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Meta-Analysis on Associations of Alcohol Metabolism Genes With Alcohol Use Disorder in East Asians

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Abstract

Aims: The current meta-analysis tested independent and composite associations of three commonly studied alcohol metabolism alleles with alcohol use disorder (AUD) within East Asians as well as characterized potential moderating factors in these associations.
Methods: For meta-analysis, 32 articles were selected that investigated *ALDH2* (n = 17,755), *ADH1B* (n = 13,591) and *ADH1C* (n = 4,093) associations with AUD in East Asians.
Results and conclusions: All three variants were associated with AUD across allelic and genotypic models: *ALDH2*, ORs = 0.25, $P < 0.001$; *ADH1B*, ORs = 0.22–0.49, $P < 0.001$; *ADH1C*, ORs = 0.26–0.46, $P < 0.001$. Composite analyses suggested genetic associations did not differ across *ALDH2*2* and *ADH1B*2*, correcting for multiple comparisons. Moderation analyses suggested *ADH1B* was more strongly associated with AUD among samples with cases recruited from treatment than the community. Also, strength of *ALDH2* and/or *ADH1B* associations varied with mean age and proportion of men in cases and controls. Findings support medium to large and unique associations of *ALDH2*, *ADH1B*, and *ADH1C* with AUD in East Asians. Results also identified novel methodological and sample characteristics that may modulate strength of these associations.

INTRODUCTION

Alcohol use disorder (AUD) is characterized by problematic alcohol consumption resulting in significant impairment. Over 1 million adolescents and adults (over age 15) met criteria for alcohol dependence worldwide in 2010, and 139 million disability-adjusted life years and 3.3 million global deaths were attributed to alcohol in 2012 (World Health Organization, 2014). Alcohol use and AUD contribute to academic/occupational impairment, social repercussions, adverse health conditions and unintentional injury, thereby resulting in substantial economic, social and public health burden across the globe.

AUD is moderately heritable (Verhulst *et al.*, 2015). Among the many candidate genes for alcohol use, variants in alcohol metabolism genes have demonstrated consistent associations with AUD across genome-wide association studies (Gelernter *et al.*, 2014). Alcohol metabolism occurs through a two-step process, whereby alcohol dehydrogenase (ADH) enzymes catalyze the conversion of alcohol to acetaldehyde and aldehyde dehydrogenase (ALDH) enzymes catalyze the subsequent conversion of acetaldehyde into acetate (Edenberg, 2007). *ADH* and *ALDH* alleles are theorized to influence AUD risk by increasing acetaldehyde levels through enhanced conversion of alcohol into acetaldehyde (via *ADH* alleles) or reduced conversion of acetaldehyde into acetate (via ALDH alleles; Thomasson *et al.*, 1995; Wall, 2005). Acetaldehyde accumulation can result in negative physical reactions (e.g. facial flushing, nausea, increased pulse; Edenberg, 2007), rendering high-activity *ADH* and/or low-activity *ALDH* alleles protective against AUD.

Of the many *ADH* and *ALDH* genes, alleles of the aldehyde dehydrogenase 2 (*ALDH2*) and alcohol dehydrogenase 1B (*ADH1B*, formally *ADH2*) and 1 C (*ADH1C*, formally *ADH3*) genes have been well-studied in relation to AUD. The *ALDH2*2* allele (rs671) involves an amino acid substitution in which **2* has reduced ALDH enzymatic activity relative to **1* (Edenberg, 2007). The *ADH1B*2* (rs1229984) and *ADH1C*1* (rs698) alleles are associated with increased conversion of alcohol to acetaldehyde relative to the *ADH1B*1* and, to a lesser extent, *ADH1C*2* alleles (see Edenberg, 2007). The alleles are more prevalent among Asians than other racial/ethic groups, such as Europeans and African Americans (Wall *et al.*, 2016). Specifically, *ALDH2*2* frequencies range from 0.11 to 0.28 among Asians while *ALDH2*2* is virtually absent in other racial/ethnic groups (Wall *et al.*, 2016). All three alleles have demonstrated consistent, protective associations with alcohol use and AUD across genome-wide association studies (Takeuchi *et al.*, 2011; Park *et al.*, 2013; Quillen *et al.*, 2014) and meta-analyses (Whitfield, 1997; Luczak *et al.*, 2006; Zintzaras *et al.*, 2006; Li *et al.*, 2011, 2012a, 2012b) among Asian, East Asian and Caucasian samples.

Although meta-analyses demonstrate consistent support for *ALDH2*, *ADH1B* and/or *ADH1C* associations with AUD, important gaps exist in previous efforts. First, some reports have combined analyses across diverse racial (Europeans and Asians; Whitfield, 1997) and ethnic (East Asians and South Asians; Luczak *et al.*, 2006; Li *et al.*, 2011, 2012a, 2012b) groups. Differences in allele frequencies across populations can lead to spurious findings when allele frequencies (and disease rates) differ across the populations from which cases and controls are drawn (i.e. population stratification). Meta-analyses on exclusive East Asian samples (Chinese, Japanese, Taiwanese, Mongolian, Korean), in which allele frequencies are relatively similar and prevalent (Eng *et al.*, 2007), are needed to minimize confounding effects of race/ethnicity.

