Effect of *ADH1B* Genotype on Alcohol Consumption in Young Israeli Jews

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Background: The alcohol dehydrogenase 1B (*ADH1B*) genotype affects the risk for alcoholism, with elevated prevalence of a protective allele in Jews. Alcohol consumption is increasing among younger Israeli Jews, reflecting environmental influences. We investigated whether the relationship of *ADH1B* genotype with alcohol consumption differed between younger and older adult Israelis.

Methods: Israeli community residents aged 22 to 65 participated in a structured interview that included questions on the maximum number of drinks on an occasion (Maxdrinks). The *ADH1B* genotype was determined for 68 participants and dichotomized into nonprotective (*ADH1B*1/1*) and protective (*ADH1B*1/2* or *ADH1B*2/2*) genotypes. Using Maxdrinks as the dependent variable, Poisson's regression was used to test an age×genotype interaction.

Results: The *ADH1B* genotype interacted significantly with age ($p = 0.01$) in a Poisson's model with Maxdrinks as the outcome. Among participants ≥33 years, Maxdrinks was low and unrelated to the *ADH1B* genotype. Among participants <33 years with *ADH1B*1/2* or *ADH1B*2/2*, Maxdrinks was also low (mean, 2.6 drinks) but among those with *ADH1B*1/1*, Maxdrinks was substantially higher (mean, 6.2 drinks).

Conclusion: Maximum lifetime drinking among younger adult Israelis without genetic protection exceeded thresholds for risky and unsafe drinking (≥5 drinks). Environmental influences promoting greater drinking among younger Israelis may particularly affect those with the nonprotective, more common *ADH1B* genotype.

Key Words: *ADH1B*, Alcohol, Israel.

ALCOHOL CONSUMPTION, A complex trait, is influenced by both genetic and environmental factors. Alcohol dehydrogenase 1B (*ADH1B*) encodes an enzyme involved in alcohol metabolism in the liver. *ADH1B*1* is a less active form (allele/variant) of *ADH1B*, while *ADH1B*2* is a more active form. *ADH1B*2* has been shown to be protective against heavy alcohol consumption in Europeans and Asians (Li, 2000; Whitfield et al., 1998). In Jewish Israeli adults (Hasin et al., 2002a; Neumark et al., 1998), *ADH1B*2* is also protective against heavier alcohol consumption. In the United States, *ADH1B*2* was associated with a lower frequency of consumption in Jewish adults in Indiana, although not in Indiana college students (Carr et al., 2000). Among California college students (Shea et al., 2001), *ADH1B*2* was associated with a lower drinking frequency but not several other consumption measures. Thus, *ADH1B* effects appear more consistent in Jewish adults than in younger (college-age) samples, although differences in *ADH1B* effects by age group have not been studied directly in either U.S. or Israeli adult Jewish samples.

Age differences in genetic effects can indicate influences that differ by developmental stage (Dick et al., 2006). However, genetic effects on lifetime phenotypes that differ by birth cohort can also suggest time trends in cultural/environmental factors influencing drinking. Variation by age/birth cohort in the relationship of specific genotypes with complex traits has not been studied often. Previously, consistent with anecdotal reports of increased heavier drinking among younger Israeli adults, we showed a significantly higher lifetime maximum number of drinks per occasion (Maxdrinks) among younger than older adult Israelis (Hasin et al., 2002a). However, we did not address whether this age difference influenced *ADH1B* effects on Maxdrinks. Because environmental risk factors potentially

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counteract genetic-protective effects, we now investigate whether *ADH1B* effects on alcohol consumption differed by age (i.e., *ADH1B*×age interaction) in Israeli Jewish adults.

