Correlations among First-Degree Relatives for Responses on the Self-Rating of the Effects of Alcohol Questionnaire in Teenagers*

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ABSTRACT. Objective: The level of response (LR) to alcohol is an intermediate phenotype related to the alcoholism risk, with a heritability of at least 0.4 as estimated from alcohol challenge experiments. A measure of LR that can be used in adolescence at a time close to the first drinking experience, and that is less expensive than alcohol challenge experiments, is the Self-Rating of the Effects of Alcohol (SRE) Questionnaire. This questionnaire contains questions related to the number of drinks required for up to four different effects early in the drinking career ("first five" score). The familial characteristics of SRE responses have been estimated in adults; however, no study has evaluated familial and potential genetic components of the first five SRE score in adolescents. This article presents data regarding the familial nature of SRE-based scores among a sample of teenagers. **Method:** As part of the Collaborative Study on the Genetics of Alcoholism Phase II (follow-up) Protocol, SRE scores were available on 251 females and 236 males ages 13-19 years. These analyses compare the correlations among father-offspring, mother-offspring, sibling pairs and comparable unrelated individuals. **Results:** For the 487 subjects, correlations among first-degree relatives ranged from 0.14 to 0.22 and were all significant. Correlations among comparable unrelated pairs ranged from 0.02 to 0.06 and were nonsignificant. When males and females were evaluated separately, the pattern of results, with higher correlations among first-degree relatives than among unrelated individuals, was similar, although, perhaps reflecting fewer subjects, correlations were more variable. **Conclusions:** Although not providing a definitive evaluation of heritability, the results are consistent with a potential proportion of the variance related to genes for first five SRE scores of between 0.3 and 0.4. These results parallel previously published data in adults and are similar to heritability estimates for LR on alcohol challenges. The data support the potential use of the first five SRE score in adolescents as a measure of LR in genetic and environmental model-based studies in young populations for whom the evaluation of LR is taking place at a time close to the onset of drinking. (*J. Stud. Alcohol* **66:** 62-65, 2005)

A LOW LEVEL of response (LR) to alcohol is one of several independent, genetically influenced characteristics or phenotypes that have an impact on the risk for alcohol abuse and dependence (Heath et al., 1999; Schuckit, 2002; Zucker et al., 2000). A lower LR to alcohol has been reported for several groups at higher risk for alcohol use disorders (AUDs), including children of alcoholics, Native Americans and Koreans, and results from four prospective studies indicate that a lower LR earlier in life is associated with a higher risk for later alcohol problems (Ehlers et al., 1999; Heath et al., 1999; Rodriguez et al., 1993; Schuckit, 2002; Schuckit and Smith, 2000; Volavka et al., 1996; Wall et al., 1999).

The heritability of LR has been established in animals and, through alcohol challenges, is estimated to be at least 0.4 in humans (Barr et al., 2003; Bell et al., 2001; Heath et

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al., 1999; Kurtz et al., 1996; Martin et al., 1985). Although some investigators discussed the importance of controlling for recent drinking histories in establishing LR through alcohol challenges (Heath and Martin, 1991), more recent evaluations support the conclusion that, even after additional factors are controlled, the heritability estimates remain above 0.4 for both alcohol-induced changes in body sway and subjective feelings of intoxication. These results do not appear to relate to either alcohol dehydrogenase forms or additional psychiatric diagnoses such as conduct disorder (Heath et al., 1999; Schuckit et al., 2000a).

Alcohol challenges as measures of LR have several drawbacks. First, alcohol cannot be administered to some subjects, including children below age 18 (the age for giving informed consent), and, thus, LR is usually established after several years of drinking. The relationship of LR to AUD risk factors such as family history and later alcoholic outcome appears robust even after controlling for recent drinking (Heath et al., 1999; Schuckit and Smith, 2000); there are, however, obvious benefits for measuring LR at an earlier age. Second, alcohol challenges require several costly day-long sessions, which preclude gathering data from large numbers of subjects. This limitation poses a problem for either genetic linkage studies or multivariate evaluations of models of risk.

