ALDH2, ADH1B, AND ADH1C GENOTYPES IN ASIANS: A LITERATURE REVIEW

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Variants of three genes encoding alcohol-metabolizing enzymes, the aldehyde dehydrogenase gene ALDH2 and the alcohol dehydrogenase genes ADH1B and ADH1C, have been associated with reduced rates of alcohol dependence. The genotype prevalence of these genes varies in general samples of different Asian ethnic groups. The ALDH2*2 allele appears to be most prevalent in Chinese-American, Han Chinese and Taiwanese, Japanese, and Korean samples. Much lower rates have been reported in Thais, Filipinos, Indians, and Chinese and Taiwanese aborigines. ADH1B*2 is highly prevalent among Asians, with the exception of Indians. ADH1C*1 also is highly prevalent in Asians, but has only been examined in a few studies of Chinese and Korean samples. Key Words: Alcohol dependence; ethanol metabolism; ethanol-to-acetaldehyde metabolism; alcohol dehydrogenase (ADH); aldehyde dehydrogenase (ALDH); acetaldehyde; ADH1B; ADH1C; risk factors; protective factors; genetic factors; ethnic groups; Asians; Chinese; Filipino; Indian; Japanese; Korean; Malaysian; Thai

People of Asian descent, as a whole, have lower rates of alcohol dependence compared with other ethnic groups (Grant et al. 2004). Within Asians, however, rates of alcohol dependence differ across ethnic subgroups. For example, relatively high rates of alcohol dependence have been found among Koreans and Korean Americans, whereas relatively low rates have been found in Chinese and Chinese Americans (Helzer et al. 1990; Luczak et al. 2004). Prevalence rates of alleles of genes encoding alcohol-metabolizing enzymes vary across Asian ethnicities (e.g., Goedde et al. 1992). This may in part account for some of the ethnic differences in rates of alcohol involvement. The purpose of this article is to review genotype prevalence rates of three genes, the aldehyde dehydrogenase gene ALDH2 and the alcohol dehydrogenase genes ADH1B and ADH1C.

These three genes code for isoenzymes that metabolize alcohol into acetaldehyde (ADH1B and ADH1C) and acetaldehyde into acetate (ALDH2). The common forms of these alleles are ADH1B*1, ADH1C*2, and ALDH2*1. The variant forms of the alleles (ADH1B*2, ADH1C*1, and ALDH2*2) are hypothesized to alter conversion rates during alcohol metabolism and lead to an excess buildup of acetaldehyde (see Eriksson 2001). The excess acetaldehyde is thought to lead to heightened responses to alcohol and thereby reduce heavy alcohol use, associated problems, and the development of alcohol use disorders (see Wall et al. 2005 for further details). A meta-analysis of 15 Asian (Chinese, Japanese, Korean, and Thai) studies with data from over 4,500 alcohol-dependent and control subjects collected between 1979 and 2004 found possession of one variant ALDH2*2 allele was associated with a five-fold reduction in alcohol dependence and possession of two ALDH2*2 alleles was associated with a nine-fold reduction (Luczak et al. 2006). In Asians with no ALDH2*2 alleles, possession of one variant ADH1B*2 allele was associated with a four-fold reduction in alcohol dependence and possession of two ADH1B*2 alleles was associated with a five-fold reduction (Luczak et al. 2006). ADH1C*1 also has been related to protection against alcohol dependence, but this association has been attributed to the ADH1C gene being in close proximity to the ADH1B gene on the chromosome so that the genotypes are correlated (Osier et al. 1999).

Determining how frequently certain genotypes occur in different populations is useful for behavioral genetics research. It is important to establish the prevalence rates of these genotypes in various ethnic groups to determine their unique contribution to alcohol involvement within each ethnicity. To achieve this goal for Asian populations, an extensive literature review of studies determining the prevalence of the ALDH2, ADH1B, and ADH1C genotypes in various Asian ethnic groups was performed, as described in the following sections.

Prevalence of ALDH2, ADH1B, and ADH1C Genotypes in Asian Populations

Study Design
To identify studies eligible for this analysis, the authors of this article surveyed the Medline literature database using the National Library of Medicine’s PubMed (January 1966 to April 2006) online search engine. The search first was conducted using the keywords “aldehyde dehydrogenase...”

