Multiple-Domain Predictors of Problematic Alcohol Use in Young Adulthood*

JOHN R. KRAMER, PH.D.,† GRACE CHAN, PH.D.,† DANIELLE M. DICK, PH.D.,† SAMUEL KUPERMAN, M.D.,† KATHLEEN K. BUCHOLZ, PH.D.,† HOWARD J. EDENBERG, PH.D.,† LINNEA A. POLGREEN, PH.D.,† VICTOR M. HESSELBROCK, PH.D.,† MARC A. SCHUCKIT, M.D.,† JOHN I. NURNBERGER, JR., M.D., PH.D.,† ELLEN S. KAPP, M.A., BERNICE PORJESZ, PH.D.,† AND LAURA J. BIERUT, M.D.†

Department of Psychiatry, Medical Education Building, University of Iowa School of Medicine, 500 Newton Road, Iowa City, Iowa 52242-1000

ABSTRACT. Objective: The goal of this study was to identify predictors of problematic young adult alcohol use. **Method:** The sample consisted of 141 subjects (81 females) participating in a national study of genetic risk factors for alcoholism. All subjects were evaluated first as children or adolescents, then approximately 5 years later as young adults. Outcome consisted of the number of alcohol symptoms (0-10) endorsed at this second time point. Predictors of outcome were drawn from five domains representing: (1) Demographic Characteristics, (2) Child/Adolescent Problematic Alcohol Use, (3) Biological Risk, (4) Externalizing Behaviors, and (5) Family Environment. A two-stage analytic strategy was used in which (1) separate multiple regression analyses were conducted within each of the five domains and (2) statistically significant predictors of problematic alcohol use from each domain were combined into one regression model to determine which remained significant. **Results:** In the final model, 31% of the variance in the number of alcohol symptoms in young adulthood was predicted by a high number of alcohol symptoms in childhood and adolescence, low initial sensitivity to alcohol, and a negative child/adolescent relationship with the father. **Conclusions:** These results demonstrated that *GABRA2*—originally associated with a diagnosis of alcohol dependence in adults—also predicted the onset of symptoms among subjects in their 20s, confirmed specific hypotheses about three other predictors in the final model, and suggested the utility of incorporating biological and nonbiological predictors to optimally predict young adult alcohol problems. (*J. Stud. Alcohol Drugs* **69:** 649-659, 2008)

ALCOHOL-USE DISORDERS (AUDs; American Psychiatric Association, 2000) are complex phenomena, with a wide range of contributing factors. Twin studies suggest that approximately half of the variance in alcohol dependence is accounted for by the combined effects of multiple genes (Heath et al., 1997; McGue, 1999; Prescott and Kendler, 1999). These genes interact with a variety of environmental circumstances to influence the risk for AUDs (Dick et al., 2006a; McGue, 1999).

Over the past several decades, investigators of child and adolescent psychopathology have identified an array of early environmental and behavioral precursors of drinking problems. Robins (1996) provided early longitudinal evidence that highly aggressive children were at risk for a variety of subsequent psychiatric disorders, including AUDs. Other researchers have replicated this finding numerous times, and conduct disorder (CD) has emerged as one of the most robust childhood predictors of alcohol disorders (Kuperman et al., 2001a; Robins, 1999). Two other externalizing conditions, attention deficit-hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD), also have been identified as precursors of problematic alcohol and drug involvement, although findings have been less consistent (Disney et al., 1999; Elkins et al., 2007; Marshal et al., 2007; Molina and Pelham, 2003; White et al., 2001).

Other established childhood and adolescent predictors of AUDs reflect characteristics of parenting and home environment (see overview by Sher et al., 2005). Some of the more widely studied precursors include parental lack of discipline and support (King and Chassin, 2004; Marshal and Chassin,

Received: October 1, 2007. Revision: March 24, 2008.

*This research was supported by National Institute on Alcohol Abuse and Alcoholism grant U10AA008401.

