Published in final edited form as:
Am J Drug Alcohol Abuse. 2012 September ; 38(5): 389–394. doi:10.3109/00952990.2012.694526.

ADH and ALDH polymorphisms and alcohol dependence in Mexican and Native Americans

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Abstract

Background—Ethanol is primarily metabolized in the liver by 2 rate-limiting reactions: conversion of ethanol to acetaldehyde by alcohol dehydrogenase (ADH) and subsequent conversion of acetaldehyde to acetate by aldehyde dehydrogenase (ALDH). ADH and ALDH exist in multiple isozymes that differ in their kinetic properties. Notably, polymorphisms within the genes that encode for these isozymes vary in their allele frequencies between ethnic groups, and thus, they have been considered as candidate genes that may differentially influence risk for the development of alcohol dependence across ethnic groups.

Objectives and Methods—Associations between alcohol dependence and polymorphisms in *ADH1B*, *ADH1C*, and *ALDH2*, were compared in a community sample of Native Americans living on reservations (n=791) and Mexican Americans (n=391) living within the same county.

Results—Two Mexican Americans and no Native Americans possessed one *ALDH2*2* allele. Presence of at least one *ADH1B*2* allele was found in 7% of the Native Americans and 13% of the Mexican Americans, but was only associated with protection against alcohol dependence in the Mexican Americans. Presence of at least one *ADH1B*3* allele was found in 4% if the Native Americans and 2% of the Mexican Americans, but was associated with protection against alcohol dependence only in the Native Americans. No associations between alcohol dependence and polymorphisms in *ADH1C* were found.

Conclusions and Scientific Significance—Polymorphisms in *ADH1B* are protective against alcoholism in these two populations; however, these findings do not explain the high prevalence of alcoholism in these populations.

Keywords

ADH; ALDH; Alcohol dependence; candidate genes; Mexican Americans; Native Americans; population genetics

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Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper. This work was supported by National Institutes of Health (NIH) grants.

INTRODUCTION

Data on drinking patterns and problems between different racial/ethnic groups highlight the importance of studying health disparities in alcohol use and abuse. In large scale U.S. epidemiological studies, Native Americans exhibit higher rates of alcohol and other drug dependence relative to other ethnic groups followed by whites, Hispanics, Blacks and Asians (1). Although Native American tribes differ in their rates of substance use and abuse, the U.S. Indian Health Service has declared that tobacco, alcohol and drug dependence are among the most urgent health problems facing Native Americans. Hispanics are heterogeneous in national origin, and have a range of alcohol use disorders between different Hispanic national groups. Among Hispanic groups the Hispanic Americans Baseline Alcohol Survey (HABLAS) found that risk factors for dependence on alcohol in Hispanics included: being male, being Puerto Rican or Mexican American having less than a college education and being U. S.-born (2). Drinking by some Hispanics also takes a heavy toll in their health consequences. For example, the National Center for Health Statistics found that white Hispanic men and women had the highest cirrhosis mortality rates of any ethnic group studied (3).

The causes for the increase in problem drinking and health problems seen in some Mexican and Native American communities are most likely a combination of genetic and environmental factors. Early ethnographic studies in Native Americans suggested that Indians may “break down” alcohol differently than Caucasians resulting in an increased risk for heavy drinking, a theory called the “firewater” myth. Thus, ethnic differences in the genetics of alcohol metabolism could potentially modify risk for alcohol dependence across individuals of different ethnic backgrounds. If such theories were true, then one would expect that Native Americans, and perhaps Mexican Americans, would have different allelic distributions of functional polymorphisms in the genes encoding for alcohol metabolizing isozymes compared to other ethnic populations such as Caucasians and Africans.

