A Genetic Association With the Development of Alcohol and Other Substance Use Behavior in Asian Americans

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Studies of Asian adults have found that alcohol use and alcohol dependence are related to variation in the aldehyde dehydrogenase (ALDH2) gene. To investigate the association of ALDH2 with the development of drug involvement, the authors analyzed retrospective information about the onset and regular use of alcohol and other substances as reported by 180 Asian American college students. Possession of an ALDH2*2 allele was not related to initiation of alcohol use or having ever been intoxicated, but individuals with ALDH2*2 alleles were less likely to be regular drinkers, were less likely to have engaged in a binge-drinking episode, reported a lower number of maximum drinks consumed in a 24-hr period, and were less likely to have used tobacco regularly than those without this genetic variant. These findings suggest that ALDH2 is associated with the development of not only alcohol-related behavior but other substance use behavior as well.

Surveys of adolescents have shown that Asian youth report not only the lowest levels of alcohol use but also the lowest levels of other substance use compared with other ethnic groups (Adlaf, Smart, & Tan, 1989; Bachman et al., 1991; Gillmore et al., 1990; Kandel, Single, & Kessler, 1976; Newcomb & Bentler, 1986). Most studies evaluating ethnic differences in adolescent substance use have focused on psychosocial influences (Barnes & Welte, 1986; Catalano et al., 1992; Gillmore et al., 1990; Landrine, Richardson, Klonoff, & Flay, 1994; Maddahian, Newcomb, & Bentler, 1988; Newcomb & Bentler, 1986; Newcomb, Maddahian, Skager, & Bentler, 1987; Wallace & Bachman, 1991; Welte & Barnes, 1987). Lower rates of substance use among Asian youth have been related to a lower prevalence of various risk factors, including adult and peer models of alcohol and other drug-taking behavior, poor family relationships, psychopathology, sensation seeking, and poor academic performance. Previous studies, however, have not addressed the possibility that genetic factors might also influence alcohol and other drug involvement among Asian adolescents, despite evidence from studies of adults that alcohol use and alcohol dependence are genetically influenced in individuals of Asian descent.

Approximately half of persons of northeastern Asian heritage (Chinese, Japanese, and Koreans) have a genetically defined deficiency in the low Km isoenzyme of aldehyde dehydrogenase (ALDH2), which results from inheritance of at least one mutant ALDH2*2 allele. The ALDH2*2 allele is prevalent among northeastern Asian populations but extremely rare in non-Asians (Goede et al., 1992). ALDH2*2 has been associated with an alcohol-induced flushing reaction (Shibuya, Yasunami, & Yoshida, 1989; Wall, Thomasson, & Ehlers, 1996) and higher levels of acetaldehyde during alcohol metabolism (Enomoto, Takase, Yasuhara, & Takada, 1991; Peng et al., 1999; Wall et al., 1997). Compared with those with the ALDH2*1/*1 homozygous genotype, adults with ALDH2*2 alleles (ALDH2*1/*2 heterozygotes or ALDH2*2/*2 homozygotes) drink less alcohol (Takeshita & Morimoto, 1999; Tu & Israel, 1995) and have lower rates of alcohol dependence (C.-C. Chen et al., 1999; Higuchi, Matsushita, Murayama, Takagi, & Hayashida, 1995; Ishiwashi, Matsu, Suwaki, Nakamura, & Ichikawa, 1995; Maekawa, Yamauchi, Toda, Suzuki, & Sakurai, 1995; Thomasson et al., 1991). ALDH2*2 homozygous individuals experience severe reactions to a moderate dose of alcohol, including tachycardia, hypotension, nausea, and vomiting (Wall, Nemeroff, Ritchie, & Ehlers, 1994; Wall, Thomasson, Schuckit, & Ehlers, 1992). Several studies conducted...
in Japan and Taiwan have found only one alcohol-dependent person with $ALDH2^{*2/*2}$ (Y.-C. Chen et al., 1999), whereas 4 to 12% of controls have this genotype (C.-C. Chen et al., 1999; Higuchi et al., 1995; Iwahashi et al., 1995; Maezawa et al., 1995; Thomasson et al., 1991). Thus, $ALDH2^{*2/*2}$ homozygotes have almost no risk for alcohol dependence. $ALDH2^{*2}$ heterozygous individuals experience more intense, but not necessarily more aversive, reactions to alcohol than matched controls without this genetic variant (Peng et al., 1999; Wall et al., 1992, 1994). Additionally, Asian alcoholics are less likely to be heterozygotes, but this genotype does not provide full protection from alcohol dependence; between 12 and 21% of Chinese and Japanese alcoholics have $ALDH2^{*1/*2}$ genotype compared with 35 to 41% of controls (C.-C. Chen et al., 1999; Higuchi et al., 1995; Iwahashi et al., 1995; Maezawa et al., 1995; Thomasson et al., 1991).

