

Genetic Epidemiology of Alcohol-Induced Blackouts

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Background: Alcohol-induced blackouts (ie, periods of anterograde amnesia) have received limited recent research attention.

Objective: To examine the genetic epidemiology of lifetime blackouts and having had 3 or more blackouts in a year, including analyses controlling for the frequency of intoxication.

Design, Setting, and Participants: Members of the young adult Australian Twin Register, a volunteer twin panel born between January 1, 1964, and December 31, 1971, were initially registered with the panel as children by their parents between 1980 and 1982. They underwent structured psychiatric telephone interviews from February 1996 through September 2000. The current sample contains 2324 monozygotic and dizygotic twin pairs (mean [SD] age 29.9 [2.5] years) for whom both twins' responses were coded for blackout questions and for frequency of intoxication.

Main Outcome Measure: Data on lifetime blackouts and having had 3 or more blackouts in a year were col-

lected within an examination of the genetic epidemiology of alcoholism.

Results: A lifetime history of blackouts was reported by 39.3% of women and 52.4% of men; 11.4% of women and 20.9% of men reported having had 3 or more blackouts in a year. The heritability of lifetime blackouts was 52.5% and that of having had 3 or more blackouts in a year was 57.8%. Models that controlled for frequency of intoxication found evidence of substantial genetic contribution unique to risk for the blackouts and a significant component of genetic risk shared with frequency of intoxication.

Conclusions: The finding of a substantial genetic contribution to liability for alcohol-induced blackouts including a component of genetic loading shared with frequency of intoxication may offer important additional avenues to investigate susceptibility to alcohol-related problems.

Arch Gen Psychiatry. 2004;61:257-263

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ALCOHOL-INDUCED BLACKOUTS (ie, periods of anterograde amnesia) are reported by most, but not all, alcohol-dependent individuals.¹⁻⁴ Blackouts also have been found to be a fairly common consequence of heavy alcohol use among those who are not alcohol dependent.⁵⁻¹⁰ In college students, the risk for blackouts has been reported to increase with binge drinking frequency.¹⁰ Factors associated with risk for blackouts in other samples include drinking on an empty stomach,^{1,2} gulping drinks,^{1,2} benders,^{1,2} drinking when fatigued,² prior brain insult or injury,¹ and alcohol consumption variously operationalized as quantity,^{1,2,6,8,9} frequency,⁸ and frequency of intoxication.^{4,5}

One group attempted¹¹ to elicit blackouts in a controlled setting in 10 subjects

who were recruited based on self-report of being healthy and able to drink heavily and quickly (8 were diagnosed as being alcoholic; 5 reported a history of blackouts). Their protocol began with 2 days of inpatient clinical assessment. On day 3, subjects fasted for 5 hours and then drank 16 to 18 oz of bourbon over a 4-hour period. Memory testing, begun 1 hour after the start of drinking, continued for 4 hours. The next day additional testing was conducted to determine whether the subjects could remember stimuli from the prior day's testing. Of the 10 subjects, 5 displayed deficits in short-term memory for both neutral and emotional stimuli that persisted to the next day. Their blood alcohol concentrations rose more quickly and reached significantly higher peaks than those of subjects who did not experience

memory loss. The most intriguing observation was that the 5 subjects in whom blackouts were induced in the laboratory setting were the same 5 individuals who had reported having had prior blackouts. These data provide evidence for substantial variation in susceptibility to alcohol-induced blackouts that is perceptible even among individuals who drink heavily.

The current investigation used data collected in recently completed telephone interviews of the Australian Twin Register^{12,13} to examine whether there was a significant genetic contribution to the variance in susceptibility to alcohol-induced blackouts. The assessment included questions regarding lifetime history of alcohol-induced blackouts and having had 3 or more blackouts in a single year. Because these analyses were conducted with data from a genetically informative twin sample, we were able to estimate additive genetic, shared (familial) environmental, and nonshared (individual-specific) environmental contributions to the risks for these blackout measures. Because alcohol consumption has been reported to be moderately heritable, additional analyses were undertaken to determine whether the genetic contribution to the blackout measures remained significant with control for alcohol consumption. We chose to use the respondents' frequency of intoxication for this purpose as prior reports have found this consumption measure to be associated with increased risk for blackouts. Our hypothesis was that a significant residual genetic component to risk for each blackout measure would be observed even after controlling for the frequency of intoxication during the heaviest drinking period.

