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Association of the *ALDH1A1*2* promoter polymorphism with alcohol phenotypes in young adults with or without *ALDH2*2*

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Abstract

Background—Prior studies suggest a possible association of a promoter polymorphism in the *ALDH1A1* gene (*ALDH1A1*2*) with alcohol use or dependence. The aim of this study was to examine the association of *ALDH1A1*2* with drinking behaviors in Asian young adults and to examine *ALDH2* genotype as a potential moderator of these associations.

Methods—Asian young adults (n = 951) were recruited from two college sites for studies of genetic associations with alcohol use behavior. Participants completed comprehensive background questionnaires on demographics and drinking behavior. Fingertip blood samples were obtained for DNA extraction and analysis.

Results—Participants with the *ALDH2*1/*2* genotype reported significantly lower levels (frequency and quantity) of drinking within the last 90 days, fewer numbers of heavy drinking episodes within the last 90 days, and lower lifetime maximum consumption levels, compared with *ALDH2*1/*1* participants. There were no significant main effects of *ALDH1A1*2* on any drinking variables, nor was there a significant interaction of *ALDH2* and *ALDH1A1* genotypes on drinking outcomes.

Conclusions—The association of *ALDH2*2* and reduced alcohol consumption replicates previous findings across numerous studies. Although *ALDH1A1*2* was not associated with drinking levels, the lack of an *ALDH1A1*2* effect in *ALDH2*2* individuals is consistent with the only other study that has examined these associations in East Asian populations.

Keywords

Alcohol use; *Aldehyde dehydrogenase*; Asian ethnicity; Genetic polymorphisms; Drinking behavior

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Introduction

Efforts to characterize genetic risk for alcohol dependence have been informed considerably by studies of genetic differences in alcohol metabolism (Li, 2000). Across numerous genetic association studies of alcohol dependence (Dick and Foroud, 2003; Gelernter and Kranzler, 2009), including recent genome-wide association studies (e.g., Baik et al., 2011; Bierut et al., 2010; Edenberg et al., 2010), the most consistently replicated associations involve genes contributing to alcohol metabolism. In particular, a well-characterized allelic variant that occurs in up to 50% of East Asians (*ALDH2*2*) encodes a functionally deficient version of the mitochondrial ALDH2 enzyme (for reviews, see Agarwal, 2001; Ramchandani et al., 2001; Vasiliou and Pappa, 2000; Yoshida, 1992). ALDH2 is primarily responsible for the elimination of acetaldehyde during alcohol metabolism. As a result, the buildup of acetaldehyde in homozygous or heterozygous *ALDH2*2* individuals (Enomoto et al., 1991; Wall, 2005) results in unpleasant physical sensations (e.g., nausea, skin flushing, tachycardia) after alcohol consumption and these individuals show decreased risk for alcohol dependence (Crabb et al., 1989; Edenberg, 2007; Luczak et al., 2006; Thomasson and Li, 1993).

Although *ALDH2* is the primary catalytic agent for acetaldehyde (for reviews, see Bosron et al., 1993; Vasiliou and Pappa, 2000), cytosolic ALDH1, encoded by the *ALDH1A1* gene, also has an affinity for acetaldehyde and contributes to its metabolism (Agarwal, 2001; Yoshida, 1992), even in people with the *ALDH2*2* allele (Edenberg, 2007). Decreases in red blood cell ALDH1 enzyme activity levels have been associated with alcohol phenotypes such as flushing (Ward et al., 1994; Yoshida et al., 1989), although these effects were limited to very small samples of Caucasians and Asians. Additionally, acetaldehyde clearance was considerably slower for a Japanese individual with extremely low red blood cell levels of ALDH1 and an *ALDH2*1/*2* genotype, compared to other heterozygous *ALDH2* individuals with normal ALDH1 enzyme function (Takada et al., 1994). Thus, in cases where ALDH2 enzyme levels are depressed, such as *ALDH2*2* homo- or heterozygous Asian drinkers, ALDH1 may have increased relevance for acetaldehyde metabolism.