Second, most meta-analyses have tested independent associations of alcohol metabolism alleles with AUD. Significant linkage disequilibrium exists within alcohol metabolism genes (Li *et al.*, 2012b), and allelic associations may not be independent. Individual studies have suggested greater associations of *ADH1B* among *ALDH2*2* carriers than noncarriers (Chen *et al.*, 1999). However, meta-analytic findings on composite associations (associations of one allele as a function of another allele) are limited; one meta-analysis reported nonsignificant differences in *ADH1B* associations as a function of *ALDH2*2* (k = 12; Luczak *et al.*, 2006), and another reported nonsignificant differences in *ADH1B* or *ADH1C* associations as a function of *ALDH2*2* (k = 4 and 2, respectively; Whitfield, 1997). Meta-analysis with recent publications may afford comparisons across a larger number of samples to explore further any potential gene–gene interactions identified in individual investigations.

Third, effect size heterogeneity across meta-analyses suggests important factors modifying these genetic associations remain unknown. Nationality may contribute, given differences in acceptability of alcohol and alcohol-related policies across East Asia. Age differences in aggregated genetic and single allelic associations with alcohol use across development (Rose *et al.*, 2001; Dick *et al.*, 2006) also suggest possible heterogeneity by age. Additionally, sex may modulate such associations, given sex differences in alcohol-promoting and -protective sociocultural (Nolen-Hoeksema, 2004) and biological (Thomasson *et al.*, 1995) factors. Recruitment source also may contribute, as associations of these alleles with alcohol-related medical conditions (Li *et al.*, 2011, 2012a, 2012b) may contribute to their uneven distribution across treatment and community settings. Diagnostic criteria may also contribute to heterogeneity, as genetic associations may be stronger among cases with alcohol dependence than those with alcohol abuse and sensitivity to detect genetic associations with AUD has differed across diagnostic systems (Van Den Bree *et al.*, 1998). Finally, publication year may be an important moderator, as *ALDH2* associations were found to change over time potentially due to cultural shifts (Higuchi *et al.*, 1994). While nationality, sex, and recruitment source moderated *ALDH2* and/or *ALDH2–ADH1B* associations in a previous meta-analysis (Luczak *et al.*, 2006), their moderating role in *ADH1B* and *ADH1C* associations remains unknown. Similarly, the moderating role of age has thus far only been tested for *ALDH2* (Luczak *et al.*, 2006). Further, meta-analysis is needed to resolve mixed findings on diagnostic system; specifically, diagnostic criteria moderated *ALDH2* associations in one (Luczak *et al.*, 2006) but not another (Li *et al.*, 2012b) meta-analysis, and it did not moderate *ADH1B* (except the recessive model; Li *et al.*, 2011) or *ADH1C* (Li *et al.*, 2012a) associations with AUD.

This meta-analysis updated and expanded upon previous work on *ALDH2*, *ADH1B* and *ADH1C* associations with AUD by focusing on East Asian samples (to reduce confounding effects of population stratification) and testing independent and composite associations with AUD. Further, this meta-analysis examined potential moderators (i.e. nationality, age, sex, recruitment source, diagnostic criteria, publication year) that may underlie heterogeneity in effect sizes across studies. This article was prepared in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2009; see Table S3); the study was not registered.

METHODS

Literature search and study selection

A systematic literature search was conducted for articles of all publication types in July 2018. Searches were conducted in *PubMed/Medline* (coverage from the 1940s) given its coverage of broad clinical and genetics topics as well as in *PsycINFO* (coverage from the 1880s) given its coverage of specialized topics in the behavioral and social science. Database searches used the following sample search: (alcohol dehydrogenase OR ADH OR aldehyde dehydrogenase OR ALDH) AND (alcoholism OR alcohol dependence OR alcohol use disorder) AND (Asian OR Chinese OR Japanese OR Korean). Reference lists from identified articles and relevant reviews/meta-analyses were also hand-searched. For inclusion, studies needed to meet the following criteria: (a) investigation of at least one of the target alleles (rs671, rs1229984, rs698); (b) diagnosis of AUD (including alcohol abuse and/or dependence) using standardized diagnostic criteria; (c) East Asian sample; (d) sufficient information for effect size calculation; (e) written in English; and (f) representing original data. Efforts were made to contact all corresponding authors for incomplete data; the laboratories of Daniel E. Irons, Sung-Gon Kim, Tamara L. Wall and K. Yoshimasu provided data by the time of manuscript submission that is included below.

Data extraction

Analyses were conducted under allelic, genotypic dominant and genotypic recessive models; the recessive model was not tested for *ALDH2* given research suggesting *ALDH2*2* may be nearly dominant (see Edenberg, 2007) and the documented low prevalence of *ALDH2*2/2* among AUD cases (Hasegawa *et al.*, 2002). Two

(allele/genotype presence) × 2 (AUD status) frequency tables were generated and used to calculate an odds ratio (OR) with 95% confidence interval (Lipsey and Wilson, 2001) when necessary; a continuity correction of 0.5 was used if a cell frequency was zero (Cox, 1970). The hypothesized protective (rather than unique) alleles were used as reference when computing ORs: *ALDH2*, allelic (**2* vs. **1*), dominant (**1/2+*2/2* vs. **1/1*); *ADH1B*, allelic (**2* vs. **1*), dominant (**1/2+*2/2* vs. **1/1*), recessive (**2/2* vs. **1/1+*1/2*); *ADH1C*, allelic (**1* vs. **2*), dominant (**1/1+*1/2* vs. **2/2*), recessive (**1/1* vs. **1/2+*2/2*). Frequency of the protective allele and adherence of genotypes to Hardy–Weinberg equilibrium were calculated for controls when possible, and sensitivity analyses compared results after excluding samples not adherent to Hardy–Weinberg equilibrium. Given associations of alcohol metabolism alleles with alcohol-related medical conditions (Li *et al.*, 2011, 2012a, 2012b), cases and/or controls with alcohol-related medical (but not psychiatric) comorbidities were excluded (Luczak *et al.*, 2006); when studies reported on multiple groups, data from those with no medical comorbidities were used (e.g. control alcoholics and control drinkers).

