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Alcohol Dependence Symptoms and Alcohol Dehydrogenase 2 Polymorphism: Israeli Ashkenazis, Sephardics, and Recent Russian Immigrants

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Background: Jews have lower rates of alcohol-related problems than other Caucasians. The *ADH2*2* allele of the alcohol dehydrogenase 2 (*ADH2*) gene protects against alcoholism in Asians and is found in approximately 20% of Jews. We studied the relationship of *ADH2*2* to DSM-IV dependence severity in a random community sample of Israeli Ashkenazis, recent Russian immigrants (also Ashkenazis), and Sephardics.

Methods: Subjects participated in a structured interview that included highly reliable questions on DSM-IV alcohol dependence symptoms. *ADH2* genotype was determined for 68 subjects.

Results: Recent Russian immigrants had more past and lifetime DSM-IV dependence symptoms. Sephardics had a higher prevalence of *ADH2*2* than Ashkenazis. Controlling for group and other potentially confounding factors, *ADH2*2* was associated with a lower lifetime DSM-IV alcohol dependence severity, although this differed somewhat within groups.

Conclusions: *ADH2*2* protects against dependence severity in Jewish samples. Future work in larger samples should address genetic and environmental factors that affect the relationship of *ADH2*2* to alcohol consumption and dependence.

Key Words: *ADH2*, Alcohol, Alcohol Dependence, Jews, Genetic.

BOTH GENETIC AND environmental factors influence the occurrence of alcoholism. Jewish individuals generally drink less and have lower rates of alcohol-use disorders than other Caucasians (Levav et al., 1997; Yeung and Greenwald, 1992). Older social explanations of the lower rates that are based on religious practices (Bales, 1962; Snyder, 1958) are no longer accepted (Flasher and Maisto, 1984). Furthermore, empirical data (Hasin and Kohn, unpublished data, 2002) from the Epidemiologic Catchment Area study (Regier et al., 1990) show that the level of religiosity cannot explain the low level of alcohol problems in Jews compared with other groups. None of this work addressed variability in drinking within the Jewish population. Understanding this dimension may lead to a better understanding of Jewish/non-Jewish differences in drinking and of the etiology of alcoholism in general.

The importance of genetic factors in the development of alcohol dependence has been well established (Heath et al., 1997). The clearest evidence for specific genes influencing this process comes from findings on alcohol-metabolizing genes (Li, 2000). The alcohol dehydrogenase (*ADH*) genes on chromosome 4 are involved in alcohol metabolism (Edenberg, 2000; Li, 2000). *ADH2*, found largely in the liver, converts ethanol to acetaldehyde. Polymorphisms in the *ADH2* gene result in isozymes that have very different catalytic properties. A protective relationship has been found between *ADH2*2* and alcoholism in Asians and Caucasians (Li, 2000; Whitfield, 1997). In most European populations, *ADH2*2* is rare (Goedde et al., 1992), but it is still generally protective against alcoholism and heavy drinking (Borras et al., 2000; Whitfield et al., 1998).

Recently, reports have shown a relatively high prevalence of *ADH2*2* in Jewish samples (Carr et al., 2002; Neumark et al., 1998; Shea et al., 2001), suggesting that *ADH2*2* might explain the low rates of alcoholism in this group. The relationship of *ADH2*2* to drinking in Jews was first studied in two independent Israeli samples: community residents and treated heroin addicts. In these samples of men, *ADH2*2* was associated with very infrequent drinking and lower peak alcohol consumption levels (Neumark et al., 1998). However, alcohol dependence was not measured in this study. Among Jewish college volunteers and adults in