METHODS

The study's methods have been described in detail elsewhere.^{12,13} A summary is provided below.

SUBJECTS

Subjects were members of the young adult cohort of the Australian Twin Register, a volunteer panel of twins born between January 1, 1964, and December 31, 1971. Almost all were registered with the panel between 1980 and 1982 by their parents in response to approaches through either school systems or mass media appeals. All data reported herein are from a comprehensive diagnostic telephone assessment completed from February 1996 through September 2000 by trained lay interviewers. Prior to the interview, verbal consent was obtained according to the terms of approval from the institutional review boards of Washington University School of Medicine, St Louis, Mo, and Queensland Institute of Medical Research, Brisbane, Australia. Of 4010 pairs that were located, interviews were completed with both members of 2765 pairs (69% pairwise response rate) and with 1 member of an additional 735 pairs (78% individual response rate).¹² The most common reasons for nonparticipation included refusal by twin, incapacitation and/or death, and lack of available contact information. Singletons were excluded from analyses as were pairs in which one or both twins reported never having used alcohol. The current sample included the remaining 2324 monozygotic (MZ) and dizygotic (DZ) same-sex pairs (mean [SD] age, 29.9 [2.5] years) in which both twins had responses coded for the blackout questions. The sample included 542 MZ female, 432 MZ male, 418 DZ female, 373 DZ male, and 559 DZ opposite-sex pairs.

ASSESSMENT

A standardized psychiatric diagnostic assessment, an adaptation of the Semi-Structured Assessment for the Genetics of Alcoholism,¹⁴ was administered by telephone. The interview enabled lifetime DSM-IV¹⁵ diagnoses of psychiatric disorders to be made and included nondiagnostic sections as well. The current analyses focused on questions that assessed alcohol-induced blackouts: "Have you ever had blackouts when you didn't pass out while drinking—that is, you drank enough so that the next day you couldn't remember things you had said or done?" Those responding affirmatively were asked: "Have you ever had 3 or more blackouts in a 12-month period?" Those who reported never having had at least 5 drinks in a 24-hour period or who denied both having at least 1 drink monthly for 6 consecutive months and ever having been drunk were skipped out of the alcohol diagnostic section without having been asked the blackout questions. These respondents were assumed never to have had a blackout and were coded as such.

The interview included several questions that assessed various aspects of alcohol consumption. We chose to control for respondents' frequency of intoxication in analyses because of this measure's previously reported association with risk for blackouts. Frequency of intoxication was assessed as follows: "Think about the period in your life lasting at least 12 months when you were drinking the most. During that period, how often did you get drunk, that is, your speech would be slurred or you would be unsteady on your feet?" The 10 response categories were collapsed into the following 6 based on response frequency and distribution: (1) less than 3 days per year, (2) 3 to 12 days per year, (3) 2 to 3 days per month, (4) 1 day per week, (5) 2 days per week, and (6) 3 or more days per week. Onset and recency information available for this measure and for 3 or more blackouts in a year (but not lifetime blackouts) revealed that these periods overlapped for 95.6% of respondents.

DATA ANALYSIS

Primary statistical analyses were performed using SAS¹⁶ and the Stata Statistical Software: Release 6.0.¹⁷ An α level of .05 was required for statistical significance. Stata's Huber-White robust variance estimator option was used to obtain 95% confidence intervals (CIs) adjusted for the statistical nonindependence of twin-pair observations. Lifetime prevalence of blackouts and of having had 3 or more blackouts in a year was examined by sex. Logistic regression was used to evaluate the relationship of each blackout measure with lifetime alcohol dependence in women and in men; the relationship of each blackout measurement with frequency of intoxication was similarly evaluated.