Among adolescents, $ALDH2$ gene status may affect the development of drinking behavior either directly through its influence on alcohol metabolism and response to alcohol or indirectly through parental modeling. Individuals with $ALDH2^{*2}$ alleles also have at least one parent with this genetic variant, which could influence parental drinking and, therefore, modeling of this behavior. Additionally, $ALDH2$ may have an indirect effect on other substance use in that adolescents or young adults who drink less alcohol may also be less likely to smoke cigarettes or use illicit drugs (e.g., gateway theory; Kandel, Yamaguchi, & Chen, 1992). We hypothesized that possession of an $ALDH2^{*2}$ allele would have a specific protective effect on the development of alcohol use behavior and possibly a nonspecific protective effect on the development of other substance use behavior. To test these hypotheses, we analyzed retrospective information about the onset and regular use of alcohol and other substances as reported by Asian American college students who were genotyped at the $ALDH2$ locus.

**Method**

**Participants**

Participants were 21- to 26-year-old college students who reported biological parents and grandparents of entirely Chinese, Korean, or Japanese heritage. The sample consisted of 180 participants with a mean age of 21.9 years ($SD = 1.1$ years); 44% were male and 56% female; 52% were Chinese, 38% were Korean, and 11% were Japanese; 49% were born in the United States and 51% were foreign born.

**Procedures**

Students at the University of California, San Diego, were recruited to participate in a paid research project through advertisements on campus and in the school newspaper. To reduce bias, the advertisements did not mention that the study related to alcohol. Potential participants were screened by telephone and rescreened in person to determine eligibility for the study. After written informed consent was obtained, each participant completed an individual assessment with a trained research assistant. To maximize self-disclosure, confidentiality was assured with a Certificate of Confidentiality from the Department of Health and Human Services.

**Measures**

The measures of interest were part of a larger battery that included the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA). The SSAGA is a lay interview designed to assess lifetime alcohol abuse and dependence, other substance abuse and dependence, and associated psychiatric disorders. Results indicate that it is a reliable and valid diagnostic instrument (Bucholz et al., 1994, 1995; Hesselbrock, Easton, Buchholz, Schuckit, & Hesselbrock, 1999).

**Use of alcohol.** Each participant was asked to report retrospectively the age at which he or she first used alcohol (a drink, not a sip). A drink was defined as 12 oz of beer, 4 oz of wine, or a single shot (1–1.5 oz) of 80 proof alcohol. Additionally, questions from the SSAGA asked participants to report the age at which they first began to drink regularly (at least one drink per month for 6 months or more), the age at which they first got drunk (experienced slurred speech or unsteady feet), and the most number of drinks that they had ever consumed in a 24-hr period. Responses to this question were used to determine whether participants had ever engaged in a heavy- or binge-drinking episode. Binge drinking was defined using a slightly modified gender-specific measure (Wechsler, Dowdall, Davenport, & Rimm, 1995): more than five drinks per 24-hr period for men and more than 4 drinks for women. Participants who reported an age of first use, intoxication, or regular use were classified as endorsing the alcohol-related behavior.

**Use of other substances.** Questions from the SSAGA also asked participants to report the age at which they first used tobacco regularly (daily use for at least 1 month), the age at which they first used and regularly used (use almost every day for at least 2 weeks) marijuana/hashish, and the age at which they first used and regularly used (11 or more times) other illicit substances (cocaine, stimulants, sedatives, opioids, phencyclidine, hallucinogens, and solvents). A list of synonyms for illicit substances, including street names, was provided to each participant. Those who reported an age of first or regular use for a drug were classified as endorsing use.