An alternative LR measure is the Self-Rating of the Effects of Alcohol (SRE) questionnaire, which asks subjects to report the number of standard (12 g of ethanol) drinks required for each of four effects (beginning to feel intoxication, slurring speech, an unsteady gait, or falling asleep when they did not want to) at different points in their lives (Schuckit et al., 1997a,b, 2000b, 2001b). SRE values have 1-year retest reliabilities as high as 0.8 and correlations with alcohol challenge results of between 0.4 and 0.6, even when the two measures are administered over a decade apart (Schuckit et al., 1997a,b). Scores of a person's recollections from the first five times of drinking ("first five") correlate in predicted directions with the family histories of alcoholism and a person's alcohol-related problems in white, Hispanic and black men and women in the United States and Europe, even when the number of effects experienced and the recent quantity and frequency of drinking are used as covariates (Daeppen et al., 2000; Schuckit et al., 1997a,b, 2000b, 2001b, in press; Wall et al., 1999). The need for a higher number of drinks for an effect indicates a lower observed LR at a given blood alcohol concentration (BAC) in alcohol challenges. A recent article assessing over 2,000 adults (mean age 39) reported that the first five SRE scores appeared to reflect genetic influences, even after controlling for additional factors (Schuckit et al., 2001a). For 449 father-son dyads, the correlation in the early drinking SRE score was 0.22 ($p < .01$); for 561 mother/daughter dyads, the correlation was 0.18 ($p < .001$); whereas for 410 unrelated female and 369 unrelated male dyads, the correlations were nonsignificant (0.02 and 0.03, respectively).

Few data are available on the performance of the early life first five SRE scores in adolescents. This is unfortunate because an adequate performance of LR using this measure in young populations could be especially useful for testing mediational models and in linkage- or association-based genetic analyses. This brief report presents data regarding the familial nature of SRE-based LR scores among a sample of teenagers.

Method

The data for these analyses were gathered as part of the Phase II evaluations from the Collaborative Study on the Genetics of Alcoholism (COGA), an investigation of alcohol dependent probands, controls and all available relatives (Bucholz et al., 1994; Schuckit et al., 2003). Participants were interviewed with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) instrument, which uses questions relevant to several diagnostic systems, including the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, to gather information relevant to 17 Axis I and several Axis II diagnoses (American Psychiatric Association, 1994; Bucholz et al., 1994; Hesselbrock et al., 1999).

In Phase II of the COGA study, subjects ages 7 or older who reported having used alcohol were also administered the SRE questionnaire. Participants were asked to report the number of standard (12 g of ethanol) drinks they believed were needed to achieve any of up to four effects (becoming intoxicated, slurring of speech, a stumbling gait, or falling asleep when they did not wish to) the approximate first five times (first five) they consumed alcohol (Daeppen et al., 2000; Schuckit et al., 1997a,b; Wall et al., 1999). The first five SRE score is calculated by summing the number of drinks required early in the drinking career for up to four effects and dividing that figure by the number of effects endorsed. The data reported in the table were generated by Pearson product-moment correlations for father-offspring, mother-offspring and full sibling pairs for all subjects, followed by male offspring with father, male with mother and brother pairs versus male with randomly chosen father, randomly chosen mother or randomly selected unrelated male, with the process repeated for females. For unrelated subjects, pairs of unrelated individuals were randomly assigned by selecting only one member of a related pair, carrying out correlations with nonrelatives using 10 iterations and reporting the mean value.

Results

The 487 subjects were 13-19 years old, 48.5% (236) were male and 64.7% had an alcohol-dependent mother or father. All had some experience with alcohol, but none met criteria for alcohol dependence at the time of filling out the

SRE. The mean (SD) age of these participants was 17.0 (1.55) years, and they had 10.9 (1.35) years of education; 72.3% were white, 8.8% Hispanic, 12.7% black and 6.2% reported another racial background. They reported drinking on an average of 4.2 (4.49) days per month and consuming an average of 1.4 (1.25) drinks per occasion in the prior 6 months. For these subjects, the mean first five SRE score was 3.6 (1.91), with a range of 1-9. Scores were 4.0 (2.02) for males and 3.2 (1.71) for females (t = 4.80, 4.62 df, p < .001). There was no significant correlation between SRE and age overall (r = 0.01, p = .90), nor for the two genders (males: r = 0.01, p = .85 and females: r = 0.03, p = .62).