The genetic and environmental contributions to twin-pair resemblance were estimated using a normal liability threshold model.^{18,19} For binary or ordinal variables, the estimates reflect the resemblance of pair members in terms of their liability to display a phenotype. Liability is assumed to have an underlying continuous and normal distribution in the population with the phenotype expressed in individuals whose risk exceeds a superimposed threshold (estimated from the data).

The twin model assumes that individual differences arise from additive genetic, shared (familial) environmental, and nonshared (individual-specific) environmental sources. The degree to which variance arises from each of these sources is determined based on their expected effects on twin-pair resemblance. Thus, while members of an MZ pair are genetically identical, DZ twins will, on average, share half of their genes. Shared environmental influences are assumed not to vary on the basis of zygosity. Based on these assumptions, structural equations are developed ($cov_{MZ} = v_G + v_{SE}$; $cov_{DZ} = \frac{1}{2} V_G + V_{SE}$)

that allow estimation of genetic and shared environmental contributions to variance in liability to blackouts. (*cov* indicates covariance; *v*, variance; *G*, additive genetic; and *SE*, shared environmental.) Nonshared environmental (NSE) effects will contribute only to differences within pairs and are estimated as $v_{NSE} = (1 - v_G - v_{SE})$. With inclusion of both female and male same-sex pairs, separate parameter values can be estimated for women and men. Furthermore, the inclusion of data from DZ opposite-sex pairs enables estimation of a sex-specific additive genetic contribution representing the effects of a set of genes specific to either sex (in the current report's univariate models, the contribution of a male-specific effect was determined).

For all genetic analyses, models were fitted using the structural equation modeling program MX,²⁰ which uses maximum likelihood estimation to calculate parameter values and likelihood-based 95% CIs. The fit of models was compared using the goodness-of-fit χ^2 test and the Akaike Information Criterion values to select the model that best combined goodness-of-fit and parsimony. When the fit of 2 models did not differ significantly, the model with fewer parameters was considered to be the more parsimonious. The current report provides only the results of the best-fitting models for each set of analyses; more detailed results including those of other models are available from the corresponding author on request. Separate univariate analyses were undertaken using contingency table data for lifetime blackouts, having had 3 or more blackouts in a year, and frequency of intoxication.

Because genetic factors were found to affect the risk for frequency of intoxication, 2 methods were then used to control for its effects on the variance for each blackout variable. The first approach fitted bivariate Cholesky decomposition models to data on frequency of intoxication and each blackout variable in turn. In these models, additive genetic, shared environmental, and nonshared environmental contributions to the variance of each variable were estimated and the variance of the blackout variable was further decomposed into unique components and those also loading on frequency of intoxication. This approach explores possible shared contributions to the liability in multiple measures arising from 1 or more latent factors. It takes advantage of the fact that the cross-correlation between frequency of intoxication in one twin and a blackout variable assessed in the co-twin is expected to vary as a function of the degree to which these 2 variables share genetic vs shared environmental influences. For example, a 2:1 ratio of MZ/DZ twin pair cross-correlations is predicted if common genetic, but not common shared environmental, factors are contributing to risk. Furthermore, if genetic influences on 2 variables completely overlap, the genetic contribution to the correlation of the 2 variables should be the geometric mean of the genetic variances of the 2 variables; the extent to which the estimated genetic contribution is attenuated from the geometric mean provides information about the extent to which there is only partial overlap of genetic influences, allowing decomposition of the total genetic variance in the blackout variable into a component specific to blackouts and a component that reflects genetic influences associated with the frequency of intoxication.²¹ The full model, in which all parameter values were allowed to vary between women and men, was again first calculated. Reduced models that dropped terms and constrained estimates between women and men were then calculated with model fit compared by the likelihood ratio χ^2 test.