For moderator analyses, sample nationality was coded as Korean, Chinese/Taiwanese or Japanese; Taiwanese samples were coded as Chinese, because the Han Chinese are the largest ethnic group in Taiwan (Zhang *et al.*, 2010). Asian American samples (k = 3) were excluded from nationality moderator analyses due to potential differences in alcohol-related cultural beliefs, norms and attitudes. For mean age and proportion of men in cases and controls, weighted means and proportions were calculated from available data. Recruitment source for cases was coded as treatment or community, with community sources including student and workforce samples; samples with cases recruited from jails (k = 1) or mixed community/treatment settings (k = 6) were excluded. Studies were coded on whether cases included alcohol abuse in addition to alcohol dependence. Diagnostic system was coded as ICD-10, *DSM-III-R* or *DSM-IV/DSM-IV-TR*; the sample using *DSM-III* criteria was excluded.

To evaluate study quality, the domain-based Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS; Kim *et al.*, 2013) was used. Sensitivity analyses compared results across all studies to results after excluding studies rated 'High' for any bias domain.

Data were extracted by two independent coders (M.J.Z. and P.A.G.) using piloted forms. Interrater agreement was strong for categorical (mean Cohen's κ = 0.91; 95% agreement) and continuous (mean intraclass correlation coefficient = 0.99) variables, with discrepancies resolved through discussion.

Data synthesis

Meta-analysis was conducted in Comprehensive Meta-Analysis, Version 3.2 with a random effects model (Lipsey and Wilson, 2001; Borenstein *et al.*, 2009). Between-study heterogeneity was estimated using Cochran's Q (Lipsey and Wilson, 2001; Borenstein *et al.*, 2009) and I^2 (Higgins *et al.*, 2003), with I^2 values of 25, 50 and 75% interpreted as low, moderate and high variance attributed to true differences in effect sizes across populations (Higgins *et al.*, 2003). Models with fewer than four samples were excluded based on power analyses (Hedges and Pigott, 2001) assuming a threshold effect size of 0.80 and a two-tailed α = 0.05 in a fixed effects model, using effect size estimates from previous meta-analyses (Li *et al.*, 2011, 2012a, 2012b) converted to Cohen's d (Borenstein *et al.*, 2009). Moderators were tested in associations with significant between-study heterogeneity. Categorical moderators were examined using the Q statistic of between-subgroups variance (Borenstein *et al.*, 2009) and subgroup random effects meta-analysis. Continuous moderators were assessed with mixed-effects meta-regression. Subgroup differences in *ALDH2–ADH1B*, *ALDH2–ADH1C* and *ADH1B–ALDH2* composite analyses were examined with an interaction test (Altman and Bland, 2003) using a Bonferroni-adjusted α = 0.01 (0.05/6 comparisons); several notable gene–gene interaction analyses (e.g. *ADH1B–ADH1C*) were precluded due to low power. Publication bias was estimated using the alternative regression test in SPSS Version 23 (Peters *et al.*, 2006).

RESULTS

Study selection and sample characteristics

A flow diagram detailing study identification, screening, eligibility and selection is shown in Fig. 1. Articles were eliminated through abstract and/or full-text review, most for not presenting empirical data or reporting on outcomes other than AUD (e.g. alcohol use, alcohol consequences, medical conditions, biological responses to alcohol). When separate articles reported on the same sample, those reporting data from more participants or alleles and/or providing more information for effect size calculation were retained (see Supplemental Information). The final sample was composed of 32 studies (see Table S1) with 41 samples. Samples included 17 investigations in Chinese/Taiwanese, 11 in Japanese and 10 in Korean samples; three samples examined Asian Americans. Most samples examined associations of *ALDH2* and AUD (n = 7857 cases and 9898 controls), with 31 examining *ADH1B* (n = 5409 cases and 8182 controls) and 17 examining *ADH1C* (n = 1906 cases and 2187 controls).

Study quality

Prevalent sources of potential bias arose from participant selection (cases and controls recruited from different sources) and confounding variables (differences in demographics across cases and controls;

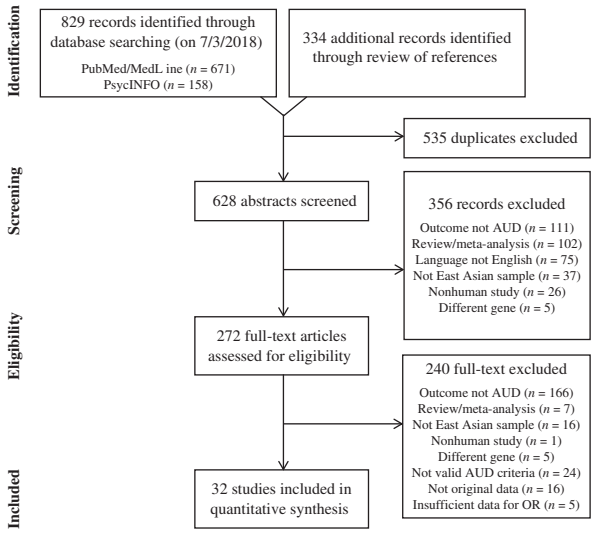

Figure 1. Flow diagram of studies selected for meta-analysis. Diagram prepared in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2009). AUD = alcohol use disorder; OR = odds ratio.