**Genotyping and Statistical Analyses**

A blood sample was collected from each participant for genotyping at the $ALDH2$ locus using polymerase chain reaction of DNA and allele-specific oligonucleotide probes (Crabb, Edenberg, Bosron, & Li, 1989). Genotyping indicated that 99 participants (55%) were $ALDH2^{*1/*1}$, 75 (42%) were $ALDH2^{*1/*2}$, and 6 (3%) were $ALDH2^{*2/*2}$. For statistical comparisons of $ALDH2$ gene status, groups were dichotomized based on the presence (+) or absence (−) of an $ALDH2^{*2}$ allele. $ALDH2$ status did not differ across gender, $\chi^2(1, N = 180) = 0.59, p = .44$, but did differ across ethnic subgroup, $\chi^2(2, N = 180) = 6.38, p < .05$. More Chinese (54%) had an $ALDH2^{*2}$ allele than Japanese (42%) or Koreans (34%). The allele and genotype frequencies for $ALDH2$ are similar to those reported for persons from China, Japan, and Korea (Goedde et al., 1992). Associations between $ALDH2$ status and categorical variables were examined using chi-square tests and logistic regression. Associations of $ALDH2$ status with continuous variables were examined using $t$ tests. Because of phenotypic differences associated with the three $ALDH2$ genotypes, all analyses were replicated excluding those participants who were homozygous for $ALDH2^{*2}$ ($n = 6$). The pattern of significant results did not differ from the aforementioned analyses.

**Results**

**Associations of $ALDH2$ With Alcohol Use**

As shown in Figure 1, $ALDH2$ status was not associated with having initiated alcohol use or having ever been drunk; 97% of the participants without $ALDH2^{*2}$ alleles and 100% of those with $ALDH2^{*2}$ alleles had consumed at least one alcoholic drink, $\chi^2(1, N = 180) = 2.50, p = .11$, and 70% of both groups had been intoxicated, $\chi^2(1, N = 180) = 0.01, p = .92$. Among those who had initiated drinking ($n = 177$), there was not a significant relationship between $ALDH2$ status and age of onset of drinking: $M = 16.4$ years, $SD = 3.3$ years for $ALDH2^{*2}$ (−) and $M = 16.9$ years, $SD = 3.0$ years for $ALDH2^{*2}$ (−), $t(175) = -1.19, r^2 = .02$.
.008, p = .24. As shown in Figure 1, participants without ALDH2*2 alleles were significantly more likely to have become a regular drinker (78%) than those with ALDH2*2 alleles (58%), \(\chi^2(1, N = 180) = 6.41, p < .01\), odds ratio (OR) = 1.3, 95% confidence interval (CI) = 1.1 to 1.6, and were significantly more likely to have engaged in a heavy- or binge-drinking episode (66%) than those with ALDH2*2 alleles (47%), \(\chi^2(1, N = 180) = 6.39, p < .01\), OR = 1.4, CI = 1.0 to 1.8. Consistent with this latter finding, those without ALDH2*2 alleles reported a greater number of maximum drinks ever consumed in a 24-hr period than those with ALDH2*2 alleles: \(M = 10.0, SD = 9.0\) for ALDH2*2 (–) and \(M = 6.0, SD = 5.7\) drinks for ALDH2*2 (+), \(t(178) = 3.40, \eta^2 = .061, p < .001\).

Associations of ALDH2 With Other Substance Use

As shown in Figure 2, a greater proportion of participants without ALDH2*2 alleles had used substances other than alcohol than those with ALDH2*2 alleles, with a statistically significant difference in those who reported regular tobacco use based on ALDH2 status, ALDH2*2 (–) = 22%, ALDH2*2 (+) = 11%, \(\chi^2(1, N = 180) = 3.86, p < .05\), OR = 2.0, CI = 1.0 to 4.1. There were similar trends for having ever used marijuana, ALDH2*2 (–) = 39%, ALDH2*2 (+) = 31%, \(\chi^2(1, N = 180) = 1.41, p = .23\), OR = 1.3, CI = 0.9 to 1.9, for having regularly used marijuana, ALDH2*2 (–) = 10%, ALDH2*2 (+) = 6%, \(\chi^2(1, \ N = 180) = 0.90, p = .34\), OR = 1.6, CI = 0.6 to 4.6, and for having ever used any other illicit substance, ALDH2*2 (–) = 18%, ALDH2*2 (+) = 11%, \(\chi^2(1, \ N = 180) = 1.75, p = .18\), OR = 1.6, CI = 0.8 to 3.4, although these differences did not reach statistical significance. Very few participants endorsed the regular use of any other illicit substance, ALDH2*2 (–) = 2%, ALDH2*2 (+) = 2%, and a significance test was not conducted because of the low frequency of this behavior.