1Every person possesses two copies of each allele; these two alleles make up the genotype.
2ADH1B and ADH1C were formerly called ADH2 and ADH3, respectively (for more information, see the accompanying article by Edenberg).
3If a person has two copies of the same allele, the person is called homozygous for that allele; if the two copies are of different alleles, the person is called heterozygous.

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nase OR ALDH) AND Asian;” then, additional searches were conducted by replacing “Asian” with specific Asian ethnicities (i.e., Chinese, Filipino, Indian, Japanese, Korean, Malaysian, and Thai). The series of searches then was repeated using the keywords “(alcohol dehydrogenase OR ADH).” The retrieved abstracts were read to identify studies that reported prevalence rates of the various \textit{ALDH2}, \textit{ADH1B}, and \textit{ADH1C} genotypes in general samples of the different ethnic groups. The studies thus identified were read in their entirety to assess whether they were appropriate for including in this analysis. Studies that reported only allele frequencies instead of genotypes, compared treatment samples with control groups, or selected samples based on specific alcohol-related medical conditions (e.g., cirrhosis or head and neck cancers) were excluded. All references cited in the appropriate articles also were reviewed to identify additional relevant publications. Despite the stringent criteria for the selection of studies to be included, the following caveats should be noted:

- Some samples included in the analysis may not be entirely random because participants were screened for certain medical disorders (e.g., diabetes, heart conditions, and stroke) that have been related to alcohol in addition to other factors.

- Samples with allele distributions that do not meet Hardy-Weinberg equilibrium\(^4\) (which are marked in the table summarizing the results) should be viewed with caution because the genotype distribution in these studies is not consistent with the expected distribution for a general sample.

\(^4\)Hardy-Weinberg equilibrium is the stable frequency distribution of genotypes, as measured by the proportion of the alleles that result as a consequence of random mating.

\(^5\)The Han are the main ethnic group found in the People’s Republic of China and Taiwan.

Results of the Analysis

\textbf{Distribution of ALDH2 Genotypes.} The \textit{ALDH2*2} allele is thought to occur exclusively in Asians; however, its prevalence varies across Asian ethnicities (see Table 1). Five studies determined the \textit{ALDH2} genotype in Han Chinese and Taiwanese people.\(^5\) In these studies, 20 to 47 percent of the participants were heterozygous and 1 to 8 percent were homozygous for \textit{ALDH2*2} (Goedde et al. 1992; Luo et al. 2001, 2005; Novoradovsky et al. 1995; Shen et al. 1997). Overall, approximately one-third of the Han Chinese possessed at least one \textit{ALDH2*2} allele. The prevalence of the \textit{ALDH2*2} allele was particularly high in one study of Han Taiwanese and two studies of Chinese Americans, with about half of these samples possessing at least one \textit{ALDH2*2} allele, including 7 to 8 percent who were homozygous for \textit{ALDH2*2} (Hendershot et al. 2005; Luczak et al. 2004; Novoradovsky et al. 1995). The large variation in prevalence rates found among Han Chinese and Taiwanese samples might be explained by the different geographic locations from which the samples were obtained. The sample with the highest prevalence was from Taiwan, where 55 percent of participants possessed at least one \textit{ALDH2} allele (Novoradovsky et al. 1995). Conversely, the samples with the lowest prevalence were from central and northern China, where 22 percent of participants possessed at least one \textit{ALDH2*2} allele (Luo et al. 2001; Shen et al. 1997). For the studies with intermediate prevalence rates (i.e., 30 to 32 percent), the samples were from southwest China (Luo et al. 2005) or their location was not reported (Goedde et al. 1992).

The \textit{ALDH2*2} allele was less commonly found in aboriginal Chinese and Taiwanese samples (e.g., Ami, Atayal, Bunun, Elunchan, Mongolian, and Paiwan), with 2 to 12 percent of study participants being heterozygous and only 0.3 percent (i.e., 2 of 585 people analyzed) being homozygous for \textit{ALDH2*2} (Chen et al. 1997; Shen et al. 1997; Thomasson et al. 1994).