Genetic association studies of *ALDH1A1* are relatively few. However, the detection of novel polymorphisms has informed several recent studies. Spence et al. (2003) identified a 17 base pair deletion in the *ALDH1A1* promoter region (*ALDH1A1*2*), which occurred at frequencies of 0.035, 0.023, 0.023, and 0.012 in Asian, Caucasian, Jewish, and African American populations, respectively. *ALDH1A1*2* has been associated with protection against high-risk drinking in Southwest California Indians (Ehlers et al., 2004), but has conversely been associated with increased risk for alcohol dependence among African American and Indo-Trinidadian samples (Moore et al., 2007; Spence et al., 2003).

In addition to other studies of *ALDH1A1*2*, recent studies have examined other common single-nucleotide polymorphisms and haplotypes in *ALDH1A1* in relation to alcohol phenotypes. Whereas some studies have reported significant associations with alcohol dependence and heavy drinking (e.g., Lind et al., 2008), others have found no significant associations with alcohol-related outcomes (Kuo et al., 2008; Sherva et al., 2009). Notably, a recent report showed significant associations of a haplotype block in the promoter region that was significantly associated with alcohol dependence status in a Southwestern American Indian population (Liu et al., 2011), adding to prior evidence that the variations in the promoter region could have implications for alcohol use behavior (Moore et al., 2007; Spence et al., 2003).

The low frequencies of *ALDH1A1* promoter polymorphisms and inconsistent associations of these variants with alcohol use suggest that further research with large samples is warranted. Additionally, a focus on East Asian samples could afford a useful context for studying *ALDH1A1* variants by allowing examination of these variants at different presumed levels of ALDH2 activity. In the context of reduced ALDH2 isoenzyme activity (e.g., presence of the *ALDH2*2* allele), *ALDH1A1* alleles may exert differential effects on acetaldehyde oxidation.

The primary aim of this study was to examine the *ALDH1A1*2* polymorphism in relation to specific drinking behaviors in a relatively large sample of Asian young adults with known *ALDH2* genotypes. Based on associations with alcohol dependence in different ethnic populations (Moore et al., 2007; Spence et al., 2003), we hypothesized that individuals with an *ALDH1A1*2* allele (compared to *ALDH1A1*1/*1* homozygous individuals) would report (a) greater average levels of drinking, (b) greater rates of heavy episodic drinking, and (c) greater maximum lifetime alcohol consumption. We also expected an interaction of *ALDH2* and *ALDH1A1*, such that the effects of *ALDH1A1*2* would be stronger in heterozygous *ALDH2*2* individuals, compared to homozygous *ALDH2*1* individuals.

Materials and Methods

Overview

This study utilized data from independent studies of Asian college students recruited at the University of California-San Diego (UCSD) and the University of Washington (UW). Given similarities in sample demographics, genetic analyses and several outcome variables across the two cohorts, we combined data across the sites while controlling for study site as a covariate. The samples were combined in order to examine a larger number of participants with the *ALDH1A1*2* allele given its low frequency.

Eligibility criteria for both the UCSD and UW studies required that participants reported full northeast Asian heritage. A primary difference between the two studies was age: the UCSD study included participants who were at least 21 years of age (mean age = 21.8 years, range = 21–26 years) whereas the UW study included college students of any age (mean age = 20.2 years, range = 18–27 years). Additionally, Japanese participants were included in the UW sample but not the UCSD sample. Table 1 presents descriptive statistics for each sample and results of chi square tests examining differences in the primary variables across samples. Consistent with the higher mean age of the UCSD sample, these students on average reported higher rates of alcohol use. Across the combined samples (N = 951, 48.5% male) the mean age was 21 years (SD = 1.4) and the racial composition was 54.2% Chinese, 44.0% Korean, and 1.9% Japanese.

Participants in both studies provided a fingertip-puncture blood sample for analysis of genetic markers related to ethanol metabolism. Genetic samples for both studies were sent to the same laboratory for analysis using identical procedures (detailed below). Recruitment procedures and assessment of drinking behavior differed to some extent between the two sites, as detailed below.