The genes that code for the isozymes that are the major enzymes involved in alcohol metabolism are the seven alcohol dehydrogenase genes (*ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, ADH7*) and the two aldehyde dehydrogenase genes (*ALDH1, ALDH2*). These genes have been considered candidates that are likely to contribute to variation in alcohol metabolism, variability in response to alcohol, and thus differences in vulnerability for alcohol dependence (4). In individuals of Far East Asian descent (perhaps 40%), a mutation in the *ALDH2* gene, referred to as the *ALDH2*2* allele, results in a largely inactive form of ALDH and is associated with alcohol induced flushing reactions, an increased level of response to alcohol, and lower rates of alcohol use and alcoholism. This *ALDH2*2* allele is very uncommon among other non-Asian ethnic groups, including American Indians (5–12) and Hispanics (13).

Recent studies suggest that variations in two of the alcohol dehydrogenase genes, *ADH1B* and *ADH1C*, may influence drinking behavior, risk for alcoholism, and/or the development of alcohol-related disease. First, genetic linkage studies have shown replicable relations for alcohol related phenotypes with a region of chromosome 4 near the ADH gene cluster in Indian and general population studies (14–15). Second, Bosron et al. (5) and Rex et al. (10) genotyped a set of functional polymorphisms in *ADH1B* and *ADH1C* and found the distributions of alleles at these polymorphisms among Navajo and Sioux to be similar to EuroAmericans but not to Japanese or Black Americans. These results suggest that *ADH1B* and *ADH1C* may be particularly relevant to alcohol use disorders in Native Americans. Following up these results, both linkage and association analysis have identified several *ADH1C* alleles that affect risk of alcohol dependence and binge drinking in an American Indian tribe (16). Further, early studies of the *ADH1B* gene identified three alleles,

*ADH1B**1, *ADH1B**2, and *ADH1B**3 with both the **3* and **2* alleles demonstrating a protective relation with alcohol dependence and related phenotypes. *ADH1B**3 allele has been observed in a Southwestern California Indian (SWC) population and has been associated with reduced risk for alcohol dependence, reduced alcohol consumption, and reduced risk for alcohol withdrawal in that community (12, 17). Notably, however, this allele has not been observed in other Native American populations.

In contrast to Native Americans, only a few studies have evaluated polymorphisms in alcohol metabolism genes and the risk for alcohol dependence in Mexican American populations. Of the studies conducted, none have identified the *ALDH2**2 allele in Mexican Americans (13), though one study found that the *ADH1B*1* and *ADH1C*2* alleles were both associated with alcoholism in Mexican Americans. The authors concluded that Mexican Americans might have a unique pattern of genetic risk that may be in part responsible for the elevated rates of alcoholism and alcohol-associated health problems in this population (18–19).

The present set of analyses were aimed at evaluating polymorphisms in *ADH1B, ADHD1C,* and *ALDH2* in a community sample of Native Americans (SWC) living on or around reservations and Mexican Americans residing in the same county. Associations between polymorphisms in *ADH1B*, *ADH1C*, *ALDH2* and alcohol use disorders have been reported previously from a smaller sample of this Native American population (11–12, 17). Data on *ADH1B*, *ADH1C,* and *ALDH2* genotypes from this Mexican American population have not been previously reported. The specific aim of the present study was to compare the frequencies of the polymorphisms in the two populations as well as their associations with alcohol use disorders.

METHODS

Native American and Mexican American sample

SWC Indians who were of at least one sixteenth Native American heritage were targeted for study participation and were recruited from 8 geographically contiguous Indian reservations with a total population of approximately 3000 individuals. Participants who were mobile and without serious medical illness and between the ages of 18 and 70 years were recruited by using a combination of a venue-based method for sampling hard-to-reach populations and a respondent-driven procedure, as reported previously (14). The protocol for the study was approved by two institutional internal review boards and the Indian Health Council, a tribal review group overseeing health issues for the reservations where recruitments took place.

Mexican American participants were recruited using a commercial mailing list that provided the addresses of individuals with Hispanic surnames in 11 zip codes in San Diego County within 25 miles of the research site that had a population of at least 20% Hispanic heritage residents. The mailed invitation stated that potential participants must be of Mexican American heritage, must be between the ages of 18 and 30 years, must be residing in the United States legally, and must be able to read and write in English. Potential participants were requested to phone research staff for more information. During the phone interview, potential participants were screened for the presence of the inclusion criteria listed on the invitation, and were excluded it they were pregnant or nursing, currently had a major medical or neurologic disorder, or a head injury. All participants were asked to refrain from alcohol or any other substance use for 24 hours before testing. On the test day, after a complete description of the study to the participants, written informed consent was obtained using a protocol approved by The Institutional Review Board of The Scripps Research Institute. Participants were compensated for their time spent in the study.