Data from 10 Japanese studies indicated that 41 to 52 percent of Japanese possessed at least one \textit{ALDH2*2} allele, including 1 to 8 percent who were homozygous for \textit{ALDH2*2} (Amamoto et al. 2002; Goedde et al. 1992; Higuchi et al. 1996; Saito et al. 2003; Sun et al. 1999; Takeshita and Morimoto 1999; Takeshita et al. 1994; Tanaka et al. 1997; Yamada et al. 2002; Yokoyama et al. 2005). Somewhat higher rates were reported in one small Japanese study (\textit{N} = 15), in which 66 percent of the participants possessed at least one \textit{ALDH2*2} allele, including 13 percent who were homozygous for \textit{ALDH2*2} (Shibuya et al. 1989).

Five studies of Korean, Korean-American, and Korean-Chinese samples found that approximately one-third (29 to 37 percent) of Koreans had at least one \textit{ALDH2*2} allele, including 2 to 3 percent who were homozygous for \textit{ALDH2*2} (Goedde et al. 1992; Hendershot et al. 2005; Lee et al. 1997; Luczak et al. 2004; Shen et al. 1997). Finally, \textit{ALDH2*2} was much less common among other Asian ethnicities, including Filipinos, Indians, Malays, Siberian Yakuts, and Thais, than in Chinese, Japanese, and Korean samples, with 0 to 10 percent of study participants possessing at least one \textit{ALDH2*2} allele (Goedde et al. 1992; Novoradovsky et al. 1995). Taken together, all the studies reviewed here demonstrate great diversity among Asian ethnic groups in the prevalence of heterozygosity or homozygosity for \textit{ALDH2*2}.

\textbf{Distribution of ADH1B Genotypes.} The \textit{ADH1B*2} allele was highly prevalent in Asian ethnic groups, particularly in northeast Asians (i.e., Chinese, Japanese, and Koreans) (see Table 1). Among the Han Chinese and Taiwanese and the Chinese Americans, 84 to 92 percent possessed at least one \textit{ADH1B*2} allele, including 40 to 60 percent who were homozygous for \textit{ADH1B*2} (Chao et al. 1987; Goedde et al. 1992; Lee et al. 1989; Luczak et al. 2004; Shen et al. 1997). Rates of having at least one \textit{ADH1B*2} allele were slightly lower in some Chinese and Taiwanese aborigine groups (e.g., 63 percent in Elunchan, 74 percent...
Table 1: Genotypes for Genes Encoding Aldehyde Dehydrogenase (ALDH2) and Alcohol Dehydrogenase (ADH1B and ADH1C)