UCSD sample

The UCSD sample included 751 students who had available genetic data. Participants were recruited using flyers and campus newspaper advertisements and screened by phone to establish eligibility criteria. Eligible students completed an in-person laboratory visit, which included a structured interview using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; 1995) and a 90-day timeline follow-back (TLFB) interview (Sobell and Sobell, 1992). Additional details on this sample have been

reported previously (e.g., Luczak et al., 2011). Four alcohol use variables were used in the current analyses: variables derived from the 90-day TLFB included drinking frequency (defined as number of days on which alcohol was consumed); average drinking quantity (defined as total number of drinks divided by total number of drinking days), and number of heavy drinking episodes (defined as 4 or more drinks for women/5 or more drinks per men in a single sitting. The fourth variable, maximum number of drinks ever consumed in a single drinking episode, was assessed by the SSAGA.

UW sample

Participants in the UW cohort (n = 200) were recruited by email and/or phone to participate in a prospective study. Those agreeing to participate attended a brief laboratory visit to provide informed consent and a blood sample. Shortly following this visit, participants received an email link to complete a web-based survey of alcohol use and related behaviors. Additional details on this sample and study method have been reported previously (Hendershot et al., 2009). The Daily Drinking Questionnaire (DDQ; Collins et al., 1985) was used to calculate typical drinking quantity over the past 90 days (i.e., total number of drinks consumed per week divided by total number of drinking days endorsed). 90-day drinking frequency was assessed using a single item: "*During the last 3 months, how many days a month (out of 30) did you drink alcohol?*" This score was multiplied by three in order to estimate total drinking days in the past 90 days. Maximum drinks consumed in a 24-hour period was assessed using an item from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) question set (NIAAA, 2003). Finally, participants reported the number of heavy drinking episodes that occurred (defined as 4 or more drinks for women/5 for men in a single sitting) in the last 90 days.

Genotyping—Genomic DNA was isolated from dried blood spots (Truett et al., 2000). The primers, ALDH1A-forward: (5'-GCACTGAAAATACACAAGACTGAT-3') and ALDH1A-reverse: (5'- AGAATTTGAGGATTGAAAAGAGTC-3'), were designed on the basis of human *ALDH1A1* exon 1 and promoter sequences (accession number M31982) and used in polymerase chain reactions (PCRs) to obtain [α-^{33}P] deoxycytidine triphosphate-radiolabeled fragments. Products were electrophoresed on 6% acrylamide denaturing gels and scored on the basis of the mobility of each resulting PCR fragment (see Spence et al., 2003). *ALDH2* genotyping was conducted using similar methods as described previously (Hendershot et al., 2009; Luczak et al., 2011).

Preliminary Analyses and Data Analytic Plan—Primary analyses were conducted with the combined samples. Lifetime abstainers (n = 43) were excluded a priori. Because preliminary descriptive analyses indicated that the alcohol outcome variables were non-normally distributed, we used a generalized linear modeling framework for the primary analyses (Hardin and Hilbe, 2007; Neal and Simons, 2007). The negative binomial distribution, which assumes overdispersed, positively skewed and non-negative integer values, was deemed most appropriate for modeling these positively skewed, count-based alcohol outcomes. We used conditional, fixed-effects models to condition out any potential site effects (i.e., differences between the UCSD and UW samples). To enhance model interpretability, exponentiated coefficients (i.e., incident rate ratios) were used. Alpha was set at p = .05, and confidence intervals were set at 95%.

Four negative binomial regression models tested the effects of *ALDH2* status, *ALDH1A1* status, and the *ALDH2*×*ALDH1A1* interaction on four alcohol outcomes, including 90-day alcohol frequency, typical quantity, and frequency of heavy-drinking episodes, as well as lifetime peak drinking quantity. All analyses controlled for gender (1 = female, 0 = male) and ethnicity (0 = Chinese, 1 = Korean or Japanese) as covariates. The *ALDH2* effect was

evaluated using a dummy-coded variable. Individuals with no variant alleles (**1/*1* genotype) were designated as the reference group (coded 0) and were compared to those with the **1/*2* genotype (coded 1). The *ALDH1A1* effect also was evaluated using a dummy-coded variable (0 = **1/*1*, 1 = **1/*2*).