Data collection and analyses

Each participant (Native Americans, *n =791*, Mexican Americans *n=391*) completed an interview with the Semi- Structured Assessment for the Genetics of Alcoholism (SSAGA), which was used to gather demographic information and make a lifetime diagnosis of alcohol dependence according to DSM-III-R criteria. The SSAGA is a polydiagnostic psychiatric interview that has undergone both reliability and validity testing. All final best-estimate diagnoses were made by one research psychiatrist/addiction specialist. A blood sample was obtained by venipuncture from each participant, and DNA was isolated from leukocytes. Dried blood samples were also collected and were sent to Indiana University for genotyping, where the relevant portions of the *ADH* and *ALDH* loci were amplified using the polymerase chain reaction followed by hybridization with allele-specific radiolabeled oligonucleotide probes (20), as previously described (11–12). DNA samples which were collected after 2005 were genotyped using TaqMan SNP assay as previously described (21). Tests for departures from Hardy-Weinberg equilibrium HWE were conducted separately for alcohol and non-alcohol dependent participants within each group as a quality control check of the genotype data. No evidence of departures from HWE were detected using a threshold of $p > 0.01$ (Table 2).

Data analyses focused on two specific aims. The first aim was to compare the allelic distributions of *ADH1B*, *ADH1C*, and *ALDH2* polymorphisms in the Native American and Mexican American samples using frequency counts. The second aim was to determine whether there was an association between alcohol dependence and the *ADH1B*, *ADH1C,* and *ALDH2* alleles in the Native and Mexican American samples. These analyses were conducted using logistic regression with the Alcohol Dependence diagnosis serving as the dependent variable and genotype as the independent variable. Presence of alcohol dependence rather than any alcohol use disorder (e.g., either alcohol abuse or dependence diagnosis) was selected as the phenotype given a previous study suggesting only severe forms of alcoholism, such as alcohol dependence, are heritable in the present Native American sample (14). Gender, age, the curvilinear effect of age, and the interactions between age and gender and the curvilinear effect of age and gender were included as covariates.

RESULTS

Native American sample

Demographic characteristics of this SWC Indian population ($n = 791$), which have been reported previously in smaller samples (12, 14), are presented in Table 1. Notably, the proportion of Native American ancestry of participants was estimated from reports on grandparent origin. Forty-four percent of participants reported a Native American ancestry at or above 50%. There were no differences in allele frequencies for any of the genotyped markers between participants of greater or less than 50% Native American heritage (all p-values > 0.45).

Table 2 displays the allele frequencies and genotype counts for participants with and without an alcohol dependence diagnosis (minor allele frequencies of the studied polymorphisms as estimated in a set of reference samples from different ethnic groups are provided for comparison). As shown, no individuals possessed an *ALDH2*2* allele, and none of the individuals reported any East Asian or African heritage. Overall, 89% of the population were homozygous for *ADH1B*1*, 7% had at least one *ADH1B*2* allele (only a single participant was homozygous for the *ADH1B*2* allele) and 4 % of the population had one *ADH1B*3* allele. Forty-two percent of the population were homozygous for *ADH1C*1* and 58% had at least one *ADH1C*2* allele (127 participants were homozygous for the

*ADH1C*2* allele). Allele frequencies for participants with and without alcohol dependence are presented in Table 3 as well as the results of the association analyses. None of the demographic variables including: age, gender, number of years of education, employment, income, or Native American blood degree (< vs. > 50% Native American blood degree) were associated with variants in any of the alleles. Notably, the presence of at least one *ADH1B*3* allele was found to be associated with protection against alcohol dependence (Wald X^2(df =1, N=737) = 6.73, p=.035, Nagelkerke R^2 = .02).

