333	0.90 0.343

ADH1B was dummy-coded such that listed variables represent the $*_2/*_2$ and $*_I/*_2$ genotypes (coded 1) versus $*_I/*_I$ genotype (coded 0). In accordance with reporting conventions, exponentiated coefficients are not reported for the Gamma and Gaussian models. Model for SRE score includes gender and body weight as covariates.

Exp(B), exponentiated parameter estimate (odds ratios for logistic model, incident rate ratios for negative binomial models); CI, confidence intervals for exponentiated parameter estimates; SRE, self-rating of the effects of alcohol.

[†] Logistic model,
[‡] Gamma model,
[§] Gaussian (all other models negative binomial).
* $p < 0.05$,
** $p < 0.01$,
*** $p < 0.001$ for model chi-squared test.