Results

In the combined sample, 6.3% of participants ($n = 60$) were heterozygous for *ALDH1A1*2* and one person was homozygous for *ALDH1A1*2* (overall allele frequency = .03). *ALDH1A1* genotype frequencies did not differ significantly by gender, ethnicity or *ALDH2* genotype. *ALDH2* genotype frequencies were 58.6% *ALDH2*1/*1* homozygotes, 34.4% *ALDH2*1/*2*, and 6.5% *ALDH2*2/*2* homozygotes. Five individuals were missing *ALDH2* genotype data. Chi square tests for Hardy Weinberg equilibrium (HWE), conducted separately for each study site, showed that genotypes did not diverge from expected distributions. (*ALDH1A1:* $p = .78$ for UCSD sample, $p = .61$ for UW sample; *ALDH2:* $p = .59$ for UCSD sample, $p = .09$ for UW sample). The *ALDH2*2/*2* group contained only four individuals with *ALDH1A1*2*; this group was omitted from further analyses because it was too small to include in tests of interaction effects. Additionally, the *ALDH1A1*2* homozygous individual was removed from further analyses. Seven participants from the UW sample were missing behavioral data due to not completing any part of the web-based survey. These criteria resulted in a final sample of 881 participants for primary analyses.

Sample comparisons on demographic, genotype and drinking variables are presented in Table 1. The UW sample included a significantly higher proportion of individuals with the *ALDH2*2* allele. This difference reflects the ethnic distribution of the two samples: the UCSD sample included a relatively higher proportion of Korean participants, a group that shows a lower prevalence of the *ALDH2*2* allele compared to Chinese or Japanese samples (Eng et al., 2007). *ALDH1A1* genotype distribution did not differ across samples. The UCSD sample reported significantly higher drinking quantity and heavy drinking, likely reflective of the significantly higher age of this sample compared to the UW sample.

Primary Analyses

The conditional fixed effects negative binomial regression for drinking frequency was significant, Wald χ^2 (5, $N = 841$) = 42.96, $p < .001$. After controlling for gender and ethnicity, there was a significant *ALDH2* main effect (see Table 2 for model parameters). Thus, participants with the *ALDH2*1/*2* genotype evinced 21% lower rates of alcohol-use frequency than participants with the *ALDH2*1/*1* genotype. As shown in Table 2, neither the *ALDH1A1* main effect nor the *ALDH1A1×ALDH2* interaction was significant.

The conditional fixed effects negative binomial regression for typical drinking quantity was significant, Wald χ^2 (5, $N = 840$) = 103.78, $p < .001$. After controlling for gender and ethnicity, there was a significant *ALDH2* main effect (see Table 2 for model parameters). Thus, participants with the *ALDH2*1/*2* genotype evinced 28% lower rates of typical quantity than participants with the *ALDH2*1/*1* genotype. As shown in Table 2, neither the *ALDH1A1* main effect nor the *ALDH1A1×ALDH2* interaction was significant.

The conditional fixed effects negative binomial regression for 90-day number of heavy drinking episodes was significant, Wald χ^2 (5, $N = 840$) = 80.76, $p < .001$. After controlling for gender and ethnicity, there was a significant *ALDH2* main effect (see Table 2 for model parameters). Thus, participants with the *ALDH2*1/*2* genotype evinced 46% lower rates of heavy drinking episodes than participants with the *ALDH2*1/*1* genotype. As shown in Table 2, neither the *ALDH1A1* main effect nor the *ALDH1A1×ALDH2* interaction was significant.