Table 1 reports the correlations for the first five drinking SRE score for 236 males and 251 females as they relate to father, mother and full siblings, and to random adult males, females and adolescents. Parent SRE values were not available for all parent-offspring pairs, and some adolescents did not have siblings. When all adolescent subjects are combined, correlations for the first five score with those reported by first-degree relatives ranged from 0.14 to 0.22, and all were significant. The correlation between these young subjects and random adult males, females and adolescents ranged from 0.02 to 0.06 and were nonsignificant. A similar pattern of correlations among first-degree relatives was seen when smaller subgroups of males were evaluated separately, with correlations ranging from 0.10 (p = 0.27) to 0.46, with only the first not significant; whereas, among unrelated individuals, correlations ranged from -0.03 to 0.03, and all were nonsignificant. For the subgroups of females, correlations among first-degree relatives ranged from 0.18 to 0.26 (p = .35), with the first significant; whereas, among unrelated individuals, correlations ranged from -0.00 to 0.05, and all were nonsignificant. The 0.11 correlation between mothers and daughters becomes significant if the Kendall-tau correlation is used (p = .04). Considering the combined subject scores in column 1, an estimate of heritability for LR as measured by the first five SRE score would approach or exceed 0.3.

Table 1. Correlations (and *N*s) for first five SRE among adolescents

	All	Boys	Girls
Correlated with			
Father	.15*	.10	.18*
	(271)	(134)	(137)
Mother	.14†	.19†	.11
	(416)	(197)	(219)
Siblings	.22*	.46*	.26
	(85)	(26)	(15)
Random adult male	.02	.00	.05
	(271)	(134)	(137)
Random adult female	.01	.03	-.00
	(416)	(197)	(219)
Unrelated adolescents	.06	-.03	.05
	(42)	(31)	(25)

Note: SRE = Self-Rating of the Effects of Alcohol.
*p < .05; †p < .01.

Discussion

The low LR to alcohol is an important intermediate phenotype indicating an enhanced risk for alcoholism (Schuckit, 2002; Schuckit and Smith, 2000). The identification of genes that contribute to LR and an enhanced understanding of additional characteristics and environmental events that might mediate the AUD risk are potentially facilitated by the development of the relatively inexpensive LR measure that can be administered to large populations. The current data support the conclusion that the first five SRE score, as a measure of the LR to alcohol among teenagers, appears to identify a characteristic that is familial and potentially genetically influenced. These conclusions are consistent with the evaluation of LR through the SRE in adults and with several studies of the importance of genetic factors to the LR to alcohol as measured by alcohol challenges (Schuckit et al., 2001a, 2004).

The SRE results reported here are generally similar to those noted in other studies (e.g., Schuckit et al., 1997a,b, 2001b). Values were a bit higher for males than females; however, the difference is consistent with the BAC differential per drink expected across the genders (Breslin et al., 1997). As shown in Table 1, all three correlations among the full set of first-degree relatives were significant, as were two of three for males. Only one of three Pearson correlations was significant for females, although the Kendall-tau correlation for mothers-daughters was also significant, and the 0.26 (p = .35) correlation among sisters reflected a medium effect size and might have reached significance if a larger number of pairs had been available. Possible differences across genders will require additional evaluations.

The results must be considered in light of the methods used. Several cells in Table 1 have relatively small numbers of subjects, most COGA families are from moderate socioeconomic strata, and several groups (e.g., Native Americans and Asians) were underrepresented. Therefore, the evaluations will need to be retested in other populations before definitive conclusions can be drawn. In addition, because the offspring were almost universally raised by their biological parents and because tests of environmental influences (e.g., drinking in peers) were not included in the analyses, it is possible that factors other than genes may have contributed to the LR correlations among relatives. Nonetheless, the data presented in Table 1 are consistent with the usefulness of the SRE first five score as a measure of a genetically influenced characteristic that reflects an intermediate phenotype related to the alcoholism risk. These data, along with the results of other studies using the SRE, support the potential usefulness of the SRE in studies in adolescents.

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