†Correspondence may be sent to John R. Kramer at the above address or via email at: john-kramer@uiowa.edu. Grace Chan and Victor M. Hesselbrock are with the Department of Psychiatry, University of Connecticut Health Center, Farmington, CT. Danielle M. Dick is with the Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA. Samuel Kuperman is with the Division of Child Psychiatry, University of Iowa Hospitals, Iowa City, IA. Kathleen K. Bucholz is with the Department of Psychiatry and Midwest Alcohol Research Center, Washington University School of Medicine, St. Louis, MO. Howard J. Edenberg is with the Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN. Linnea A. Polgreen is with the Department of Pharmacy, University of Iowa, Iowa City, IA. Marc A. Schuckit is with the Department of Psychiatry, University of California at San Diego, San Diego, CA. John I. Nurnberger, Jr., is with the Department of Psychiatry, Institute of Psychiatric Research, Indiana University Medical Center, Indianapolis, IN. Bernice Porjesz is with the Department of Psychiatry, State University of New York Downstate Medical Center, Brooklyn, NY. Laura J. Bierut is with the Department of Psychiatry, Washington University School of Medicine, St. Louis, MO.

2000; Stice et al., 1993), family conflict (Zhou et al., 2006), negative parent-child relationships (Kuperman et al., 2001b), and religion as a protective factor (Koopmans et al., 1999; Wallace et al., 2004; Winter et al., 2002).

Investigations of familial and behavioral precursors of AUDs are increasingly including biological risk factors. These integrative studies use multivariate approaches to address not only psychosocial and behavioral predictors but also biological variables that correlate with alcohol use, including high-risk genes and single nucleotide polymorphisms (SNPs), electrophysiological functioning, and initial alcohol sensitivity. Heath (Heath et al., 2001) jointly considered *ADH2*1/*2,* alcohol sensitivity, history of CD, birth cohort, education, and religious affiliation as predictors of alcohol symptom count among male Australian twins. *ADH2*1/*2* and high alcohol sensitivity were associated with a decrease in symptoms, whereas a history of CD and having an alcohol-dependent monozygotic co-twin or female dizygotic twin predicted an increase in such symptoms. Some more recent multiple-domain investigations have addressed alcohol use in young populations. Hill (Hill et al., 2000), investigating children and adolescents from high- and low-risk families, found that the onset of regular drinking was predicted jointly by family density for alcoholism, auditory and visual P300 amplitude, body sway, extraversion, and reading achievement. Hinckers (Hinckers et al., 2006) examined potential predictors of average alcohol intake in 16-year-old subjects. Using multiple regression, the authors reported that alcohol sensitivity and externalizing behavior together predicted such intake. In a study of 16- and 19-year-old subjects, Nilsson (Nilsson et al., 2005) found that 5-hydroxytryptamine (5-HTT, or serotonin), in combination with neutral or poor family relationships, best predicted alcohol intake and frequent intoxication. Covault and colleagues (2007) conducted a multiple regression analysis of college students and observed that individuals who were homozygous for the s-allele of the 5-HTTLPR genotype and who experienced multiple stressful events in the previous year also reported the most frequent drinking and heavy drinking. On balance, these investigations suggest that the prediction of early problematic alcohol use may benefit by incorporating both biological and psychosocial variables (Moffitt et al., 2005).

To date, such studies evaluating both the biological underpinnings of early problematic alcohol use and its familial and behavioral precursors are relatively small in number, and much work remains. For example, a number of investigators have demonstrated that the observed link between externalizing behaviors and AUD is partly attributable to environment and learning. Specifically, individuals with externalizing symptoms seek activities and friends that provide access to, modeling of, and reinforcement for intensive substance use (Catalano et al., 1996; Lonczak et al., 2001). However, work by genetic researchers also suggests that a substantial portion of the externalizing symptom-AUD relationship may be attributable to shared genetic underpinnings (Dick et al., 2004; McGue et al., 2006; Slutske et al., 1998), in particular *GABRA2* (Dick et al., 2006b) and *CHRM2* (Dick et al., 2008). In addition to a possible influence of *GABRA2* both on CD and alcoholism (Dick et al., 2004), *GABRA2*'s impact also may operate through its influence on alcohol sensitivity (Pierucci-Lagha et al., 2005), which at low levels is a known predictor of AUDs (Schuckit et al., 2003, 2007).