Table S2). Sensitivity analyses excluding studies rated 'High' on any domain yielded the same pattern of significance and generally comparable effect sizes for *ALDH2* (allelic: OR = 0.30 [0.18,0.51], $P < 0.001$; dominant: OR = 0.28 [0.16,0.52], $P < 0.001$), *ADH1B* (allelic: OR = 0.49 [0.38,0.65], $P < 0.001$; dominant: OR = 0.53 [0.40,0.69], $P < 0.001$; recessive: OR = 0.24 [0.14,0.38], $P < 0.001$), and *ADH1C* (allelic: OR = 0.49 [0.30,0.81], $P = 0.005$; dominant: OR = 0.49 [0.29,0.83], $P = 0.008$; recessive: OR = 0.25 [0.07,0.91], $P = 0.04$), suggesting protective associations may exist regardless of such methodological limitations.

Independent associations with AUD

ALDH2: *ALDH2* was associated with AUD in allelic (OR = 0.25 [0.20,0.31], $P < 0.001$, $n = 26{,}144$) and dominant (OR = 0.25 [0.20,0.33], $P < 0.001$, $n = 17{,}252$) models (Table 1). There was significant, large between-study heterogeneity in allelic ($Q_{33} = 148.37$, $P < 0.001$, $I^2 = 78\%$) and dominant ($Q_{38} = 221.07$, $P < 0.001$, $I^2 = 83\%$; Table 1) models. *ALDH2* genotypes were not adherent to Hardy–Weinberg equilibrium in 10 control samples (Fig. S1), although sensitivity analyses excluding these samples yielded the same pattern of significance as main analyses (Table 1).

ADH1B: *ADH1B* was associated with AUD in allelic (OR = 0.46 [0.39,0.54], $P < 0.001$, $n = 22{,}730$), dominant (OR = 0.49 [0.42,0.59], $P < 0.001$, $n = 11{,}365$), and recessive (OR = 0.22 [0.16,0.29], $P < 0.001$, $n = 11{,}228$) models (Table 1). There was significant moderate to high between-study heterogeneity in allelic ($Q_{30} = 142.78$, $P < 0.001$, $I^2 = 80\%$), dominant ($Q_{30} = 80.60$, $P < 0.001$, $I^2 = 63\%$), and recessive ($Q_{28} = 89.63$, $P < 0.001$, $I^2 = 69\%$) models (Table 1). *ADH1B* genotypes deviated from Hardy–Weinberg equilibrium in two control samples (Fig. S2), although sensitivity analyses excluding these samples yielded the same pattern of significance as main analyses (Table 1).

ADH1C: *ADH1C* was associated with AUD in allelic (OR = 0.46 [0.37,0.59], $P < 0.001$, $n = 7964$), dominant (OR = 0.45 [0.35,0.58], $P < 0.001$, $n = 3982$), and recessive (OR = 0.26 [0.14,0.47], $P < 0.001$, $n = 3530$) models (Table 1). Nonsignificant between-study heterogeneity was found across models (Table 1), and *ADH1C* genotypes were adherent to Hardy–Weinberg equilibrium in all control samples.

Composite associations with AUD

ALDH2–ADH1B: Subgroup analyses indicated nonsignificant differences in *ADH1B* associations among *ALDH2*2* carriers compared to noncarriers in allelic ($z = 1.57$, $P = 0.12$), dominant ($z = 0.30$, $P = 0.76$), and recessive ($z = 1.94$, $P = 0.05$) models, adjusting for multiple comparisons. *ADH1B* was associated with AUD among *ALDH2*2* carriers (ORs = 0.14–0.47, $P < 0.001$) and noncarriers (ORs = 0.33–0.55, $P \leq 0.001$; Table 1).

ALDH2–ADH1C: Subgroup analyses indicated nonsignificant differences in *ADH1C* associations among *ALDH2*2* carriers compared to noncarriers in allelic ($z = 0.45$, $P = 0.65$) and dominant ($z = 0.10$, $P = 0.92$) models, adjusting for multiple comparisons. *ADH1C* was associated with AUD among *ALDH2*2* carriers (ORs = 0.37–0.40, $P < 0.05$) and noncarriers (ORs = 0.32–0.43, $P < 0.01$; Table 1).

ADH1B–ALDH2: Subgroup analyses indicated nonsignificant differences in *ALDH2* associations among *ADH1B*2* carriers compared to noncarriers in the dominant ($z = 1.81$, $P = 0.07$) model, adjusting for multiple comparisons. *ALDH2* was associated with AUD among *ADH1B*2* carriers (OR = 0.17, $P < 0.001$) and noncarriers (OR = 0.37, $P = 0.01$; Table 1).