Test of Mediation Model for Regular Smoking

Of the 31 regular smokers, all but 1 were regular drinkers and all but 3 had engaged in a heavy- or binge-drinking episode. It is possible that the association of ALDH2 with regular smoking is due to the effects of another variable, such as regular heavy drinking (Shiffman & Balabanis, 1995). Following Baron and Kenny’s (1986) guidelines, regular drinking and binge drinking were tested as mediators of the direct effect of ALDH2 on regular smoking. For a third variable to act as a mediator, it is necessary to meet three conditions. First, the independent variable (ALDH2 status) and outcome variable (smoking status) have to be related. Second, the independent variable (ALDH2 status) and mediating variable (drinking status) have to be related. Finally, when regressing the outcome variable simultaneously on the independent variable and mediator, the mediator has to be related to the outcome and the relation between the independent variable and the outcome has to be no longer significant. Significant relationships were found among ALDH2 status, regular drinking status, binge-drinking status, and regular smoking status. Using logistic regression analysis, regular smoking was regressed onto ALDH2 and
regular drinking after adjusting for ethnic subgroup. The effect of regular drinking remained significant ($\beta = 2.73$, $SE = 1.04$, $p < .01$, OR = 15.3, CI = 2.0–116.5), whereas that for ALDH2 did not ($\beta = -0.50$, $SE = 0.46$, $p = .27$, OR = 0.6, CI = 0.2–1.5). Similarly, when regular smoking was regressed onto ALDH2 and binge drinking adjusting for ethnic subgroup, the effect of binge drinking remained significant ($\beta = 1.94$, $SE = 0.64$, $p < .01$, OR = 6.9, CI = 2.0–24.3), whereas that for ALDH2 did not ($\beta = -0.47$, $SE = 0.46$, $p = .31$, OR = 0.6, CI = 0.3–1.5). These results support regular drinking and heavy drinking as mediators of the association between ALDH2 and regular smoking, but the specific causal pathway regarding the relationship between drinking and smoking behavior cannot be definitively determined using this cross-sectional data set.

**Discussion**

Compared with those included in population surveys, which found that the average age of first alcohol use in the United States is between 13 and 14 years (Blane & Hewitt, 1977; Johnston, O'Malley, & Bachman, 1998), participants in this study reported initiating alcohol use at a relatively later age ($M = 16.6$ years) irrespective of ALDH2 status. These results suggest that the onset of alcohol use for Asian American youth may be at a relatively later age than for non-Asian American youth, and that this is likely due to nongenetic or indirect genetic (e.g., parental modeling) influences. These findings are consistent with studies of predominantly White twins, which have found that initiation of alcohol use is primarily influenced by environmental rather than genetic factors (Heath & Martin, 1988; Koopmans & Boomsma, 1996; Prescott et al., 1994). Additionally, this study found no association of ALDH2 with having ever been drunk, a finding consistent with results from a twin study of White adolescents, which found that initiation of drinking to intoxication, like initiation of drinking, is primarily influenced by nongenetic factors (Rose, 1998).

Unlike initiation of drinking and having ever been drunk, ALDH2 status had a significant association with regular drinking, binge drinking, and maximum drinks ever consumed in a 24-hr period. Similar to findings of alcohol consumption in Asian adults (Takeshita & Morimoto, 1999; Tu & Israel, 1995), individuals with ALDH2*2 alleles were less likely to be regular drinkers, were less likely to have ever engaged in a heavy- or binge-drinking episode, and reported a lower maximum number of drinks consumed than those lacking this genetic variant. These results are also consistent with twin studies, which found that once alcohol use is initiated differences in alcohol consumption patterns are strongly influenced by genetic factors (Heath, 1995). Moreover, a study of adolescent twins suggests that the influence of genetics increases with greater experience with alcohol as evidenced by greater differences between monozygotic and dizygotic twins over