Mexican American sample

Demographic characteristics of this Mexican American population (n=391) have also been reported previously on a smaller sample (22) and are presented in Table 1. Notably, the proportion of Hispanic ancestry of participants was estimated from reports on grandparent origin. Seventy-two percent of participants reported a Hispanic ancestry at or above 50%. There were no differences in allele frequencies for any of the genotyped markers between participants of greater or less than 50% Hispanic heritage (all p-values > 0.30).

Table 2 displays the allele frequencies and genotype counts for participants with and without an alcohol dependence diagnosis. As shown, two individuals were found to have one *ALDH2*2* allele, both individuals reported having a second degree relative of East Asian heritage. None of the remaining participants reported evidence of East Asian or African heritage. Overall, 85% of the population were homozygous for the *ADH1B*1* allele, 13% possessed at least one *ADH1B*2* allele (only a single participant was homozygous for the *ADH1B*2* allele), and 2% had one *ADH1B*3* allele. None of the participants possessed both an *ADH1B*2* and *ADH1B*3* allele. Forty-nine percent of the population was homozygous for the *ADH1C*1* allele and 52% of the population was found to have at least one *ADH1C*2* allele (51 participants were homozygous for the *ADH1C*2* allele). Allele frequencies for participants with and without alcohol dependence are presented in Table 3 as well as the results of the association analyses. Demographic data including age, gender, number of years of education, employment, income, were not found to be significantly associated with variants in any of the alleles. Notably, the presence of at least one *ADH1B*2* allele was found to be associated with protection against alcohol dependence (Wald X^2(df=1, N=429) = 8.74, p=.003, Nagelkerke R^2 = .04).

DISCUSSION

The present study examined the prevalence of alleles at known functional polymorphisms in the *ALDH2, ADH1B, and ADH1C* genes, and tested for associations between these polymorphisms and DSM-III-R alcohol dependence. *ALDH2*, located on chromosome 12q24.2, is the primary enzyme responsible for acetaldehyde metabolism in the liver, and thus, represents a logical candidate gene for alcohol dependence. A mutation in *ALDH2* (commonly referred to as the *ALDH2*2* allele) produces a largely inactive aldehyde dehydrogenase enzyme that leads to elevated acetaldehyde levels that produces an aversive flushing reaction when alcohol is consumed. This *ALDH2*2* allele is relatively frequent in Far East Asian populations and has been associated with lower rates of alcohol use and alcoholism in Japanese and Chinese samples (23). As a result, the *ALDH2*2* allele serves as a protective factor against the development of alcoholism, but several studies, including the present report, have failed to detect the presence of this allele in Native American populations. Two individuals in the Mexican American population had one *ALDH2*2* allele, though both of these individuals reported having a grandparent of East Asian descent. These findings are similar to that reported by Konishi et al. (19) who found *ALDH2*2* alleles in 0.6% of a Mexican American sample living in Los Angeles. Thus, the general absence of *ALDH2*2* alleles from Native and Mexican Americans who do not report any East Asian Heritage is consistent with other studies in the literature.

The alcohol dehydrogenase genes located on chromosome 4q22 encode for the isozymes responsible for the metabolism of alcohol into acetaldehyde, and thus represent the initial step in alcohol metabolism. The class 1 ADH isoforms account for the majority of alcohol metabolism in the liver and are encoded by the *ADH1A*, *ADH1B*, and *ADH1C* genes. Each of these genes has shown evidence of association with alcohol dependence and related phenotypes. For example, the *ADH1B*2* allele, located in exon 3 of *ADH1B* results in an arginine to histidine amino acid change that has demonstrated a protective relation with alcohol dependence and related phenotypes. In the present study this allele was found in 13% of the Mexican American and 7% of the Native American participants and was associated with protection from alcohol dependence in the Mexican Americans but not in the Native Americans. The prevalence of the *ADH1B*2* allele in the present Mexican American sample was higher than previously reported in two samples of Mexican Americans residing in Los Angeles where the frequencies were 5% (19) and 6% (13).