Potential moderators

Associations of *ADH1B* (but not *ALDH2*) differed as a function of case recruitment source ($Q_{between} = 7.41$–22.40, $P \leq 0.01$), such that protective associations were stronger among samples with cases recruited from treatment settings than the community (Table 2). Mean age of cases was significantly associated with strength of *ALDH2* ($b = -0.04$, $P = 0.01$) and *ADH1B* ($bs = -0.06$ to -0.03, $P < 0.05$) associations across allelic and genotypic models, except in the *ALDH2* dominant model ($b = -0.03$, $P = 0.05$; Table 3). Mean age of controls was only associated with strength of *ADH1B* associations in allelic ($b = -0.03$, $P = 0.01$) and recessive ($b = -0.04$, $P = 0.04$) models (Table 3). Proportion of men in cases and controls was significantly associated with strength of *ALDH2* (but not *ADH1B*) associations across allelic and genotypic models ($bs = -2.74$ to -1.15, $P < 0.05$; Table 3). Proportion of males in cases was relatively more strongly related to strength of genetic protection than proportion of males in controls; although preliminary, these results suggest studies with a greater proportion of males in cases may be somewhat more likely to demonstrate stronger *ALDH2* genetic protection than studies with a greater proportion of males in controls. Publication year, nationality, diagnostic system and inclusion of cases meeting criteria for alcohol abuse did not moderate *ALDH2* or *ADH1B* associations (Tables 2 and 3).

Publication bias

Alternative regression tests suggested no significant publication bias in *ALDH2*, *ADH1B* or *ADH1C* associations across allelic, dominant or recessive models; funnel plots available on request.

DISCUSSION

This meta-analysis updated literature on associations of three alcohol metabolism alleles with AUD by (a) focusing on exclusively East Asian samples to reduce confounding effects of race and population stratification; (b) examining independent and composite associations with AUD; and (c) testing potential moderators that have been understudied in recent work. All three variants were associated with AUD in East Asians across allelic and genotypic models: *ALDH2*, OR = 0.25; *ADH1B*, ORs = 0.22–0.49; *ADH1C*, ORs = 0.26–0.46. Protective associations increased with increases in mean age of cases (for *ALDH2* and *ADH1B*) and proportion of men (for *ALDH2*). *ADH1B* was more strongly associated with AUD among samples with cases recruited from treatment than the community.

Carriers of *ALDH2*2* had approximately one-fourth the odds (OR = 0.25) of meeting criteria for AUD as noncarriers, an estimate comparable to previous meta-analyses with more racially diverse Asian samples (ORs = 0.23; Zintzaras *et al.*, 2006; Li *et al.*, 2012b). Meta-analysis also identified significant heterogeneity in effect sizes. Specifically, *ALDH2* protective associations increased as mean age of cases increased, consistent with research suggesting increases in overall genetic influences on substance use over development (Kendler *et al.*, 2008). Increasing genetic protection with age across these 32 studies (sample *M* ages = 18.0–61.6 years) is somewhat contradictory to findings within 4879 Japanese men over age 40 (*M* age = 55.7 years), which suggested absence of protective alcohol metabolism alleles may be less influential with increasing age (Yokoyama *et al.*, 2013). Future research is needed to examine these discrepancies, with the possibility

Table 1. Results from Random Effects Meta-Analysis on Associations of ALDH2, ADH1B, and ADH1C with Alcohol Use Disorder (AUD) in East Asians

	Allelic Model					Dominant Model					Recessive Model				
	k	OR [95% CI]	*p*	*Q*	*p*	*k*	OR [95% CI]	*p*	*Q*	*p*	*k*	OR [95% CI]	*p*	*Q*	*p*
Independent Associations															
ALDH2 (rs671)															
All	34	0.25 [0.20,0.31]	<0.001	148.37	<0.001	39	0.25 [0.20,0.33]	<0.001	221.07	<0.001	–	–	–	–	–
HWE	24	0.22 [0.18,0.28]	<0.001	57.50	<0.001	29	0.25 [0.19,0.33]	<0.001	139.92	<0.001	–	–	–	–	–
ADH1B (rs1229984)															
All	31	0.46 [0.39,0.54]	<0.001	142.78	<0.001	31	0.49 [0.42,0.59]	<0.001	80.60	<0.001	29	0.22 [0.16,0.29]	<0.001	89.63	<0.001
HWE	29	0.45 [0.38,0.53]	<0.001	133.87	<0.001	29	0.49 [0.41,0.59]	<0.001	79.08	<0.001	27	0.22 [0.16,0.29]	<0.001	77.64	<0.001
ADH1C (rs698)															
All	17	0.46 [0.37,0.59]	<0.001	25.16	0.07	17	0.45 [0.35,0.58]	<0.001	24.48	0.08	12	0.26 [0.14,0.47]	<0.001	9.27	0.60
HWE	17	0.46 [0.37,0.59]	<0.001	25.16	0.07	17	0.45 [0.35,0.58]	<0.001	24.48	0.08	12	0.26 [0.14,0.47]	<0.001	9.27	0.60
Composite Associations															
ALDH2 in *ADH1B*2* carriers															
All	3	–	–	–	–	13	0.17 [0.11,0.26]	<0.001	30.70	0.002	–	–	–	–	–
HWE	1	–	–	–	–	8	0.14 [0.07,0.30]	<0.001	20.64	0.004	–	–	–	–	–
ALDH2 in *ADH1B*2* noncarriers															
All	3	–	–	–	–	13	0.37 [0.18,0.77]	0.01	18.60	0.10	–	–	–	–	–
HWE	1	–	–	–	–	6	0.32 [0.10,1.00]	0.05	7.26	0.20	–	–	–	–	–
ADH1B in *ALDH2*2* carriers															
All	12	0.34 [0.21,0.55]	<0.001	25.38	0.01	12	0.47 [0.33,0.67]	<0.001	10.19	0.51	14	0.14 [0.07,0.27]	<0.001	23.01	0.04
HWE	7	0.29 [0.13,0.67]	0.004	16.95	0.01	7	0.45 [0.24,0.83]	0.01	6.52	0.37	7	0.16 [0.06,0.47]	0.001	9.69	0.14
ADH1B in *ALDH2*2* noncarriers															
All	13	0.55 [0.38,0.78]	0.001	57.28	<0.001	13	0.51 [0.34,0.75]	0.001	36.67	<0.001	15	0.33 [0.19,0.56]	<0.001	37.18	0.001
HWE	8	0.58 [0.37,0.92]	0.02	26.36	<0.001	8	0.55 [0.31,0.96]	0.04	20.95	0.004	8	0.51 [0.30,0.86]	0.01	7.84	0.35
ADH1C in *ALDH2*2* carriers															
All	4	0.37 [0.22,0.62]	<0.001	2.40	0.49	4	0.40 [0.17,0.93]	0.03	3.43	0.33	1	–	–	–	–
HWE	1	–	–	–	–	1	–	–	–	–	0	–	–	–	–
ADH1C in *ALDH2*2* noncarriers															
All	7	0.43 [0.29,0.64]	<0.001	8.75	0.19	7	0.42 [0.28,0.64]	<0.001	7.97	0.24	7	0.32 [0.14,0.74]	0.007	1.71	0.94
HWE	4	0.43 [0.21,0.89]	0.02	5.89	0.12	4	0.41 [0.19,0.89]	0.03	5.36	0.15	4	0.34 [0.08,1.42]	0.14	1.07	0.78