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the Midwestern US (Carr et al., 2002), *ADH2*2* was protective against frequent consumption in male adults. Although not protective against frequent consumption in college-age men, *ADH2*2* was associated with unpleasant reactions to drinking in both male college students and adults. Alcohol dependence was not measured in this study either. In Jewish college volunteers in the Southwestern US (Shea et al., 2001), *ADH2*2* was protective against frequent consumption in men, although it was not related to other consumption measures or DSM-IV alcohol dependence, which was rare. Thus, although significant relationships between *ADH2*2* and alcohol use were found in all Jewish groups studied, the results were not consistent across all measures. Furthermore, dependence was measured in only one of the studies (Shea et al., 2001), in which it was rare. Assessing dependence in categorical rather than continuous form may have resulted in some loss of information. Inconsistencies between the studies could have occurred for several reasons, including differences in measurement of the phenotype, other methodological differences (e.g., sampling or statistical analysis), or between-sample differences in other influences on alcohol. Using consistent methods and continuous dependence measures in contrasting Jewish groups seemed to offer an opportunity to better understand the influence of *ADH2*2* on the severity of alcohol dependence in Jews.

A setting to study such groups exists in Israel. Since the founding of Israel in 1948, large waves of immigration have resulted in population subgroups from different areas of the world (Dohrenwend et al., 1992; Israeli Central Bureau of Statistics, 1999). Until the early 1990s, the two main population subgroups were Ashkenazis (European and Russian background) and Sephardics (Middle Eastern and North African background). Analyses of 1995 Israeli national survey data indicated that Sephardics were less likely than Ashkenazis to be drinkers and to have gotten drunk recently (Aharonovich et al., 2001). Sephardics and Ashkenazis also differ in some genetic respects (Pollack et al., 2000; Roitberg-Tambur et al., 1995).

A third group has emerged more recently. Since late 1989, approximately 780,000 immigrants from the former Soviet Union (FSU) arrived in Israel, many of them arriving in the early 1990s. These immigrants now constitute approximately 15% of Israel's population (Israeli Central Bureau of Statistics, 1999). Russia has one of the world's highest levels of alcohol consumption (Treml, 1997), whereas Israel has one of the lowest (Verhoek, 1995). The 1995 national survey data showed that recent Russian immigrants were more likely to be drinkers and to become drunk than other Israelis (Rahav et al., 1999). Furthermore, recent Russian immigrants were more likely to be drinkers than those from earlier waves of immigration from Russia to Israel (Hasin et al., 1998). The 1995 national data did not include information on alcohol dependence. However, when summarized, the results indicated that Ashkenazis, Sephardics, and recent Russian immigrants to Israel constituted contrasting groups in terms of drinking.

Using standardized methodology across a small community sample of these three population subgroups, we previously showed that *ADH2*2* was associated with a lower peak lifetime alcohol consumption (Hasin et al., 2002). This relationship seemed to differ by population subgroup, because within-group exploration did not indicate decreased consumption among Russian subjects with *ADH2*2*. In this study, we addressed the relationship of *ADH2*2* to alcohol dependence in the three contrasting Jewish-Israeli groups: Ashkenazis, Sephardics, and recent Russian immigrants.

METHODS

Setting, Sample Design, and Procedures

The study was conducted in an Israeli city of approximately 140,000. To balance the number of Ashkenazis, Sephardics, and recent Russian immigrants, subjects were sampled from three neighborhoods, each identified (via census information) as having a high concentration of one of the groups. Households were sampled within these three neighborhoods, and introduction letters were sent to the households. Each household was then called, and adult household members from age 22 to 65 years were enumerated (individuals between the ages of 18 and 21 were unavailable due to military service). With oversampling for men, one member from each household was randomly chosen and invited to participate in a personal interview. Of 103 designated households, subjects from 75 participated (response rate, 73%). After obtaining written informed consent, nurses or physicians conducted in-person interviews in privacy, mainly in the subject's home. Data verification was later conducted with a randomly selected subset of subjects by telephone from New York. DNA for genotyping was obtained from 68 subjects (91% of those interviewed). *ADH2* genotype (*ADH2*1* and *ADH2*2*) was determined by enzymatic amplification of genomic DNA followed by hybridization with allele-specific oligonucleotides (Xu et al., 1988). *ADH2*3* was not tested, because it ordinarily occurs only in African Americans (Ehlers et al., 2001; Thomasson et al., 1995) and Native Americans (Wall et al., 1997).