Following the example of integrative studies previously cited, we examined young participants in a national alcohol study, incorporating potential environmental, behavioral, and biological precursors of early, problematic alcohol use. We assessed a sample spanning childhood and adolescence through primarily the early 20s, thereby encompassing early alcohol use and problem development. Our outcome measure, young adult problematic alcohol use, was defined as a count of drinking problems rather than the presence or absence of alcohol dependence or abuse, in order to include individuals who were experiencing problems but were below diagnostic thresholds.

Our goals were threefold. First, we wanted to determine whether several SNPs, identified originally in conjunction with alcohol dependence in a wide age range of adults (*GABRA2* and *GABRG3*), also predicted early alcohol problems (rather than the diagnosis of dependence) in a very young adult sample.

Second, we wanted to incorporate, in the same investigation, risk factors that are less directly biological in nature. Selection of these demographic (e.g., gender), familial (e.g., relationship with mother), and behavioral (e.g., ADHD symptoms) variables was based on their repeated emergence as significant risk factors in previous studies and on their availability in this sample. The strategy we chose enabled us first to identify significant predictors of problematic young adult alcohol use that emerged from each of several specific domains (e.g., family environment) and then to identify those that remained significant after combining them in a multiple-domain analysis. We also incorporated measures of baseline child and adolescent alcohol use and symptoms as covariates. This information was expected to correlate strongly with symptoms reported at young adulthood because child/adolescent and adult measures of problematic alcohol use are influenced by a similar set of biological and environmental influences over time and exhibit substantial autocorrelations (Malone et al., 2004; Moffitt et al., 2005).

Third, we posited several hypotheses in conjunction with this strategy. To begin with, we expected that higher levels of problematic alcohol use in childhood, coupled with biological risk factor(s), would be associated with a greater likelihood of problematic alcohol use in young adulthood (Edenberg et al., 2004; Malone et al., 2004). In addition, we anticipated that initial sensitivity to alcohol would prevail as a major predictor of problematic alcohol use, given other studies in which this variable prevailed in conjunction with

psychosocial variables (Hinckers et al., 2006; Schuckit et al., 2006). Further, we hypothesized that poor parent-child relationships would also predict outcome, even in the presence of biological risk factors (Nilsson et al., 2005). Finally, we anticipated that *GABRA2* would be significantly correlated with child/adolescent CD symptoms (Dick et al., 2006b), as well as with alcohol sensitivity (Pierucci-Lagha et al., 2005). This last hypothesis addressed mechanisms through which *GABRA2* might influence the risk for alcohol problems.

Method

The present analyses were conducted on data collected by the Collaborative Study on the Genetics of Alcoholism (COGA; Begleiter et al., 1995), a National Institute on Alcohol Abuse and Alcoholism-funded consortium in which subjects were recruited from the surrounding areas of six research institutions: (1) University of California at San Diego, (2) University of Connecticut, (3) University of Iowa, (4) Indiana University, (5) Washington University in St. Louis, and (6) The State University of New York at Brooklyn. The primary purpose of COGA is to identify specific genes associated with alcohol dependence, alcohol abuse, and related phenotypes. All participants signed informed consent in accordance with institutional review board requirements at their respective sites.

Subjects

Participants in the project were drawn from two samples. The first sample consisted of alcohol-dependent probands and their family members. Probands were ascertained through treatment centers and were required to meet criteria for Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), alcohol dependence (American Psychiatric Association, 1987) and definite Feighner alcoholism (Feighner et al., 1972). Nuclear families that contained at least two other alcohol-dependent members were extended to more distant relatives and evaluated with interviews, electrophysiological measures, a neuropsychological test battery, and DNA assessment. The most genetically informative of such families were later comprehensively genotyped.

The second comparison sample was composed of nuclear families containing at least three adolescent offspring, as well as the availability of both parents. These families were recruited through a variety of means (e.g., dental clinics, churches, and drivers' license bureaus) and were ascertained without regard to the presence of psychiatric disorders, including AUDs. Family members in this comparison sample had approximately half the prevalence of psychiatric disorders as relatives of alcohol-dependent probands in the high-risk sample (Nurnberger et al., 2004). All COGA participants were required to speak English, be free of extensive or recent intravenous drug use, and have no life-threatening or incapacitating medical illness (except conditions that were alcohol related). In addition to an initial assessment, families from both samples were evaluated again approximately 5 years later with many of the same procedures, including interviews. Further details about ascertainment and study design can be found elsewhere (Begleiter et al., 1995; Nurnberger et al., 2004).