In the second approach, genetic models were fitted in which the normal liability threshold model for the blackout variable was modified to control for the regression of the blackout variable on the reported frequency of intoxication. For these analyses, frequency of intoxication was recoded as 5 binary dummy control variables (with the reference group

being <3 days per year), to allow for possible nonlinearities in the relationship between frequency of intoxication and risk of blackouts. We modeled jointly the probit regression of each blackout variable on the frequency of intoxication variables, and the genetic and environmental contributions to the residual variance in the blackout variable. In this approach, the threshold value for each individual is defined by a probit regression equation, in which the intercept corresponds to the sex-specific mean threshold, and the β coefficients estimate the probit regression of the dependent variable on the control variables. Thus, an individual with a reported high frequency of intoxication will be more likely to experience blackouts, corresponding to a lower threshold on the liability distribution. This process tests for residual genetic and environmental contributions to variance in risk for the blackout variable, controlling for the regression of the risk for that blackout variable on the frequency of intoxication. It, thus, removes any effects related to the frequency of intoxication on the risk for the blackout variables without directly estimating the degree of shared underlying liability. The fit of the full model and that of reduced models was again compared using the likelihood ratio χ^2 test.

RESULTS

A lifetime history of blackouts was reported by 39.3% of women and 52.4% of men (odds ratio [OR], 1.71; 95%CI, 1.50-1.93). Having had 3 or more blackouts in a year was reported by 11.4% of women and 20.9% of men (OR, 2.06; 95%CI, 1.73-2.45).

In both women and men, having had a blackout was significantly associated with a lifetime diagnosis of alcohol dependence (**Table 1**) and similar, stronger associations were seen with having had 3 or more blackouts in a year. Blackouts also were common among non-alcohol-dependent individuals with prevalence rates of 31.5% in woman and 40.3% in men. Those reporting having had a blackout also had more frequent drinking to intoxication during their heaviest drinking year (ORs ranging from 2.51 [95% CI, 2.06-3.05] for 3-12 days per year to 16.37 [95% CI, 12.29-21.81] for ≥ 3 days per week). A similar pattern was noted for having had 3 or more blackouts in a year (ORs ranging from 4.89 [95% CI, 2.67-8.96] for 3-12 days per year to 78.31 [95% CI, 43.90-139.70] for ≥ 3 days per week).

Separate univariate genetic models were fitted for lifetime blackouts, having had 3 or more blackouts in a year, and frequency of intoxication. The best-fitting model for each variable (**Table 2**), obtained by dropping or constraining individual terms and determining whether the change in model fit was significant, retained only terms representing additive genetic and nonshared environmental contributions to variance which, in each case, could be constrained to be equal across gender. The heritability estimates for these variables (with 95% CIs) were as follows: lifetime blackouts 53% (95% CI, 45%-60%), 3 or more blackouts in a year 58% (95% CI, 48%-67%), and frequency of intoxication 43% (95% CI, 37%-48%).

Genetic and environmental contributions for the blackout variables are subdivided in **Table 3** into effects that were associated with differences in frequency of intoxication and effects that seemed to be specific to blackouts based on the results of fitting bivariate genetic models. The best-fitting models did not retain any

Table 1. Association Between Reported History of Blackouts and Lifetime Alcohol Dependence and Frequency of Intoxication in Heaviest Drinking Year

Blackout Variable and Status	Alcohol Dependent, %	Frequency of Intoxication Heaviest Drinking Year, %					
		<3 Days per Year	3-12 Days per Year	2-3 Days per Month	1 Day per Week	2 Days per Week	≥3 Days per Week
Women (n = 2480)							
Lifetime blackouts (-)	7.4*	40.0	30.0	8.7	13.0	6.4	2.0
Lifetime blackouts (+)	34.4*	12.8	25.2	12.4	23.0	15.4	11.2
≥3 Blackouts in a year (-)	10.6†	32.8	30.1	10.2	15.3	8.6	3.1
≥3 Blackouts in a year (+)	75.9†	2.1	12.8	9.9	29.1	20.6	25.5
Men (n = 2168)							
Lifetime blackouts (-)	14.5‡	25.9	26.9	10.7	18.5	12.1	5.9
Lifetime blackouts (+)	47.5‡	6.2	14.7	10.9	22.3	25.9	20.0
≥3 Blackouts in a year (-)	19.2§	19.3	24.2	11.6	20.6	15.6	8.8
≥3 Blackouts in a year (+)	79.6§	1.6	6.4	8.0	20.3	33.3	30.5

Abbreviations: minus sign, absent; plus sign, present.