MATERIALS AND METHODS

Setting, Sample Design, and Procedures

The study was conducted in an Israeli city with a population of about 140,000. The study methods are detailed elsewhere (Hasin et al., 2002a, 2002b). In brief, members of residential households aged 22 to 65 were randomly selected for participation in an in-person interview, with oversampling for males. Nurse or physician interviewers were trained by D. H. and an experienced research nurse supervisor (Z. M.), who subsequently monitored interviewing and fieldwork. Written informed consent was obtained for interviews and blood samples using procedures approved by the Helsinki (human subjects) committee at Ness Ziona Psychiatric Hospital. Interviews took place in the subject's homes. Subjects were compensated for their time. Of households identified for the study, 75 subjects (response rate, 73%) participated, and 68 of these (91% of those interviewed) gave blood for DNA extraction. At the Indiana Alcohol Research Center, genotyping at the *ADH1B* locus was determined by enzymatic amplification of genomic DNA, followed by hybridization with allele-specific oligonucleotides (Xu et al., 1988). Interview data were checked for completeness and sent to New York for entry and analysis. Telephone verification with randomly selected subjects confirmed the authenticity of the information received.

Measures

Measures of alcohol consumption and a family history of alcohol problems were derived from the Alcohol Use Disorders and Associated Disabilities Schedule (AUDADIS; Grant et al., 1995, 2003). This instrument, designed for lay interviewers, has been used in national and community epidemiologic research in the United States (Grant, 1997; Grant et al., 2004; Hasin et al., 1997a, 2007). The AUDADIS has excellent psychometric properties in United States and international samples (Grant et al., 1995, 2003; Hasin et al., 1997b, 1997c) including psychiatrist reappraisals (Canino et al., 1999). The AUDADIS items were translated into Hebrew and Russian, reviewed by bi-lingual individuals, adjusted, and further adjusted after pretesting. The interview was offered in Hebrew or Russian according to respondent preference.

Respondents were asked about consumption of wine, beer, and liquor in the last 12 months and in the past (before the last 12 months). From these questions, a measure of maximum lifetime number of drinks per occasion (Maxdrinks) was constructed (Hasin et al., 2002a; Saccone et al., 2005). Other demographic variables were derived from the AUDADIS, adapted as needed for Israel. Ethnicity measures were based on self-report of personal/family origin, following standard Israeli procedures (Aharonovich et al., 2001). Recent Ashkenazi immigrants from the Former Soviet Union (recent FSU) were those who immigrated after 1989. The origins of remaining Ashkenazi Jews in the sample (other Ashkenazi) included Europe, the former Soviet Union, the Americas, Australia, or South Africa. The origins of non-Ashkenazi Jewish Israelis (non-Ashkenazi Jewish) included North Africa or other areas of the Middle East.

Analysis

Kruskal–Wallis tests were used to determine bivariate differences in Maxdrinks. Poisson's regression was used to examine the relationship between *ADH1B* genotype, age, and Maxdrinks, controlling for origin, sex, and other characteristics. A Poisson's model was selected because Maxdrinks is a count variable with a right-skewed distribution and mean proportional to the variance, making Poisson's regression preferable to an ordinary least squares regression model based on the normal distribution (Hasin et al., 2002a). To confirm that the dispersion of the dependent variable was consistent with the Poisson distribution rather than the negative binomial, the LaGrange multiplier test was used (Cameron and Trivedi, 1998). The resulting test statistic was not significant ($p = 0.13$), indicating that overdispersion was not present and that the Poisson model was therefore appropriate. To aid in interpreting the results, we provide the antilog of the regression coefficients, which can be interpreted as the ratio of means for alternative values of the covariate.

Following our previous procedures (Hasin et al., 2002a), age was dichotomized at 33 years to differentiate respondents exposed to different cultural influences on drinking. (Among the recent FSU immigrants, this year differentiated respondents who immigrated as adults from those immigrating at an earlier age.) *ADH1B* was dichotomized as homozygous *ADH1B*1/1* versus all others (*ADH1B*1/2* and *ADH1B*2/2*). The prevalence of the *ADH1B* genotype was in Hardy–Weinberg equilibrium in all 3 ethnic groups (Hasin et al., 2002a). The prevalence of the *ADH1B* genotype did not differ significantly between the recent FSU group and other Ashkenazis, but was higher in the non-Ashkenazi Jewish group (Hasin et al., 2002a). Therefore, ethnicity was included as a control variable, as well as gender and socio-demographic characteristics (marital status, employment, and education). An interaction term was used to indicate the joint effect of the *ADH1B* genotype with age.