Note. Significant moderator analyses shown in bold. Recessive models were not conducted for *ALDH2* given research suggesting *ALDH2*2* may be nearly dominant (see Edenberg, 2007) and the documented low prevalence of *ALDH2*2/2* homozygotes among AUD cases (Hasegawa *et al.*, 2002). The number of samples included in analyses differs across allelic and genotypic models, because there were several samples that provided only combined genotype groupings (e.g. *ALDH2*1/1* vs. *ALDH2*1/2* + *ALDH2*2/2*) and several samples in which the recessive homozygous genotype was not reported in either cases or controls (e.g. only one sample reported the *ADH1C*2/2* genotype among *ALDH2*2* cases). Models with fewer than four samples were excluded based on power analyses, including composite analyses of *ALDH2* in *ADH1C*1* carriers and noncarriers. *ALDH2* = aldehyde dehydrogenase 2; *ADH1B* = alcohol dehydrogenase 1B; *ADH1C* = alcohol dehydrogenase 1 C; AUD = alcohol use disorder; HWE = ancillary random effects meta-analysis excluding samples whose control genotypes were not adherent to Hardy-Weinberg equilibrium; OR = odds ratio; CI = confidence interval.

Table 2. Categorical Moderators in the Associations of ALDH2 and ADH1B with Alcohol Use Disorder (AUD) in East Asians

	Allelic Model					Dominant Model					Recessive Model				
	k	OR [95% CI]	*p*	*Q*	*p*	*k*	OR [95% CI]	*p*	*Q*	*p*	*k*	OR [95% CI]	*p*	*Q*	*p*
Sample nationality															
ALDH2															
Chinese/Taiwanese	15	0.28 [0.24,0.34]	<0.001	4.27	0.12	18	0.27 [0.22,0.34]	<0.001	0.76	0.69	–	–	–	–	–
Japanese	9	0.20 [0.15,0.27]	<0.001			11	0.22 [0.14,0.34]	<0.001			–	–	–		
Korean	10	0.30 [0.14,0.61]	0.001			10	0.29 [0.13,0.66]	0.003			–	–	–		
ADH1B															
Chinese/Taiwanese	16	0.53 [0.42,0.67]	<0.001	2.43	0.30	16	0.58 [0.46,0.73]	<0.001	3.30	0.19	14	0.25 [0.15,0.40]	<0.001	0.73	0.69
Japanese	6	0.40 [0.27,0.60]	<0.001			6	0.46 [0.30,0.69]	<0.001			6	0.17 [0.09,0.33]	<0.001		
Korean	9	0.41 [0.30,0.55]	<0.001			9	0.40 [0.29,0.56]	<0.001			9	0.22 [0.13,0.36]	<0.001		
Recruitment source															
ALDH2															
Treatment	16	0.24 [0.18,0.32]	<0.001	0.16	0.69	19	0.25 [0.18,0.36]	<0.001	0.01	0.95	–	–	–	–	–
Community	10	0.27 [0.16,0.45]	<0.001			11	0.26 [0.15,0.43]	<0.001			–	–	–		
ADH1B															
Treatment	**15**	**0.38 [0.32,0.45]**	**<0.001**	**22.34**	**<0.001**	**15**	**0.43 [0.36,0.52]**	**<0.001**	**7.41**	**0.01**	**15**	**0.18 [0.13,0.25]**	**<0.001**	**22.40**	**<0.001**
Community	**8**	**0.77 [0.61,0.96]**	**0.02**			**8**	**0.73 [0.52,1.03]**	**0.07**			**8**	**0.61 [0.41,0.92]**	**0.02**		
Diagnostic system															
ALDH2															
DSM-III-R	16	0.23 [0.18,0.28]	<0.001	2.19	0.34	19	0.25 [0.18,0.36]	<0.001	4.21	0.12	–	–	–	–	–
DSM-IV/DSM-IV-TR	11	0.27 [0.16,0.47]	<0.001			13	0.28 [0.17,0.46]	<0.001			–	–	–		
ICD-10	5	0.16 [0.10,0.26]	<0.001			5	0.13 [0.07,0.24]	<0.001			–	–	–		
ADH1B															
DSM-III-R	15	0.44 [0.35,0.55]	<0.001	2.60	0.27	15	0.48 [0.37,0.61]	<0.001	0.89	0.64	13	0.18 [0.11,0.27]	<0.001	4.61	0.10
DSM-IV/DSM-IV-TR	9	0.39 [0.30,0.51]	<0.001			9	0.45 [0.35,0.59]	<0.001			9	0.18 [0.11,0.29]	<0.001		
ICD-10	5	0.57 [0.39,0.82]	0.002			5	0.59 [0.36,0.98]	0.04			5	0.36 [0.21,0.63]	<0.001		
Inclusion of alcohol abuse															
ALDH2															
No	25	0.22 [0.16,0.32]	<0.001	0.29	0.59	29	0.22 [0.16,0.30]	<0.001	1.54	0.21	–	–	–	–	–
Yes	7	0.25 [0.19,0.33]	<0.001			9	0.31 [0.20,0.48]	<0.001			–	–	–		
ADH1B															
No	25	0.47 [0.39,0.57]	<0.001	0.02	0.88	25	0.50 [0.40,0.62]	<0.001	0.04	0.85	23	0.22 [0.15,0.32]	<0.001	0.37	0.54
Yes	4	0.49 [0.29,0.83]	0.008			4	0.53 [0.32,0.88]	0.01			4	0.28 [0.13,0.60]	0.001		