A second polymorphism in *ADH1B*, located in exon 9, harbors the *ADH1B*3* allele, which results in an arginine to cysteine change that has shown a protective association in the development of alcohol dependence in multiple samples of African descent (24) and the Indian population described in the present study (12). In this expanded sample of Native Americans, 4% of the Native Americans and 2% of the Mexican Americans had one *ADH1B*3* allele, and this allele was associated with protection from alcohol dependence in the Native American sample but not in the Mexican American sample. *ADH1B*3* is most often observed in individuals of African descent; however, none of the individuals in the present study reported any African heritage. Additionally, neither the *ADH1B*2* or the *ADH1B*3* allele were associated with the individuals degree of Native American heritage.

Associations between alcohol dependence and the *ADH1C*2* allele have been reported in some populations (16, 18); however, neither the Mexican American nor the Native American population evaluated in the present study showed evidence of an association between the *ADH1C*2* allele and alcohol dependence. These data are generally consistent with studies of this allele in other Native and Mexican American populations (25), although one study reported that *ADH1C*2* was associated with alcohol dependence in Mexican American heavy drinkers in Los Angeles (19).

As stated, the present study tested for associations between polymorphisms in a set of alcohol metabolism genes and DSM-III-R alcohol dependence. Comparisons across the two studied populations are relevant given that they each experienced admixture between an indigenous and Caucasian population. Notably, the *ADH1B*2* and **3* did not show consistent evidence of association across these two groups. One possible explanation for this lack of consistency could be the relatively low minor allele frequencies of the associated alleles, which resulted in fewer participants carrying these alleles. It may be that the association results across groups would converge with increased power, and thus larger studies conducted in Mexican American and Native American samples are needed.

The reported findings should be interpreted in the context of the broader literature examining the relations between the ALDH and ADH genes and alcohol use disorders. As described, associations between the *ADH1B*2* and **3* alleles and alcohol dependence have been reported in multiple studies (21–24), but polymorphisms in other ALDH and ADH genes have also shown replicable evidence of association with these phenotypes. For example, several recent studies of *ADH4* polymorphisms have reported an association between a SNP in the promoter region (rs3762894) and alcohol dependence, alcohol withdrawal, and other related phenotypes (17, 26–27). Though less well replicated, associations between polymorphisms in the other ALDH and ADH genes have also been reported (16, 25). Thus, the present report provides an important replication of previously

reported associations, but captures only a portion of the variation in alcohol misuse disorders resulting from polymorphisms in the ALDH and ADH genes.

CONCLUSIONS

Studies investigating the genes that code for alcohol metabolizing enzymes have to date failed to reveal any variants that differ in the Native or Mexican American populations, relative to other ethnic populations investigated, that could explain the elevated rates of alcohol dependence in these groups. As a result, molecular genetic studies provide little support for the hypothesis that Native American groups have an "unusual metabolism of alcohol." Further studies conducted in other Native American tribal groups and other Hispanic populations will be necessary to determine the generalizability of the findings. Additionally, the young age of the Mexican-American participants raises the possibility that a proportion of Mexican-American control participants may develop alcohol dependence at a later age, which could impact the findings of the present report. Thus, caution should be taken in extrapolating the findings to other Native or Hispanic American subgroups. Further, it is likely that substance dependence in Native and Mexican Americans, as in other populations, is a result of both genetic and environmental factors. Therefore, the cause of increased substance dependence risk in Native and Mexican Americans will most likely be explained by theories that include both genetic and environmental determinants.

Acknowledgments

This work was supported by National Institutes of Health (NIH) grants: AA006420, AA010201 and to National Center on Minority Health and Health Disparities (NCMHD) to CLE; DA030976 to CLE and IRG and P60 AA007611 to TL.