Measures

DSM-IV alcohol dependence and abuse criteria and diagnoses were derived from the Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS; Grant et al., 1995). This instrument, designed for lay interviewers, has been used in national and community epidemiological research in the US (Grant, 1997; Hasin et al., 1997c). The AUDADIS has excellent psychometric properties in US and international samples (Canino et al., 1999; Chatterji et al., 1997; Grant et al., 1995; Hasin et al., 1996, 1997a,b). AUDADIS items were translated into Hebrew and Russian (available on request from DH). The AUDADIS interviewer training took 2 days and was based on procedures used in US and international studies.

In the AUDADIS, detailed questions covered the seven symptoms used to diagnose DSM-IV alcohol dependence in two time frames: the last 12 months (current) and prior to the last 12 months (past) (Grant et al., 1995; Hasin et al., 1997a). Computer algorithms combined this information to create current, past, and lifetime diagnoses of DSM-IV alcohol dependence (Grant et al., 1995; Hasin et al., 1997c). In addition to the diagnosis, a lifetime severity indicator was created from the AUDADIS dependence items consisting of a count of DSM-IV criteria for dependence (range, 0–7). The α coefficient for the dependence severity indicator was 0.73. An interrater reliability study of dependence severity in 23 Israeli subjects showed excellent reliability (intraclass correlation coefficient, 0.93).

Table 1. Israeli Population Groups: Demographics and Drinking, $n = 75$

Variable	Population Group: Ashkenazi, new Russian ($n = 27$)	Ashkenazi, all other ($n = 23$)	Sephardic ($n = 25$)	p Value
Demographics				
Gender (male)	0.74	0.70	0.64	NS[a]
Education (college or higher)	0.85	0.22	0.28	<0.001[a]
Marital status (married)	0.70	0.83	0.64	NS[a]
Employment (full-time)	0.67	0.70	0.56	NS[a]
Age [mean (SD)]	42.30 (11.0)	48.70 (9.8)	36.30 (10.8)	<0.001[b]
Drinking				
Current drinker (last 12 months)	0.81	0.65	0.64	NS[a]
Past drinker	0.85	0.65	0.60	NS[a]
Ever had five or more drinks	0.56	0.22	0.16	0.004[a]
Past period of heavier drinking	0.63	0.26	0.20	0.002[a]
MAXDRINKS [mean (SD)]	5.30 (3.3)	2.70 (2.5)	3.00 (0.4)	<0.001[d]

NS, not significant.
[a] Result from χ^2 test.
[b] Result from ANOVA test.
[c] Hasin et al., 2002.
[d] Kruskal-Wallis χ^2 test.

Subjects

Due to some mixing of population subgroups within the three neighborhoods, final determination of Ashkenazi, Sephardic, or recent Russian immigrant status used self-reported origin (Flasher and Maisto, 1984). Ashkenazi origin ($n = 23$) included Europe, the Americas, Australia, South Africa, or the FSU (arriving before 1989). Sephardic origin ($n = 25$) included those from North Africa or other Middle Eastern countries. Recent Russian immigrants ($n = 27$) were those who had immigrated from the FSU since 1989. Among the Russians, 70.3% had been in Israel longer than 5 years; only one had immigrated to Israel within the last 12 months. Of the full sample, approximately 70% of subjects were men. Most were married and working. More Russian immigrants finished college (87%) than Ashkenazis (23%) or Sephardics (30%). Ashkenazis were older (48.7 years; SD, 9.8) than recent Russian immigrants (42.3 years; SD, 11.0) or Sephardics (36.3 years; SD, 10.8).

Analysis

To test differences in proportions, the χ^2 test was used when suitable. When a contingency table has more than 25% of cells with small expected values, the χ^2 test may not be valid. When this happened, a likelihood ratio test (LRT) based on the log-linear model was used (Fienberg, 1985). Group differences in count variables (e.g., number of alcohol-dependence symptoms) with skewed distributions and heterogeneous variances across groups were tested with the nonparametric Kruskal-Wallis test, which does not assume a given distribution or homogeneous variance across groups (Bickel and Doksum, 1977).