Note. Recessive models were not conducted for *ALDH2* given research suggesting *ALDH2*2* may be nearly dominant (see Edenberg, 2007) and the documented low prevalence of *ALDH2*2/2* homozygotes among AUD cases (Hasegawa *et al*., 2002). Moderator analyses were not conducted for *ADH1C* due to nonsignificant residual heterogeneity. The number of samples included in analyses differs across allelic and genotypic models, because there were several samples that provided only combined genotype groupings (e.g. *ALDH2*1/1* vs. *ALDH2*1/2* + *ALDH2*2/2*) and several samples in which the recessive homozygous genotype was not reported in either cases or controls (e.g. only one sample reported the *ADH1C*2/2* genotype among *ALDH2*2* cases). Nationality subgroup analyses were conducted excluding the three Asian American samples. *ALDH2* = aldehyde dehydrogenase 2; *ADH1B* = alcohol dehydrogenase 1B; AUD = alcohol use disorder; *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.); *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.); *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.); ICD-10 = International Statistical Classification of Diseases and Related Health Problems, Tenth Edition; OR = odds ratio; CI = confidence interval.

Table 3. Continuous Moderators in the Associations of ALDH2 and ADH1B with Alcohol Use Disorder (AUD) in East Asians

	Allelic Model			Dominant Model			Recessive Model		
	k	*b* [95% CI]	*p*	*k*	*b* [95% CI]	*p*	*k*	*b* [95% CI]	*p*
Mean age									
ALDH2									
Case	**18**	**–0.04 [–0.07, –0.01]**	**0.01**	20	–0.03 [–0.07, –0.00]	0.05	–	–	–
Control	20	–0.00 [–0.03,0.02]	0.75	23	0.01 [–0.02,0.03]	0.71	–	–	–
ADH1B									
Case	**16**	**–0.04 [–0.06, –0.01]**	**0.01**	**16**	**–0.03 [–0.06, –0.00]**	**0.02**	**16**	**–0.06 [–0.11, –0.00]**	**0.04**
Control	**16**	**–0.03 [–0.05, –0.01]**	**0.01**	16	–0.02 [–0.04, 0.00]	0.06	**16**	**–0.04 [–0.07, –0.00]**	**0.04**
Proportion of males									
ALDH2									
Case	**32**	**–2.71 [–3.71, –1.72]**	**<0.001**	**36**	**–2.74 [–4.02, –1.46]**	**<0.001**	–	–	–
Control	**31**	**–1.30 [–2.15, –0.45]**	**0.003**	**35**	**–1.15 [–2.14, –0.15]**	**0.02**	–	–	–
ADH1B									
Case	29	0.36 [–0.55,1.27]	0.43	29	0.30 [–0.78,1.39]	0.59	27	0.58 [–0.97,2.13]	0.46
Control	28	0.03 [–0.64,0.71]	0.92	28	–0.01 [–0.75,0.74]	0.98	26	0.03 [–1.13,1.20]	0.95
Publication year									
ALDH2	33	0.03 [–0.00,0.07]	0.05	37	0.03 [–0.01,0.07]	0.12	–	–	–
ADH1B	30	0.01 [–0.01,0.03]	0.45	30	0.01 [–0.01,0.04]	0.27	28	0.02 [–0.02,0.07]	0.34

Note. Significant moderator analyses shown in bold. Meta-regressions regressed log OR of genetic associations onto each continuous covariate; more negative coefficients (corresponding to smaller ORs moving further away from 1.00) indicate greater protective genetic associations with increases in the covariate. Recessive models were not conducted for *ALDH2* given research suggesting *ALDH2*2* may be nearly dominant (see Edenberg, 2007) and the documented low prevalence of *ALDH2*2/2* homozygotes among AUD cases (Hasegawa *et al.*, 2002). Moderator analyses were not conducted for *ADH1C* due to nonsignificant residual heterogeneity. The number of samples included in analyses differs across allelic and genotypic models, because there were several samples that provided only combined genotype groupings (e.g. *ALDH2*1/1* vs. *ALDH2*1/2* + *ALDH2*2/2*) and several samples in which the recessive homozygous genotype was not reported in either cases or controls (e.g. only one sample reported the *ADH1C*2/2* genotype among *ALDH2*2* cases). Further, the number of samples for cases and controls differ in moderator analyses, because several studies provided information for mean age and/or proportion of males within only cases or controls (see Table S1). *ALDH2* = aldehyde dehydrogenase 2; *ADH1B* = alcohol dehydrogenase 1B; AUD = alcohol use disorder; CI = confidence interval.