The sample for the current analysis was composed of 141 unrelated subjects, 57.5% of whom were females, and who (1) were evaluated first as children or adolescents (baseline; mean [SD] = 15.1 [1.8] years), (2) had corroborative information provided by a parent or guardian interview at this baseline evaluation, and (3) were evaluated again an average of 5.5 [1.4] years later as young adults (follow-up) at a mean age of 20.6 [1.9] years. The sample was restricted to whites to reduce the effect of population stratification on the genetic analyses. Furthermore, only one subject was selected from nuclear families with multiple offspring to avoid statistical dependence among them. Sibling selection was made on the basis of the most complete genetic data because of the relative scarcity of such information among younger COGA participants. The derivation of the final sample is as follows: Of all 649 children and adolescents who were genotyped at baseline, 257 of them had corroborative parent interviews and follow-up evaluations. One hundred seventy-eight individuals were selected from the 257 participants to represent separate families; 141 of these 178 subjects were white. The sample size for specific analyses was sometimes less than 141 because of missing data, most often specific SNPs (Foroud et al., 2000). Slightly more than half of the 141 subjects (56.0%) came from the immediate or extended families of alcoholic probands (high-risk families); the remainder were drawn from the comparison families.

Measures

Interviews. During the first evaluation, conducted during adolescence (ages 13-17; $n = 126$) or childhood (ages 7-12; $n = 15$), subjects were assessed by trained interviewers with the child or adolescent version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), created for COGA (Kuperman et al., 1999). The version used in the current analyses (C-SSAGA-I) addressed a broad spectrum of DSM-III-R child and adolescent psychiatric diagnoses (American Psychiatric Association, 1987). Parents or guardians were administered SSAGA interviews about themselves, as well as a parent version of the child or adolescent SSAGA that contained identical questions about the offspring and provided a second informant's perspective. At the five-year follow-up evaluation, offspring were administered the Adult SSAGA-II (Bucholz et al., 1994; Hesselbrock et al., 1999), which addresses full diagnostic criteria for a broad range of

TABLE 1. Baseline (child/adolescent) and follow-up Young Adult Alcohol Symptom Scale results

Scale item	% Endorsed	
	Baseline	Follow-up
1. Experienced tolerance to feel an effect or to become drunk	17.0	39.0
2. Wanted to reduce alcohol intake 3+ times or not always successful	11.4	18.4
3. Became drunk when didn't want to	18.4	27.0
4. Gave up or greatly reduced important activities	0.7	7.8
5. Went on binges or benders or had periods of primarily drinking and recovering	5.0	19.2
6. Continued to drink despite health problems created or worsened by alcohol	4.3	7.8
7. Alcohol often interfered with work, school, or family responsibilities	12.8	14.2
8. Used alcohol 3+ times in hazardous situations (e.g., with drugs or while driving)	16.3	41.8
9. Was arrested for drunk driving	[a]	11.4
10. Experienced serious or repeated relationship problems because of alcohol	7.8	24.8
Mean (SD)	0.94 (1.93)	2.11 (2.49)
Cronbach's α	.88	.83

[a]Child/adolescent interview did not include this item.

primarily Axis I DSM-IV psychiatric disorders, including AUDs (American Psychiatric Association, 2000).

Outcome variable. Items from the Adult SSAGA-II formed the basis for measuring problematic alcohol use at follow-up. The Young Adult Alcohol Symptom Scale consisted of the number of positive responses to 10 SSAGA lifetime alcohol-related items, selected to represent core problems associated with dependence and abuse (Table 1).

Predictor variables. Figure 1 presents a schematic overview of risk domains and variables within each.