RESULTS

Of the 68 subjects, 70.6% were male (consistent with the sampling strategy), 22.1% were <33 years old, 55.9% had completed high school, 75.0% were married, and 64.7% were working full time. A family history of alcohol problems was rare (16.2%). Consistent with the sample design (Hasin et al., 2002b), ethnicity was approximately evenly divided, with 33.8% recent FSU, 32.4% other Ashkenazis, and 33.8% non-Ashkenazi Jewish.

Table 1 shows the Poisson regression results for the relationship between Maxdrinks and the *ADH1B* genotype, age, and their interaction. With the age×*ADH1B* interaction term in the model, the main effects for age and *ADH1B* genotype were not significant, but the *ADH1B*×age interaction term was statistically significant ($p = 0.01$). Further inspection of the mean Maxdrinks

Table 1. Poisson Regression Results for Maxdrinks: *ADH1B* Genotype, Age, and Control Variables in Israeli Household Residents ($N = 68$)

Variable	Ratio (mean drinks)	Coefficient (SE)	*p*
Gender (male)	2.27	0.82 (0.25)	<0.01
Age <33 (y)	0.94	−0.07 (0.41)	0.88
High school (yes/no)	1.08	0.08 (0.19)	0.69
Married (yes/no)	1.40	0.34 (0.26)	0.20
Employed full time (yes/no)	1.18	0.17 (0.22)	0.45
Family history of alcohol disorders (yes/no)	1.31	0.27 (0.24)	0.25
Other Ashkenazi versus recent FSU	0.65	−0.42 (0.22)	0.05
Non-Ashkenazi Jewish versus recent FSU	0.56	−0.57 (0.21)	<0.01
ADH1B (1/1 vs 1/2 or 2/2)	0.91	−0.10 (0.20)	0.63
Interaction: *ADH1B*×age	2.95	1.08 (0.43)	0.01

Table 2. Mean Maxdrinks (SE) by *ADH1B* Genotype and Age

	Age ≥ 33 y	Age < 33 y
ADH1B genotype		
1*1	3.1 (0.40)	6.2 (1.5)
1*2 or 2*2	2.9 (0.51)	2.6 (0.8)

level by age and genotype provides additional information (Table 2). Among older respondents, the mean Maxdrinks was similar among those with homozygous *ADH1B*1* and an *ADH1B*2* genotype (3.1 and 2.9, respectively). However, in the younger adults, among those lacking a protective genotype (i.e., homozygous *ADH1B*1*), the mean Maxdrinks was substantially higher (6.2) than among those with a protective genotype that included the *ADH1B*2* allele (2.6).

For comparative purposes, we determined the mean lifetime Maxdrinks levels in corresponding age groups in the U.S. 2001–2002 National Epidemiologic Survey on Alcoholism and Related Conditions (NESARC; Grant et al., 2004; Hasin et al., 2007). In NESARC participants aged 22 to 32, the mean lifetime Maxdrinks was 6.1 (SE 0.2), and in participants aged 33 to 65, the mean lifetime Maxdrinks was 5.1 (SE 0.1). Thus, among younger Israeli adults without the protective genotype, Maxdrinks was similar to U.S. levels, while for younger Israeli adults with the protective *ADH1B* genotype and for older Israelis regardless of genotype, lifetime Maxdrinks was much lower than among a representative sample of U.S. adults.

DISCUSSION

In this study of Israeli household residents, the maximum lifetime drinking level among the older participants was fairly low, regardless of the *ADH1B* genotype. However, the results for younger respondents were quite different. In these, the *ADH1B* genotype had a marked effect, as those without the protective *ADH1B* allele had substantially higher Maxdrinks than those with at least 1 copy of the protective allele. In fact, Maxdrinks in the younger Israeli adults with the nonprotective genotype exceeded the National Institute on Alcoholism and Alcohol Abuse (2005) guidelines for risky drinking. The contrast in drinking levels by genotype among the younger but not older Israeli adults suggests the possibility that time trends in environmental factors moderated the genetic effects on drinking.