that genetic protection increases with age across adolescence to middle/late adulthood yet subsequently decreases in later adulthood. *ALDH2* protective associations also increased as proportion of men in cases and controls increased, consistent with research suggesting stronger genetic influences on alcohol use in men than women (Prescott, 2002), but see (Heath *et al.*, 1997). Men may have greater opportunities for genetically based protection against AUD to manifest given their increased likelihood to consume alcohol than women (World Health Organization, 2014), although additional research is needed.

*ADH1B*2* corresponded to approximately one-half the odds of AUD in allelic analyses (OR = 0.46), and it was also associated with AUD in dominant (OR = 0.49) and recessive (OR = 0.22) models, relatively consistent with previous meta-analyses among Asians/East Asians (ORs = 0.45 for allelic, ORs = 0.46–0.51 for dominant, ORs = 0.21–0.24 for recessive models; Zintzaras *et al.*, 2006; Li *et al.*, 2011). Similar to *ALDH2*, protective associations of *ADH1B* increased as mean age of cases (and controls, but not in the dominant model) increased. *ADH1B* was more strongly associated with AUD in samples whose cases were recruited from treatment than the community. Compared to cases recruited from the general population, cases from treatment tend to endorse more symptoms and report fewer social supports (Caetano, 1991) that could modify genetic associations. Nevertheless, significant between-study heterogeneity existed regardless of recruitment source, suggesting additional moderators remain uncharacterized.

ADH1B associations did not differ significantly as a function of *ALDH2*2* and *ALDH2* associations also did not differ significantly as a function of *ADH1B*2*, adjusting for multiple comparisons. These results are consistent with previous meta-analyses finding nonsignificant differences in *ALDH2–ADH1B* associations with AUD (Whitfield, 1997; Luczak *et al.*, 2006). Rather than interactive associations, *ALDH2* and *ADH1B* may instead have independent or additive associations. Research into mechanisms underlying *ADH1B* associations with AUD has been less consistent than for *ALDH2* (Wall, 2005), and the two alleles may contribute unique protection through partially independent mechanistic pathways. Alternatively, any gene–gene interaction effects of *ALDH2* with *ADH1B* may be small and, thus, difficult to detect even within this most comprehensive meta-analytic investigation.

*ADH1C*1* was associated with one-half the odds of AUD in allelic analyses (OR = 0.46), and was associated with AUD across dominant (OR = 0.45) and recessive (OR = 0.26) models. These estimates were similar but on the stronger end of those in previous meta-analyses (ORs = 0.47–0.52 for allelic, ORs = 0.45–0.52 for dominant, ORs = 0.26–0.36 for recessive; Zintzaras *et al.*, 2006; Li *et al.*, 2011). Previous estimates may have been weaker due to confounding effects of population stratification and/or lower specificity of diagnostic criteria, both of which were minimized in current analyses. Consistent with *ALDH2–ADH1B* analyses, *ADH1C* associations were similar after considering *ALDH2*2*. Notably, *ADH1C*1* frequencies have been 0.98 among Asian populations (Wall *et al.*, 2016), and *ADH1C* associations with AUD may be confounded by other alcohol protective factors also common in this ethnic group.

Findings should be interpreted with respect to several limitations. First, a small number of studies and concerns with low power precluded notable moderator and gene–gene interaction analyses, such as *ADH1B–ADH1C* interactions (Osier *et al.*, 1999). Second, findings are bounded by the methodological rigor of included studies. Genotyping success rates were not reported in many studies, so it

remains unknown to what extent an uneven distribution of AUD diagnoses across indeterminate cases may have artificially biased associations. Additionally, studies in which controls were recruited regardless of their exposure to alcohol may have minimized true genetic associations (since alcohol consumption is required for the hypothesized acetaldehyde-based mechanisms of such genetic protection; Thomasson *et al.*, 1995; Wall, 2005) and/or conflated associations by including nondrinkers who may refrain from alcohol use regardless of genetics due to religious, cultural and/or medical reasons. Further, the majority of included studies were case–control investigations, introducing potential selection bias that may overestimate genetic associations. Among individuals with AUD, alcohol metabolism gene carriers may be more likely to enter treatment than noncarriers given associations of these alleles with alcohol-related medical conditions (Li *et al.*, 2011, 2012a, 2012b). Genetic associations may appear larger in case–control investigations, particularly those with cases recruited from treatment, and future work is needed to examine consistency of the genetic effect sizes identified here. Finally, ethnic differences in genetic associations with AUD may be considerably more nuanced within East Asians, and future research is needed.

Notwithstanding these limitations, this meta-analysis supported the importance of alcohol metabolism gene variants with risk of AUD among East Asians, including unique associations of *ADH1B* and *ADH1C* among *ALDH2*2* carriers, and identified methodological and sample characteristic that may modify genetic associations. Future research is needed to better understand the mechanisms underlying genetically based protection, interactions of alcohol metabolism alleles with genes beyond the alcohol metabolism gene cluster, and additional factors that may underlie the heterogeneity in effect sizes demonstrated across studies.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Alcohol And Alcoholism* online.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

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