The conditional fixed effects negative binomial regression for lifetime peak drinking quantity was significant, Wald χ^2 (5, N = 840) = 189.91, p < .001. After controlling for gender and ethnicity, there was a significant *ALDH2* main effect (see Table 2 for model parameters). Thus, participants with the *ALDH2*1/*2* genotype evinced 23% lower rates of lifetime peak drinking than participants with the *ALDH2*1/*1* genotype. As shown in Table 2, neither the *ALDH1A1* main effect nor the *ALDH1A1×ALDH2* interaction was significant.

Discussion

This study examined the joint effects of *ALDH2* and *ALDH1A1* genotypes on drinking behaviors in Asian young adults. Individuals with the *ALDH2*1/*2* genotype reported lower rates of drinking frequency and quantity, fewer heavy drinking episodes in the last 3 months, and lower lifetime peak consumption, compared to those people with the *ALDH2*1/*1* genotype. Numerous studies have shown that possessing an *ALDH2*2* allele results in acetaldehyde accumulation after alcohol consumption (Enomoto et al., 1991; Wall et al., 1997), which in turn leads to more intense physical reactions to alcohol including skin flushing, tachycardia, and nausea (Crabb et al., 1989; Edenberg, 2007; Luczak et al., 2006; Thomasson and Li, 1993). Thus, the association of *ALDH2*2* with reduced drinking was expected and is consistent with previous studies (Luczak et al., 2006).

*ALDH1A1*2* was not associated with any of the drinking variables assessed in this study, nor did *ALDH1A1*2* interact with *ALDH2* to predict any specific drinking behaviors. The current study is the largest to date to examine *ALDH1A1*2* in an Asian sample. The lack of significant *ALDH1A1*2* effects is consistent with a smaller case-control study (Spence et al., 2003) in which *ALDH1A1*2* did not relate to alcohol dependence status in an Asian sample after controlling for *ALDH2* genotype. In contrast, *ALDH1A1*2* has been significantly associated with alcohol phenotypes in other ethnic populations, albeit not consistently in the same direction (Ehlers et al., 2004; Moore et al., 2007; Spence et al., 2003). Despite findings demonstrating that *ALDH1A1* promoter variants may influence gene expression *in vitro* (Spence et al., 2003), there is not a clear mechanism to explain associations of *ALDH1A1* with drinking behaviors in previous studies (Ehlers et al., 2004; Moore et al., 2007; Spence et al., 2003). It has been noted that *ALDH1A1* promoter variations could have differential effects on enzyme activity levels in different cell types, such as hepatic and blood, which could contribute to contradictory effects (Edenberg, 2007; Hansell et al., 2005). Some findings suggest differential acetaldehyde clearance rates based on ALDH1 activity levels in differing *ALDH2* genotypes (Takada et al., 1994). Experimental studies examining the rate of acetaldehyde clearance in different *ALDH1A1* genotypes while controlling for *ALDH2* are a possible focus for future research.

Despite the lack of association between *ALDH1A1*2* and drinking phenotypes, one strength of this study was the relatively large sample size, considering the low frequency of *ALDH1A1*2*. In addition, only one other study to date has examined *ALDH1A1*2* while controlling for *ALDH2* genotype, although those findings were confined to alcohol dependence status, rather than consumption levels (Spence et al., 2003). Although the sample size of East Asians in this study is the largest to date, the very low frequency of *ALDH1A1*2* means that an even larger sample size is warranted to capture effects of *ALDH1A1*2* in the presence of *ALDH2* variants, as this study was underpowered to find significant differences for *ALDH1A1*2* on the drinking outcomes. This study also did not have sufficient power to examine the effects of *ALDH1A1*2* among *ALDH2*2* homozygous individuals. Some additional limitations of this study warrant consideration. The use of two separate sample sites provided increased statistical power, but the individual variables differed slightly in their measurement and administration and all outcomes relied

on retrospective recall. The combined sample was also a rather specific population – Asian college students – restricting generalizability to other samples. However, this approach allowed us to examine the combined effects of *ALDH1A1*2* and *ALDH2*2*. Although analyses for this study did not include measures of alcohol dependence status – a main focus for other studies investigating effects of *ALDH1A1* – we examined a broad range of drinking variables, all of which related to *ALDH2*2*. It is possible that *ALDH1A1*2* could show stronger associations with potential mediating factors, such as laboratory-based measures of response to alcohol, than with self-reported drinking behaviors.