*Odds ratio 6.52 (95% CI, 5.13-8.29) for association of alcohol dependence with lifetime blackouts in women.

†Odds ratio 26.53 (95% CI, 19.33-36.41) for association of alcohol dependence with 3 or more blackouts in 1 year for women.

‡Odds ratio 5.33 (95% CI, 4.31-6.60) for association of alcohol dependence with lifetime blackouts in men.

§Odds ratio 16.48 (95% CI, 12.63-21.50) for association of alcohol dependence with 3 or more blackouts in 1 year for men.

Table 2. Genetic and Environmental Variance Components and 95% Confidence Intervals (CIs) of Best-Fitting Univariate Models, With Associated Goodness-of-Fit Indices, for Lifetime History of Blackouts, 3 or More Blackouts in a Year, and Frequency of Intoxication in Heaviest Drinking Year

Dependent Variable	Variance Components (95% CIs)		Model Fit		
	Additive Genetic	Nonshared Environmental	χ^2	df	AIC
Lifetime blackouts	0.53 (0.45-0.60)	0.47 (0.40-0.55)	10.44	9	-7.56
≥3 Blackouts in a year	0.58 (0.48-0.67)	0.42 (0.33-0.52)	14.04	9	-3.96
Frequency of intoxication	0.43 (0.37-0.48)	0.57 (0.52-0.63)	225.9	153	-80.13

Abbreviation: AIC, Akaike Information Criterion.

Table 3. Best-Fitting Bivariate Models for Blackout Variables Controlling for Frequency of Intoxication by Means of Cholesky Decomposition*

Blackout Variable	Variance Components (95% Confidence Intervals)			
	Loading Also on Frequency of Intoxication		Specific to Blackout Variable	
	Additive Genetic	Nonshared Environmental	Additive Genetic	Nonshared Environmental
Lifetime blackouts	0.31 (0.24-0.39)	0.02 (0.01-0.05)	0.21 (0.13-0.29)	0.46 (0.39-0.53)
≥3 Blackouts in a year	0.36 (0.27-0.46)	0.06 (0.03-0.10)	0.23 (0.13-0.32)	0.35 (0.27-0.44)

*Variance component values for frequency of intoxication in the bivariate models were essentially identical to those of the univariate model shown in Table 2 and are thus not repeated here.

shared environmental terms and constrained all parameters to be equal in women and men. Evidence was found for additive genetic and nonshared environmental contributions to the variance in the blackout variables that also loaded on frequency of intoxication and similar contributions specific to blackouts. For lifetime blackouts, the components that also loaded on frequency of intoxication represented 59.6% [0.31/(0.31+0.21)] of the total additive genetic variance and 4.2% [0.02/(0.02+0.46)] of the total nonshared environmental variance. The best-fitting model for having had 3 or more blackouts in a year reduced to a similar form with an estimated 61.0% of the additive genetic and 14.6% of the nonshared environ-

mental variance found to be shared with those for frequency of intoxication.

In analyses that controlled for the regression of the risk for lifetime blackouts on the frequency of intoxication, there was again no evidence of a significant shared environmental component nor of significant variation in parameters estimates by sex. The best-fitting model, thus, contained only a residual additive genetic component that was somewhat attenuated (heritability=37% [95% CI, 28%-46%]) and a nonshared environmental term. The corresponding model for having had 3 or more blackouts in a year could be similarly reduced yielding a residual heritability estimate of 41% (95% CI, 29%-53%).

The current investigation found evidence of a substantial genetic contribution to the risk for lifetime blackouts and for having had 3 or more blackouts in a year (respective heritability estimates of 53% and 58%). Our sample's high alcohol consumption made it well suited to detect a trait such as blackout sensitivity that is dependent on alcohol exposure for its expression. Given the current availability of animal models (eg, spatial working memory tasks)²² appropriate for the study of alcohol-induced blackouts, it is conceivable that the genetic loci underlying our findings could be readily identified.