To examine the relationship of *ADH2* genotype to severity of DSM-IV dependence while controlling for population group and other variables, the Poisson regression model (McCullagh and Nelder, 1989) was used. This model was selected due to the form of the outcome variable and its distribution. Ordinary linear regression assumes a normal distribution and a constant variance. Poisson regression is suitable for outcome variables that are in count form, have an approximate Poisson distribution, are skewed, or have variance proportional to the mean. In our case, the outcome was in count form, the distribution was quite skewed and approximated a Poisson distribution, and the variances of the three groups (Russian, other Ashkenazi, and Sephardic) increased with the group means. Thus, the Poisson regression model was the preferred statistical approach.

The regression coefficient for a binary predictor variable in a Poisson model is the log of the ratio of the means of the outcome (in this case, alcohol-dependence severity) for each of the two levels of the binary predictor. To aid in interpretation of the results, we also presented the unlogged ratios of these two means for each of the binary predictor variables. These are interpreted similarly to an odds ratio (1.0 indicates no association, >1.0 indicates a positive association, and < 1.0 indicates an inverse relationship). In the model, the control variable represented by age was dichotomized at 33 years because among the Russians, this would differentiate subjects who immigrated as adults from others who immigrated at a younger age. Including other forms of the age variable in the model (e.g., dichotomizing at the median) did not affect the main results.

Within-group associations between genotype and alcohol-dependence severity were explored with the Spearman rank correlation coefficient, which uses rank information in the two variables regardless of their joint distribution (Bickel and Doksum, 1977). This applies to the case of *ADH2*1/*1, ADH2*1/*2,* and *ADH2*2/*2,* considered to indicate ascending order of the *ADH2* effect. All p levels reflect two-tailed tests.

RESULTS

Demographics and Drinking by Population Subgroup

The Russians, other Ashkenazis, and Sephardics did not differ on gender, marital status, or employment, but the Russians were significantly more likely to have completed college (as expected), and the Sephardics were significantly more likely to be younger (Table 1). A high proportion of all three groups were current or past drinkers, variables on which the groups did not differ. In contrast, when heavier drinking was considered, significant differences between the Russians and the other groups emerged. This included ever having had five or more drinks on an occasion, an indicator of at-risk drinking in epidemiological samples (Caetano et al., 1997; Hasin et al., 1996). The Russians were also significantly more likely to have had a past period of heavier drinking and MAXDRINKS, an indicator of the largest number of drinks consumed on an occasion over the lifetime (Hasin et al., 2002; Saccone et al., 2000).

Table 2. Genotype by Israeli Population Group, $n = 68$

ADH2	Population group: Ashkenazi, new Russian ($n = 23$)	Ashkenazi, all other ($n = 22$)	Sephardic ($n = 23$)
Genotype[a]			
*ADH2*1/*1*	0.65	0.64	0.39
*ADH2*1/*2*	0.35	0.32	0.39
*ADH2*2/*2*	0.00	0.05	0.22
Allele frequency[b]			
*ADH2*1*	0.83	0.80	0.59
*ADH2*2*	0.17	0.20	0.41

[a] Likelihood ratio test; $\chi^2 = 9.72$; $df = 4$; $p = 0.045$.
[b] Chi-square test; $\chi^2 = 7.97$; $df = 2$; $p = 0.019$.

Table 3. Lifetime DSM-IV Alcohol-Dependence Symptoms by *ADH2:* Ratio of Means and Regression Parameters Estimated (SE) From the Poisson Regression Model

Variable	Ratio of mean number of symptoms	Regression coefficient (SE)	*p* Value
Male versus female	2.99	1.10 (0.58)	0.058
Age < 33 years	1.82	0.60 (0.43)	0.158
Married (y/n)	0.59	−0.53 (0.40)	0.193
Employed full-time (y/n)	1.90	0.64 (0.43)	0.131
Education more than high school (y/n)	0.61	−0.50 (0.40)	0.207
Family history of alcohol disorder (y/n)	0.48	−0.73 (0.58)	0.208
Asheknazi versus recent Russian	0.39	−0.94 (0.43)	0.029
Sephardic versus recent Russian	0.29	−1.25 (0.44)	0.004
ADH2 (*1/2* or *2/2* vs. *1/1*)	0.46	−0.78 (0.36)	0.032