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Table 1

Demographics

	Mexican Americans	Native Americans
N	**437**	**791**
Males	**177** (40.5%)	**327** (41.3%)
Females	**260** (59.5%)	**464** (58.7%)
Age	**23.53** (SD 3.83)	**31.22** (SD 13.13)
Ancestry ≥50%	**315** (72.2%)	**345** (43.7%)
Education	**13.34** (SD 1.81)	**11.59** (SD 1.58)
Married	**73** (16.7%)	**135** (17.1%)
Employed	**284** (65.0%)	**299** (37.8%)
Ecostat	**333** (76.2%)	**402** (50.8%)
Alcohol Dependence	**126** (28.8%)	**434** (54.9%)
Alcohol Abuse	**83** (19.0%)	**133** (16.8%)

Table 2

ADH and ALDH2 SNPs: allele and genotype frequencies.

		HapMap Database				Present Study Samples						
		Minor Allele Frequencies (MAF)					Mexican Americans			Native Americans		
SNP (allele)[1]	**Minor Allele**	**Mexican**	**Caucasian**	**African**	**Asian**	**Alcohol Dependence Status**	**MAF**	**Genotype Counts[2]**	**HWE *p*-val**	**MAF**	**Genotype Counts[2]**	**HWE *p*-val**
rs1229984 (*ADH1B*2*)	T	0.11[2]	0.02	0.00	0.82	No Alc. Dep.	0.08	265/47/1	0.71	0.04	329/27/1	0.45
						Alc. Dep.	0.03	119/7/0	1.00	0.06	408/26/0	1.00
rs2066702 (*ADH1B*3*)	A	0.03	0.00	0.25	0.00	No Alc. Dep.	0.02	305/8/0	1.00	0.03	335/21/0	1.00
						Alc. Dep.	0.01	125/2/0	1.00	0.01	423/11/0	1.00
rs698 (*ADH1C*2*)	C	0.26	0.47	0.15	0.07	No Alc. Dep.	0.31	153/121/37	0.09	0.35	160/142/54	0.02
						Alc. Dep.	0.32	58/54/14	0.84	0.38	175/186/73	0.05
rs671 (*ALDH2*2*)	A	0.02	0.00	<0.01	0.22	No Alc. Dep.	<0.01	309/2/0	-	0.00	357/0/0	-
						Alc. Dep.	0.00	126/0/0	-	0.00	434/0/0	-

Notes:

[1] possession of the described allele is indicated by possession of the minor allele at that SNP;

[2] genotype counts are presented as homozygous major allele/ heterozygous/ homozygous minor allele;

[3] Allele frequency from SNP500CANCER database; Alc. Dep. = Alcohol Dependence.

Table 3

ADH and ALDH2 association analyses.

	Mexican American						Native American					
	ALC DEP	**NO ALC DEP**	**Wald X^2**	***p*-value**	**OR**	**R^2**	**ALC DEP**	**NO ALC DEP**	**Wald X^2**	***p*-value**	**OR**	**R^2**
ADH1B1 *	117 (93%)	257 (82%)					398 (91%)	308 (86%)				
ADH1B2 carriers	**7 (5%)**	**48 (15%)**	**8.74**	**0.003**	**0.28**	**0.04**	26 (6%)	28 (8%)	0.64	0.423	1.36	0.00
ADH1B3 carriers	2 (2%)	8 (3%)	0.15	0.699	0.85	0.00	**11 (3%)**	**21 (6%)**	**6.728**	**0.035**	**2.90**	**0.02**
ADH1C1 *	58 (46%)	153 (49%)					175 (40%)	160 (45%)				
ADH1C2 carriers	68 (54%)	158 (51%)	0.22	0.638	1.11	0.00	*259 (60%)*	*196 (55%)*	*2.865*	*0.091*	*1.29*	*0.01*
ALDH21	126 (100%)	309 (99%)					434 (100%)	357 (100%)				
ALDH22 carriers	0 (0%)	2 (1%)	-	-	-	-	0	0		-		-

* - Served as reference group in regression analysis. Two Native American participants possessed an *ADH1B*2* and an *ADH1B*3* allele and thus are counted twice. All Wald X^2 tests represent 1 *df* tests. OR = Odds Ratio. Bolded text indicates significant results at $p<.05$. Italicized text indicates a statistical trend at $p<.10$.