One possible time trend that could explain such an effect involves alcohol marketing in Israel. Commercial television broadcasting did not begin in Israel until 1993, after which beer and wine commercials began to appear on television regularly. These commercials feature attractive young adults drinking alcohol in appealing social situations. These commercials could influence drinking norms, i.e. attitudes about the acceptability of drinking (or amounts of drinking) in different situations. Other marketing strategies introduced in Israel in recent years include sponsorship of special events, competitions, and promotions, and the widespread distribution of flavored alcoholic beverages, all known to appeal to younger drinkers (Hastings et al., 2005; Mosher and Johnsson, 2005). These strategies would be expected to particularly influence younger adults because they are closer to the developmental periods of risk for lifetime heaviest drinking, while older Israeli adults passed through such periods before these marketing practices were widespread. Consistent with this, Israel did not have a minimum legal drinking age until 2004, but public concern about increased risky drinking among young adults resulted in the first-time establishment of a national minimum drinking age (18 years) at that time.

Concerning methodological issues, we used the cut-point of age 33 for the interaction term to be consistent with the age variable used in our previous papers from this study (Hasin et al., 2002a, 2002b). To determine the robustness of the interaction effect to variation in the cut-point, we retested the model with several lower ages. The interaction term remained significant ($p < 0.05$) with different cut-points down to age 28. Thus, the interaction effect applied to a general differentiation between younger and older adults, and was not specific to one particular year.

An unresolved issue in alcohol and drug genetic association studies is whether to include abstainers. As discussed elsewhere (Heiman et al., unpublished data), the composition of control groups may influence the nature of the results obtained. Most studies of alcohol-metabolizing genes did not indicate whether abstainers were included or excluded (e.g., Edenberg et al., 2006; Guindalini et al., 2005; Luo et al., 2005; Neumark et al., 1998; Shea et al., 2001) or explicitly *included* abstainers (e.g., Carr et al., 2002; Chen et al., 1999; Shen et al., 1997; Sun et al., 2002); understanding the effects of homozygous *ALDH2*2* actually required inclusion of abstainers. However, there have been studies of alcohol-metabolizing genes that explicitly excluded abstainers (Wall et al., 2005) on the grounds that such genes could only affect drinking among those exposed to alcohol.

Another unresolved issue is the most appropriate definition of "abstainer," and how much exposure to a substance (Eissenberg and Balster, 2000) is sufficient to characterize subjects as abstainers. For many carriers of *ALDH2*2*, 1 sip of alcohol is sufficient to produce an unpleasant reaction. In our sample, abstainers were defined as those who never consumed a full drink of alcohol, similar to Wall et al. (2005). When the 4 subjects meeting this definition were excluded from the sample, the *p*-level for the interaction term was 0.06. However, the Maxdrinks measure was not sensitive to consumption of alcohol in amounts less than 1 full drink, which may have been sufficient to discourage further drinking. For consistency with most of the literature on alcohol-metabolizing genes and because of the lack of closure on this issue, we retained these 4 subjects in the main analysis. Future studies of

alcohol-metabolizing genes should include measures of alcohol consumption that are sensitive to quantities smaller than a full drink to clarify this issue.

Study limitations are noted. First, the findings clearly require replication in a larger sample. Second, differences in drinking norms between younger and older Israelis should be tested directly. Third, information on additional genetic variation associated with the risk for heavy drinking and/or alcohol dependence (e.g., *GABRA2*, *CHRM1*, *ADH4*) should be incorporated. Accordingly, such a study is now underway. Finally, prospectively collected information on drinking from a young age throughout the years of adulthood on sequential birth cohorts would provide finer-grained data than can be collected in cross-sectional genetics studies, potentially allowing more specific attribution of causality.

Strengths of the study are noted as well. First, the use of a community sample precluded potential biases that arise in convenience or other selected samples. Second, the excellent psychometric properties of the measures have been demonstrated in U.S. and international studies. Third, interviewer training and supervision was carefully standardized and maintained throughout. Fourth, the interview was administered in the language choice of the respondent (Russian or Hebrew). Fifth, data analysis was carefully designed to suit the distribution of the alcohol phenotype. Therefore, the study provides excellent heuristic information that may guide additional investigations.

Relatively few studies have examined the effects of a specific genotype on alcohol phenotypes in groups exposed to contrasting environmental conditions. Consideration of the environmental context is important to arrive at correct inferences concerning the role of genes in disease etiology (Khoury, 1997). Better knowledge about environmental factors that increase or decrease genetic protection or vulnerability should facilitate the development of more effective prevention and intervention programs.

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