DSM-IV Alcohol Dependence by Population Subgroup

Past DSM-IV alcohol dependence was found among 14.8% ($n = 4$), 4.4% ($n = 1$), and 0% of the Russians, Ashkenazis, and Sephardics, respectively (LRT; $\chi^2_2 = 5.86$; $p = 0.05$). Current dependence was found among 4% ($n = 1$), 0%, and 4% ($n = 1$) of the Russians, Ashkenazis, and Sephardics, respectively (LRT; $\chi^2_2 = 1.49$; $p = 0.47$). Lifetime dependence was found among 14.8% ($n = 4$), 4.4% ($n = 1$), and 4.0% ($n = 1$) of the Russians, Ashkenazis, and Sephardics, respectively (LRT; $\chi^2_2 = 2.54$; $p = 0.28$). All subjects with current dependence had lifetime dependence, by definition. Of subjects with current dependence, one was a new-onset case, whereas the other (a Russian) had also met criteria in the past.

DSM-IV Dependence Severity by Population Subgroup

The mean number of past alcohol dependence criteria in the Russians, Ashkenazis, and Sephardics was 1.44 (SD, 1.60), 0.57 (SD, 0.99), and 0.52 (SD, 1.29), respectively (Kruskal-Wallis test; $\chi^2_2 = 9.73$; $p = 0.008$). The level of current dependence severity in the three groups was much lower: 0.33 (SD, 0.78), 0.22 (SD, 0.060), and 0.28 (SD, 1.02) in the Russians, Ashkenazis, and Sephardics, respectively (Kruskal-Wallis test; $\chi^2_2 = 0.53$; $p = 0.77$). The mean number of lifetime alcohol dependence criteria in the Russians, Ashkenazis, and Sephardics was 1.44 (SD, 1.60), 0.57 (SD, 0.99), and 0.56 (SD, 1.29), respectively (Kruskal-Wallis test; $\chi^2_2 = 8.81$; $p = 0.01$). Thus, the Russians had significantly greater past and lifetime dependence severity than the other Israeli groups.

ADH2 *and Population Subgroup*

Table 2 shows the genotype and allele frequencies for *ADH2* among the Russians, Ashkenazis, and Sephardics. The distribution of genotypes is consistent with Hardy-Weinberg equilibrium in all three groups. Sephardics were more likely to have *ADH2*2* than the other two groups and, notably, had the most homozygous *ADH2*2* subjects ($\chi^2_1 = 6.75$; $p = 0.009$). The frequency of the *ADH2*2* allele did not differ significantly between the Russian Ashkenazis and the other Ashkenazis ($\chi^2_1 = 0.01$; $p = 0.92$).

DSM-IV Alcohol Dependence by ADH2

Lifetime DSM-IV alcohol dependence was rare, occurring in only 3 of the 68 subjects in whom there was *ADH2* genotype information. The percentage of subjects meeting criteria for lifetime DSM-IV alcohol dependence by genotype was 5.3, 4.2, and 0.0% among subjects *with ADH2*1/1*, *ADH2*1/2*, and *ADH2*2/2*, respectively (LRT; $\chi^2_2 = 0.61$; $p = 0.74$).

Regression Analysis

Table 3 shows the Poisson regression model of the relationship of *ADH2* genotype to the outcome of lifetime DSM-IV dependence severity. In this analysis, a three-level *ADH2* variable was not used, because of zero cells (no subject homozygous for *ADH2*2* had dependence symptoms, and no Russian was homozygous for *ADH2*2*). Therefore, *ADH2* was dichotomized into homozygous *ADH2*1/*1* versus homozygous or heterozygous *ADH2*2.* In this model, controlling for population subgroup and other variables, the *ADH2*2* allele was significantly related to a lower lifetime DSM-IV alcohol dependence severity. Variance in current dependence severity was very low in this sample and was unrelated to *ADH2* (not shown).