Risk factors for problematic alcohol use were selected to represent five predictor domains: (1) Demographic Characteristics, (2) Child/Adolescent Alcohol Involvement, (3) Biological Risk, (4) Externalizing Behaviors, and (5) Family Environment. Demographic Characteristics consisted of gender, age at baseline, and age at follow-up. Gender was included because there is evidence that the predictors of problematic male and female alcohol use, although overlapping, may differ to some degree (Gogineni et al., 2006; Heath et al., 2001). Age was incorporated as a potential covariate of either baseline or follow-up problematic alcohol use.

The second predictor domain, Child/Adolescent Alcohol Involvement, included two baseline interview variables: (1) the typical quantity of alcohol consumed weekly during the 6 months before the interview; and (2) a count of nine lifetime alcohol symptoms that closely matched the 10-item Young Adult Alcohol Symptom Scale collected at adult follow-up (Table 1).

The third domain, Biological Risk, consisted of selected SNPs associated with adult alcohol dependence and a variable measuring initial alcohol sensitivity. SNPs were drawn from *GABRA2* (rs279826 and rs279871; Edenberg et al., 2004) and *GABRG3* (rs140679, rs3097493, and rs3097490; Dick et al., 2004). Other SNPs linked with AUDs in the articles by Dick et al. and Edenberg et al. were excluded because information was not widely available for subjects in the current sample. "High-risk alleles" were classified as such because of the overtransmission of that particular allele to adult alcohol-dependent individuals in the previously cited, family-based analyses of the adult COGA sample. For each SNP, three different genetic models were examined: (1) an additive model (number of high-risk alleles), (2) a dominant model (presence/absence of at least one high-risk allele), and (3) a recessive model (presence/absence of two high-risk alleles). Initial sensitivity to alcohol was measured retrospectively at follow-up by Schuckit's Self-Rating of the Effects of Alcohol (SRE; Schuckit et al., 1997). Subjects were asked to recall the first five times they drank and the number of drinks they required to (1) feel different, (2) feel dizzy or have slurred speech, (3) stumble, and (4) unintentionally fall asleep. For each subject, a single initial sensitivity score was computed as the average number of drinks necessary to achieve any of the previously described effects experienced by the subject, with higher scores indicating less sensitivity (and higher risk).

Externalizing Behaviors comprised the fourth domain and were drawn from the baseline child/adolescent and parent interviews about the child. Consistent with common practice in child psychiatric research (Bird et al., 1992), each behavior item was counted positive if either the parent or the offspring endorsed it. Two informants were employed because offspring are more comprehensive reporters of CD, whereas parents are more accurate at detecting ADHD and ODD (Jensen et al., 1999; Loeber et al., 1989; Mannuzza et al., 2003). Three behavior symptom count variables were created from specific questions in these interviews, drawn from DSM-III-R criteria: (1) 13 items representative of CD (e.g., frequent lying), (2) 5 items reflecting ODD (e.g., refusing to do things), and (3) 8 items representative of ADHD (e.g., trouble staying seated, daydreaming).

Family Environment, the fifth predictor domain, included family type (high-risk vs comparison). In addition, variables suggested by other studies to be significant predictors of problematic alcohol use were collected from the baseline