The association of *ALDH2*2* with reduced drinking in this sample replicates robust findings in the literature, providing further support for the influence of alcohol-metabolizing genes in alcohol use behavior. In contrast, conclusions about *ALDH1A1* have been mixed, as *ALDH1A1*2* has been significantly associated with both a risk for and protection against alcohol dependence (Ehlers et al., 2004; Moore et al., 2007; Spence et al., 2003), while the null effects of *ALDH1A1*2* in these analyses replicate findings in an Asian sample from a previous study (Spence et al., 2003). These inconsistencies strongly suggest the need for further research. Considering the significant associations of *ALDH1A1* with alcohol dependence in prior studies (Kuo et al., 2006; Liu et al., 2011), future investigations might address these limitations.

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Table 1

Descriptive characteristics by study site

Variable	UCSD (*n* = 751)	UW (*n* = 200)	*p*
Gender (%)			.53
Male	49.0	53.5	
Female	51.0	46.5	
Age	21.8	20.2	<.001
Ethnicity (%)			<.001
Chinese	53.3	57.5	
Korean	46.7	33.5	
Japanese	0.0	9.0	
ALDH1A1 (%)			.79
*ALDH1A1*1/*1*	93.7	93.0	
*ALDH1A1*1/*2*	6.1	7.0	
*ALDH1A1*2/*2*	0.1	0.0	
ALDH2 (%)			.01
*ALDH2*1/*1*	60.6	52.5	
*ALDH2*1/*2*	34.0	36.5	
*ALDH2*2/*2*	5.4	11.0	
Drinking frequency			.59
	3.49 (4.21)	3.68 (4.81)	
Drinking quantity			<.001
	2.46 (2.25)	1.58 (1.87)	
Heavy episodes			<.001
	3.04 (6.54)	1.02 (1.52)	
Maximum drinks lifetime			
	8.93 (7.22)	6.35 (6.27)	<.001

Note. *p* values for variables presented in % represent chi square tests; all other *p* values represent ANOVA tests.

Table 2

Model Parameters

Predictors	*IRR*	Semi-robust *SE*	*CI* (95%)	*z*	*p*
Typical drinking frequency					
Gender	.73	.05	.64–.83	−4.88	<.001
Ethnicity	1.18	.08	1.04–1.35	2.58	.01
ALDH1A1	.83	.14	.59–1.16	−1.09	.28
ALDH2	.79	.06	.69–.91	−3.22	.001
ALDH1A1×ALDH2	1.65	.45	.97–2.80	1.84	.07
Typical drinking quantity					
Gender	.69	.04	.62–.77	−6.68	<.001
Ethnicity	1.32	.07	1.19–1.47	5.06	<.001
ALDH1A1	.92	.12	.70–1.20	−0.62	.53
ALDH2	.72	.04	.64–.81	−5.29	<.001
ALDH1A1×ALDH2	1.49	.34	.96–2.33	1.77	.08
Lifetime maximum drinks					
Gender	.64	.03	.58–.69	−9.99	<.001
Ethnicity	1.41	.06	1.29–1.54	7.55	<.001
ALDH1A1	.91	.10	.73–1.14	−0.83	.41
ALDH2	.77	.04	.69–.84	−5.32	<.001
ALDH1A1×ALDH2	1.34	.25	.92–1.94	1.54	.12
Number of heavy-drinking episodes					
Gender	.69	.07	.58–.84	−3.86	<.001
Ethnicity	1.68	.16	1.39–2.03	5.38	<.001
ALDH1A1	.93	.20	.61–1.44	−0.31	.76
ALDH2	.54	.06	.43–.67	−5.52	<.001
ALDH1A1×ALDH2	.99	.46	.39–2.47	−0.03	.98

Note. *IRR* = incident rate ratios. *CI* (95%) = 95% confidence intervals