Between-Group Exploration

Although the sample size was limited, within-group tests of the *ADH2*/alcohol-dependence relationship were explored with Spearman correlations to provide preliminary information. Among Israeli Ashkenazis, the relationship of *ADH2* genotype and severity of alcohol dependence symptoms was in the predicted direction at a trend level ($r = -0.39$; $p = 0.07$). Among Sephardics, results were also in the predicted direction but not statistically significant ($r = -0.28$; $p = 0.19$). Among recent Russian immigrants, the correlation was weaker than in the other two groups ($r = -0.12$; $p = 0.57$).

DISCUSSION

This is the first report to investigate *ADH2* and dependence severity among contrasting Jewish groups. In the full

group, *ADH2*2* was protective against the severity of DSM-IV alcohol-dependence symptoms, controlling for numerous environmental factors. The direction of the relationship was similar for a diagnosis of DSM-IV alcohol dependence but did not reach statistical significance. This indicates the value of incorporating more information into an analysis through an outcome variable in continuous or count form. Compared with other Caucasian populations (Borras et al., 2000; Heath et al., 2001), Ashkenazis, Sephardics, and recent Ashkenazi immigrants from the FSU had a higher prevalence of *ADH2*2,* the protective form of *ADH2*. This is consistent with other reports on *ADH2* in Jewish groups in the United States and Israel. Furthermore, the *ADH2*2* allele frequency was higher in the Sephardics, a result not found in the one previous study that included both Ashkenazi and Sephardic Jews (Neumark et al., 1998). Because these Jewish groups differ in other genetic respects (Bonne-Tamir and Adam, 1992), this finding is not entirely surprising. However, it should be confirmed in larger samples.

Before this article, data comparing alcohol dependence in recent Russian immigrants and other Israelis have not been available. Consistent with their background in a country with very high per capita alcohol consumption, the recent Russian immigrants had a higher prevalence of past DSM-IV alcohol-dependence diagnoses and greater mean past and lifetime dependence severity than the other two Israeli groups. However, the differences were found on past but not current dependence, consistent with their drinking histories. The lack of group differences in current drinking variables may have resulted from the general tendency for individuals to reduce their drinking as they age or from acculturation to Israeli drinking patterns after arrival in Israel. Further research in larger samples is needed to clarify these issues.

Previously, we presented results suggesting that the effects of *ADH2*2* on peak alcohol consumption were inconsistent in the recent Russian immigrants compared with the other Ashkenazis and Sephardics (Hasin et al., 2002). Within-group exploration suggested that *ADH2*2* was protective against peak lifetime alcohol consumption among the Ashkenazis and Sephardics, but not among the Russians. This suggested that the immigrants' exposure to the heavy-drinking environment of Russian culture, a powerful environmental factor, overcame genetic protective effects. In this study, within-group exploration showed a protective effect for *ADH2* against alcohol dependence across all three groups—Ashkenazis, Sephardics, and recent Russian immigrants—although the correlation was smaller among the Russians. It is not clear why somewhat different results emerged for these two important types of alcohol variables. Reasons might include more pronounced cross-cultural influences on drinking levels than dependence symptoms, cross-cultural differences in the emergence of dependence symptoms in the presence of heavy drinking, or instability due to small samples. Replication in a larger sample is definitely warranted; this would allow testing of interactions between *ADH2*2* and population group by using both alcohol consumption and dependence as outcomes.

It is possible to speculate that the higher mean dependence severity among the Russian subgroup can be attributed to the absence of subjects with homozygous *ADH2*2* rather than environmental exposure to very heavy drinking. However, we favor the environmental explanation due to the within-genotype distribution of dependence severity when Russians were compared with the other two groups. Within subjects homozygous for *ADH2*1* as well as within heterozygous subjects (*ADH2*1/2*), dependence severity was higher among the Russians than among the other subjects. However, the issue could usefully be addressed in future studies, in which larger samples of Russian-Jewish subjects should yield some with homozygous *ADH2*2*.