The analyses controlling for the frequency of intoxication provide a useful frame of reference for consideration of potential pathways by which genetic influences on alcohol-induced blackouts may be mediated. The bivariate Cholesky model-fitting approach is generally more conservative in its estimation of the additive genetic variance for the blackout variables that is not shared with frequency of intoxication with assignment to shared variance, for example, of that arising through the effects of a third variable on both risk of blackouts and drinking to intoxication. The probit regression method more directly estimates the residual genetic and environmental contributions to the risk for blackouts when the effects of frequency of alcohol intoxication have been controlled statistically. These 2 approaches confirm significant genetic contributions to the risk of blackouts that are not explained by (probit regression approach) and not correlated with (bivariate model) genetic effects on drinking to intoxication. Thus, our results suggest the involvement of multiple factors in the susceptibility to blackouts, some of which also contribute risk for frequency of alcohol intoxication. We will first consider potential sources of genetic risk for blackouts that are not shared with those for frequency of intoxication.

The genetic contribution unique to blackout risk most likely arises from genes whose products mediate alcohol's effects on hippocampal neurotransmission.^{23,24} Blackouts appear to result from the following 2 actions of alcohol²⁵: (1) potentiation of γ -aminobutyric acid A ($GABA_A$)-mediated inhibition and (2) antagonism at excitatory N-methyl-D-aspartate (NMDA) glutamate receptors. An investigation²⁵ in which subanesthetic doses of a benzodiazepine, midazolam hydrochloride, and ketamine hydrochloride were given to humans found that their coadministration resulted in a significantly greater memory deficit than that seen with either drug alone, suggesting that these actions could operate in tandem.

Both $GABA_A$ agonists²⁶ and benzodiazepines²⁷ have been shown to cause periods of anterograde amnesia in a dose-dependent fashion. The degree to which alcohol has direct effects on hippocampal $GABA_A$ receptors remains controversial²⁸⁻³⁰; however, evidence suggests that several routes exist by which indirect effects may be mediated (neuroactive steroids,^{31,32} the septohippocampal pathway,³³ and nicotinic acetylcholine [nACh] receptors).³⁴⁻³⁶ Neuroactive steroid levels increase markedly after alcohol ingestion and are known to lead to enhanced $GABA_A$ transmission.^{31,32} When administered systemically to rats, neuroactive steroids produce

a spatial reference memory impairment similar to that seen with alcohol.³² Direct infusion into the medial septum of either alcohol or $GABA_A$ agonists results in impairment on memory tasks similar to that seen with systemic alcohol.³³ The current at $\alpha 4\beta 2$ nACh receptors at presynaptic and postsynaptic locations on $GABA_A$ neurons, potently enhanced by alcohol, results in increased GABA release.³⁴⁻³⁶ Thus, genes whose products have either direct or indirect involvement in $GABA_A$ -mediated transmission could be contributing genetic risk specific to blackouts. Respective examples in mice include a point mutation introduced^{37,38} into the $GABA_A$ receptor's α -1 subunit that resulted in elimination of the amnestic effects of benzodiazepines and an $\alpha 4\beta 2$ nACh receptor polymorphism found³⁹ to have greater alcohol responsiveness.

The administration of NMDA antagonists have been reported to cause periods of anterograde amnesia in humans²⁵ and rodents.⁴⁰ Impairment in both spatial and non-spatial hippocampus-dependent memory has been observed in NMDA receptor subunit-1 knockout mice.^{41,42} Transgenic mice overexpressing the NMDA receptor subunit-2B demonstrated superior learning and memory in contextual and cued fear conditional tasks.⁴³ The degree to which alcohol inhibits NMDA receptors varies with their subunit composition⁴⁴ and is reduced by altering subunit 1.⁴⁵ Thus, polymorphisms that affect the structure of NMDA receptors,^{41,42,45} their subunit composition,⁴⁴ or the degree to which various receptor types are expressed⁴³ could be contributing genetic risk specific to blackouts.