| Study Authors | Sample | ALDH2 Genotypes prevalence (%) | ADH1B Genotypes prevalence (%) | ADH1C Genotypes prevalence (%) |
|---------------|--------|-------------------------------|--------------------------------|-------------------------------|
| **Han Chinese and Taiwanese** |        | *1/*1 | *1/*2 | *2/*2 | *1/*1 | *1/*2 | *2/*2 | *1/*1 | *1/*2 | *2/*2 |
| Chao et al. 1987 | 60 male and 11 female liver specimens | 10 | 31 | 59 | 70 | 29 | 1 | 8 | 48 | 44 |
| Goedde et al. 1992 | 132 subjects* | 78 | 20 | 2 | 68 | 28 | 4 | 1 | 32 | 66 |
| Lee et al. 1989 | 53 lung specimens | 45 | 47 | 8 | 78 | 20 | 2 | 16 | 44 | 40 |
| Luo et al. 2001 | 50 subjects | 45 | 47 | 8 | 78 | 20 | 2 | 16 | 44 | 40 |
| Luo et al. 2005 | 444 males and 204 females | 45 | 47 | 8 | 78 | 20 | 2 | 16 | 44 | 40 |
| Novoradovsky et al. 1995 | 173 blood donors | 45 | 47 | 8 | 78 | 20 | 2 | 16 | 44 | 40 |
| Shen et al. 1997* | 100 male | 45 | 47 | 8 | 78 | 20 | 2 | 16 | 44 | 40 |
| **Total** |        | 66 | 30 | 4 | 11 | 40 | 49 | 83 | 14 | 3 |
| **Chinese American** |        |     |   |   |     |   |   |   |   |   |
| Hendershot et al. 2005 | 110 male and 113 female college students | 48 | 44 | 8 | 8 | 33 | 58 | 49 | 43 | 7 |
| Luczak et al. 2004 | 92 males and 98 females college students | 48 | 44 | 8 | 8 | 33 | 58 | 49 | 43 | 7 |
| **Total** |        | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| **Chinese and Taiwanese Aborigine** |        |     |   |   |     |   |   |   |   |   |
| Chen et al. 1997 | 46 subjects* | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| Ami | 67 subjects* | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| Atayal | 118 subjects* | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| Piaowan | 71 subjects* | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| Shen et al. 1997 | 68 males | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| Elunchan* | 66 males | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| Mongolian | 66 males | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| Thomasson et al. 1994 | 80 males and 80 females* | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| **Total** |        | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| **Filipino** |        |     |   |   |     |   |   |   |   |   |
| Goedde et al. 1992 | 86 subjects* | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| **Indian** |        |     |   |   |     |   |   |   |   |   |
| Goedde et al. 1992 | 179 subjects* | 95 | 5 | 0 | 10 | 32 | 58 | 88 | 11 | 1 |
| **Japanese** |        |     |   |   |     |   |   |   |   |   |
| Amamoto et al. 2002* | 749 males and 1,286 females | 48 | 45 | 7 | 55 | 43 | 2 | 16 | 50 | 34 |
| Goedde et al. 1992 | 53 subjects* | 48 | 45 | 7 | 55 | 43 | 2 | 16 | 50 | 34 |
| Higuchi et al. 1996 | 230 male and 221 female hospital employees and relatives | 55 | 43 | 2 | 16 | 50 | 34 |
| Saito et al. 2003 | 335 males | 55 | 43 | 2 | 16 | 50 | 34 |
| Shibuya et al. 1989 | 15 males* | 55 | 43 | 2 | 16 | 50 | 34 |
| Sun et al. 1999 | 643 male hospital and civil service employees | 55 | 43 | 2 | 16 | 50 | 34 |
| Suzuki et al. 2004 | 1,126 males | 55 | 43 | 2 | 16 | 50 | 34 |
| Takeshita & Morimoto 1999 | 389 males and 34 females medical students | 55 | 43 | 2 | 16 | 50 | 34 |
| Takeshita et al. 1994 | 424 male and 100 females metal plant workers | 55 | 43 | 2 | 16 | 50 | 34 |
| Takeshita et al. 1996 | 424 male and 100 females metal plant workers | 55 | 43 | 2 | 16 | 50 | 34 |
| Tanaka et al. 1997* | 189 males | 55 | 43 | 2 | 16 | 50 | 34 |
| Yamada et al. 2002 | 855 male factory workers | 55 | 43 | 2 | 16 | 50 | 34 |
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Table 1 Genotypes for Genes Encoding Aldehyde Dehydrogenase (ALDH2) and Alcohol Dehydrogenase (ADH1B and ADH1C) (continued)

| Study Authors           | Sample                        | ALDH2 Genotypes prevalence (%) | ADH1B Genotypes prevalence (%) | ADH1C Genotypes prevalence (%) |
|-------------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                         |                               | *1/*1  | *1/*2  | *2/*2  | *1/*1  | *1/*2  | *2/*2  | *1/*1  | *1/*2  | *2/*2  |
| **Japanese** (continued)|                               |        |        |        |        |        |        |        |        |        |
| Yin et al. 1984         | 97 liver samples              |        |        |        | 13     | 29     | 58     |        |        |        |
| Yokoyama et al. 2005    | 139 male and 112 female workers|        |        |        | 59     | 33     | 8      | 54     | 40     | 6      |
| **Total**               |                               |        |        |        | 6      | 35     | 60     |        |        |        |
| **Japanese American**   |                               |        |        |        | 19     | 34     | 47     |        |        |        |
| Yin et al. 1984         | 97 liver samples              |        |        |        | 72     | 27     | 4      | 31     | 65     |        |
| **Total**               |                               |        |        |        | 71     | 26     | 3      | 4      | 65     |        |
| **Korean**              |                               |        |        |        | 67     | 32     | 2      | 10     | 36     | 53     |
| Hendershot et al. 2005  | 97 male and 108 female college students |        |        |        | 66     | 31     | 3      | 10     | 36     | 53     |
| Luczak et al. 2004      | 107 male and 107 female college students |        |        |        |        |        |        |        |        |        |
| **Total**               |                               |        |        |        | 66     | 32     | 2      | 10     | 36     | 53     |
| Korean Chinese          |                               |        |        |        | 63     | 34     | 3      | 11     | 38     | 50     |
| Shen et al. 1997        | 105 males                     |        |        |        | 93     | 7      | 0      | 17     | 48     | 35     |
| **Total**               |                               |        |        |        | 90     | 10     | 0      | 46     | 41     | 13     |
| Malay                   |                               |        |        |        | 99     | 0      | 0      |        |        |        |
| Goedde et al. 1992      | 73 subjects*                  |        |        |        | 100    | 0      | 0      |        |        |        |
| **Totals**              |                               |        |        |        |        |        |        |        |        |        |