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2 Although the logistic regression analyses controlled for ethnic subgroup, similar results were obtained without such statistical control.
time (Rose, 1998). Thus, ALDH2 status may affect certain aspects of alcohol drinking behavior, such as sensitivity to alcohol (Wall et al., 1992, 1994), and this influence becomes relevant only after alcohol use has been initiated and with increased drinking experience. ALDH2, to date, is the candidate gene with the strongest association with alcohol dependence (C.-C. Chen et al., 1999; Higuchi et al., 1995; Iwahashi et al., 1995; Maезawa et al., 1995; Thomasson et al., 1991). These findings suggest an early influence of ALDH2 on alcohol behavior as well, first occurring at some point between the onset of drinking and the transition to increased alcohol involvement.

This study also provides the first evidence of an association of ALDH2 with regular tobacco use. Results suggest that possession of an ALDH2*2 allele is related not only to reduced alcohol use but also to reduced tobacco use, and there were similar but nonsignificant trends toward reduced marijuana and other illicit drug use. It is possible that there may be a direct biological influence of ALDH2 on tobacco use because acetaldehyde is produced during cigarette smoking (McLaughlin, Scott, & Peterson, 1990), but it is not known whether sufficient acetaldehyde is produced for ALDH2*2 to have a protective effect on smoking. It is also possible that Asians with ALDH2*2 alleles are less likely to smoke because they are less likely to drink (Shiffman & Balabanis, 1995). National surveys have found that Asian college students both drink less heavily (Wechsler, Dowdall, Maenner, Gledhill-Hoyt, & Lee, 1998) and smoke less (Wechsler, Rigotti, Gledhill-Hoyt, & Lee, 1998) than White college students.

Studies of adolescents showed that the progression of drug use follows a predictable pattern in which youth first try licit drugs (alcohol and cigarettes) before they try marijuana and other illicit drugs (Kandel, 1975; Kandel et al., 1992). In addition, increased involvement with alcohol is an important step in the transition to other drug use for most, but not all, adolescents (Donovan & Jessor, 1983; Ellickson, Hays, & Bell, 1992). Ellickson et al. (1992) found that regular alcohol use followed marijuana use and preceded regular cigarette use and the use of all other illicit drugs for Hispanic, White, and Black youth but not for Asian youth. For Asians, the regular use of alcohol followed the regular use of cigarettes and the use of other illicit drugs. They hypothesized that either cultural or biological factors could account for the “late” escalation of alcohol involvement among Asian adolescents. Results from the present study suggest that possession of an ALDH2*2 allele inhibits, in part, regular and heavy drinking among Asian youth.

In addition, a mediation model (regular and heavy drinking mediating the relationship between ALDH2 and regular smoking) was supported, but the cross-sectional and retrospective nature of the present data limits the ability to examine substance use progression and to test mechanisms. It is also possible that ALDH2 interacts with other genetic or environmental factors that predispose a person to both heavy alcohol and tobacco use.

This study had other limitations as well. Because ALDH2*2 is extremely rare in non-Asians, the findings apply only to persons of Chinese, Korean, or Japanese heritage. Researchers exploring the genetics of tobacco and other substance use and dependence, however, may want to include assessment of the ALDH2 gene when examining samples that include individuals of Asian descent. Additionally, this is an association study conducted combining three Asian American subgroups and, thus, is subject to problems of population stratification, in which persons with and without the characteristics under evaluation may come from different populations. Future research with larger samples should be conducted to replicate these findings within each of these subgroups. Moreover, because only college students were included, the results may be unique to this selected sample and may not generalize to different age groups or to a similar-age noncollege sample. The definitions of substance involvement were taken from the SSAGA and did not assess initial tobacco use. In addition, alternative definitions of regular alcohol, tobacco, and illicit drug use could lead to different conclusions. Finally, as with all self-report data, there are concerns about the validity of responses; however, there is no reason to suspect that there might be differential response biases on the basis of ALDH2 status. Despite these limitations, this study provides evidence that possession of an ALDH2*2 allele in Asian American college students is associated with lower rates of regular and heavy drinking as well as lower rates of regular tobacco use.

References


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