Genetic factors contributing to individual differences in alcohol metabolism are one likely source of the risk shared between blackouts and frequency of intoxication. A significant relationship has been reported⁴⁶ between alcohol consumption, variously assessed across multiple time points in an older cohort of Australian twins, and genotype at the loci for alcohol dehydrogenase (ADH) isozymes ADH1B and ADH1C. The results were in a pattern that suggested greater alcohol consumption was associated with slower metabolism of alcohol to acetaldehyde. The phenotype, maximum 24-hour alcohol consumption, has been reported to display evidence for linkage close to the ADH loci.⁴⁷ The finding of Goodwin et al¹¹ that the blood alcohol concentrations of those in whom blackouts were induced rose more rapidly and reached higher peaks suggests that these subjects may have had slower alcohol metabolism and perhaps more rapid absorption. However, another report⁴⁸ found that genotype at ADH1B and ADH1C loci made only a limited contribution to postalcohol challenge test blood alcohol concentrations. Gastric emptying speed^{49,50} and gastric ADH activity⁵¹ also contribute to individual differences in alcohol metabolism and, thus, could be a source of shared genetic variance.

One major source of shared genetic risk not related to alcohol metabolism is likely to result from variation in the level of response to the sedative effects of alcohol. Specifically, those in whom alcohol is less sedating are able to drink more and, while doing so, will be predisposed to experience a blackout rather than just passing out. Interest in this area (eg, lower level of response also

has been implicated as a risk factor for alcohol dependence⁵² has led to the selective breeding of mice and rat strains on the basis of their level of response. Alcohol, at a dose that leads to observable behavioral changes, was found³⁰ to significantly enhance the peak amplitude of hippocampal GABA_A inhibitory postsynaptic currents in highly sensitive mice and rats while causing no significant change in the inhibitory postsynaptic currents of the low sensitivity strains. Thus, genes that regulate GABA_A receptor sensitivity to alcohol appear to play a significant role in the sedative response. However, as with other alcohol-related phenotypes, level of alcohol response is a polygenic trait for which a number of contributing loci have already been identified in rodents.^{53,54}

When interpreting our results, a number of methodological limitations must be considered. Reliance on self-report may have led to bias due to false-negative responses in some participants (eg, those who drink alone) because awareness of a blackout generally requires either that someone else be present to retain and report memory for events or that something memorable transpire (eg, the individual was injured or has no recollection of having returned home). It is unclear how those whose blackouts were due to a combination of drugs and alcohol responded in our assessment. Although some error could have been introduced by our coding as negative for blackouts those who were skipped out before the blackout questions because of their very limited alcohol use, a more conservative reanalysis of our data (coding these individuals as missing) only slightly decreased the heritability estimates observed. It is possible that the total number of lifetime blackouts would have been a better dependent variable, but it was not included in our assessment. Similarly, the frequency of severe intoxication, if available, might have better controlled for alcohol consumption. In terms of temporal association, the best choice for a control variable might have been the quantity of alcohol consumed to induce a blackout, an interesting, but not realistically obtainable, alternative. Finally, the generalizability of our results to other less heavily drinking populations remains to be established.

The finding of a substantial genetic contribution to blackout risk offers an important clue to the underlying susceptibility to alcohol-related problems. Given the great societal costs of alcohol misuse,⁵⁵ we are hopeful that our work will motivate attempts to identify in animals the genes underlying our findings. Additional investigations could then be undertaken to determine the degree to which this work is pertinent to alcoholism risk in humans. Even if blackout susceptibility is only indirectly associated with alcoholism risk, it may prove to be associated with greater levels of other alcohol-related risk-taking behavior, victimization, and susceptibility to periods of anterograde amnesia associated with other drugs (eg, benzodiazepines).

Submitted for publication September 4, 2002; final revision received June 9, 2003; accepted July 2, 2003.

This study was supported in part by grants AA00277 (Dr Nelson), AA07728, AA10249, AA11998, and AA13321 (Dr Health), DA00272 and DA12854 (Dr Madden), and AA13326 (Dr Martin) from the National Institutes of Health,

Bethesda, Md, and grants 941177 and 981351 from the Australian National Health and Medical Research Council, Canberra (Dr Martin).

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