Association studies of the relationship between an allele and a trait or disease can be powerful tools for gene mapping (Risch and Merikangas, 1996). However, a disease or trait and an allele may both be increased within a subgroup of a sample for unrelated reasons. If such a subgroup is undetected, confounding due to population stratification can lead to spurious findings (Lander and Schork, 1996; Reich and Goldstein, 2001). This has led some investigators to conclude that association studies can be conducted only in related individuals (Ewens and Speilman, 1995). However, such a restriction may lead to a different set of biases, and the issue remains controversial.

Many factors suggest that the results of this study were not spurious due to undetected population stratification. First, the results on *ADH2* remained significant even after the three main groups were identified and controlled in the analysis. Second, the *ADH2* literature shows that *ADH2* effects on alcohol dependence are consistent in many countries and population groups, including samples of twins (Heath et al., 2001; Neale et al., 1999). Third, methodological research (Wacholder et al., 2000) indicates that the degree of possible bias decreases as the number of undetected potential strata (population subgroups) increases. In this study, 18 countries of origin were reported among the 68 subjects (including many European countries for the Ashkenazis and many countries in the Middle East and North Africa for the Ashkenazis). Therefore, if country of origin constituted strata, the large number of potential strata reduced the likelihood of confounding (Wacholder et al., 2000). Finally, the direction of results was consistent in all three of our main subgroups and thus could not have been determined entirely by an undetected trend among subjects from only one country (i.e., one undetected stratum).

Other methodological aspects of the study warrant noting. Collaborative reports or biological indicators of alcohol-consumption or -dependence measures were not available. Although these could be included in future research on this topic, they are probably most useful in studies of current drinking. Our research pertained more to

peak times of heavier drinking in the past. In addition, the informed consent procedures on privacy of the data as well as the protection of privacy in the interview itself should have reduced underreporting caused by concerns about confidentiality. Also, future research on this topic would benefit from larger samples that would allow more detailed analysis of within- and between-group similarities and differences in alcohol consumption, alcohol dependence, and the relationship of *ADH2* to these.

As noted previously, we oversampled for men. In the previous study that showed *ADH2* effects on drinking among Israelis, only men were included. In previous reports on American Jews (Carr et al., 2002; Shea et al., 2001), *ADH2* effects were found only for men. The generally light drinking among the American Jews was even lower among women than men, possibly limiting variance and making it more difficult to show effects among female American Jews. It was known from the outset that our sample of Israelis would be too small to detect weak effects, expected among women on the basis of the previous reports. Therefore, we oversampled for men to maximize the utility of this sample while including some women to check for consistency between Israeli and American Jewish women. Among the women in the sample, *ADH2* effects were consistent with those found for men (not shown), but variance was very low. A future investigation of male-female differences in *ADH2* effects would be helpful in elucidating this issue but will require a larger sample.

We did not report on DSM-IV abuse. Although we collected data on this diagnosis, the α coefficient for current and past DSM-IV alcohol abuse was low, indicating poor internal consistency reliability. Other reports have also found poor reliability and validity for DSM-IV alcohol abuse.

The results of this study indicate a protective effect of *ADH2*2* against alcohol-dependence symptoms in Jewish samples. Thus, the *ADH2*2* allele may constitute part of the explanation for low levels of alcoholism among Jewish groups. Work is needed in larger samples to clarify group similarities and differences in these effects, as well as variability in results when different alcohol phenotypes are studied. Furthermore, studies of gene-environment interactions can provide valuable general information on the relative contribution of genetic and environmental causes to etiology. Little research in the area of alcoholism has focused on the effects of a specific gene across contrasting environmental circumstances. Because consensus exists on the causal influence of both genetic and environmental factors in the etiology of alcohol dependence, consideration of both types of factors conjointly may provide a clearer understanding of the effects of each when studying disease etiology.

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