* Sample size varies by gene analyzed.

in Mongolian, and 78 percent in Ami) but were higher in others (e.g., 98 to 100 percent in Atayal, Bunun, and Paiwan) (Chen et al. 1997; Shen et al. 1997; Thomasson et al. 1994).

The ADH1B*2 allele also was commonly found in Japanese people. In 10 studies of Japanese, 81 to 100 percent of participants possessed at least one ADH1B*2 allele, including 34 to 71 percent who were homozygous for the allele (Goedde et al. 1992; Higuchi et al. 1996; Saito et al. 2003; Shibuya et al. 1989; Sun et al. 1999; Suzuki et al. 2004; Takeshita et al. 1996; Tanaka et al. 1997; Yamada et al. 2002; Yin et al. 1984). The results of one of the studies (Yin et al. 1984), in which ADH1B*2 prevalence rates were among the lowest for Japanese and Japanese Americans, however, must be viewed with caution because the distributions were not in Hardy-Weinberg equilibrium.

The prevalence of ADH1B*2 also was high in three Korean samples, with 88 to 96 percent of participants possessing at least one ADH1B*2 allele and 50 to 65 percent possessing two ADH1B*2 alleles (Goedde et al. 1992; Luczak et al. 2004; Shen et al. 1997). Among Filipinos and Malays, more than 80 percent of study participants carried at least one ADH1B*2 allele (Goedde et al. 1992) as well. Intermediate rates were found in Thais (54 percent), and ADH1B*2 was least common in Indians, where only 15 percent possessed at least one copy of the allele (Goedde et al. 1992).

**Distribution of ADH1C Genotypes.** ADH1C genotypes only have been examined in a few Chinese and Korean samples, but in these samples the ADH1C*1 allele was highly prevalent. In one study of Han Chinese, 97 percent of participants possessed at least one ADH1C*1 allele, including 83 percent who were homozygous (Shen et al. 1997). Comparably high proportions (97 to 100 percent) of seven Chinese aboriginal populations possessed at least one ADH1C*1 allele, although the rates of homozygosity for ADH1C*1 were more variable (59 to 99 percent in Mongolian, and 78 percent in Ami) but were higher in others (e.g., 98 to 100 percent in Atayal, Bunun, and Paiwan) (Chen et al. 1997; Shen et al. 1997; Thomasson et al. 1994).
percent) in these populations (Chen et al. 1997; Shen et al. 1997; Thomasson et al. 1994). Finally, the prevalence of ADH1C*1 in one Korean Chinese sample was similar to the rates reported in Chinese samples, with 99 percent of subjects possessing at least one ADH1C*1 allele, including 86 percent who were homozygous for the allele (Shen et al. 1997).

Summary
This literature review highlights the fact that the prevalence of ALDH2, ADH1B, and ADH1C alleles vary greatly across Asian ethnic groups. For example, whereas approximately half of Chinese-American and Japanese samples and approximately one-third of Korean and Han Chinese and Taiwanese studied carry at least one ALDH2*2 allele, the prevalence of this allele is much lower (10 percent) in Thais, and almost no Filipinos, Indians, or Chinese and Taiwanese aborigines carry the allele, with the exception of Mongolians (12 percent). Similarly, the ADH1B*2 allele is found in 80 percent or more of Han Chinese and Taiwanese, Filipino, Japanese, Korean, and some Chinese and Taiwanese aborigine people but only in about 15 percent of Indians. Finally, the ADH1C*1 allele was found in almost all Chinese and Korean people studied, but it has not been analyzed yet in other Asian ethnic groups. Such summaries of general-sample prevalence rates are important for understanding risk and protective factors for alcohol use disorders because they facilitate comparisons of the contribution of these alcohol-metabolizing enzymes and their variants to alcohol-related behaviors within and across ethnic groups.

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