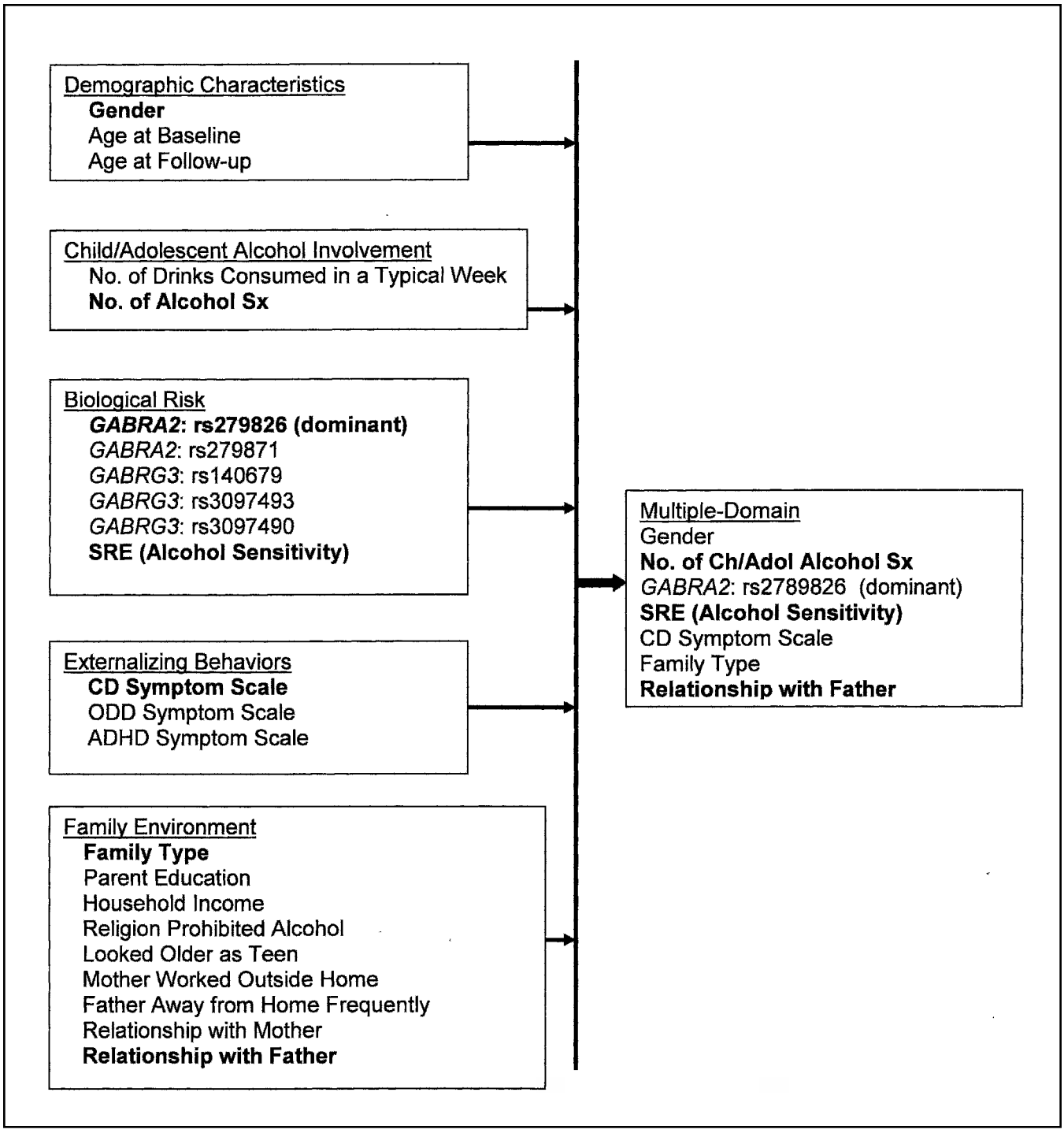

FIGURE 1. Overview of analytic domains and significant predictors of Young Adult Alcohol Scale (**boldface** predictors significant at $p < .05$). ADHD = attention deficit-hyperactivity disorder; CD = conduct disorder; ch/adol = child/adolescent; ODD = oppositional defiant disorder; SRE = self-rating of the effects of alcohol; Sx = symptoms.

parent interviews (about themselves) and the follow-up young adult interviews. Socioeconomic status (Curran et al., 1999; Gogineni et al., 2006) was measured by two variables from parent self-interviews: (1) the highest level of education attained by either parent and (2) household income. Six retrospective variables, addressing primarily ages 6-13, were drawn from the offspring follow-up interview: (1) whether subjects' religion of origin had explicit prohibitions against alcohol (Koopmans et al., 1999; Wallace et al., 2004; Winter et al., 2002); (2) whether subjects looked older than their

peers as teenagers (Dick et al., 2000; Gogineni et al., 2006); (3) whether the mother worked outside the home; (4) whether the father was away from home frequently (Gogineni et al., 2006); (5) the offspring's relationship with the mother while growing up (dichotomized from the original 4-point scale to excellent/good vs fair/poor); and (6) the offspring's childhood relationship with the father, scored in the same fashion (Gogineni et al., 2006; Kuperman et al., 2001b; Nilsson et al., 2005). Because of human subjects concerns at certain COGA sites, many subjects were missing data for other, more sensitive parenting variables (e.g., physical/sexual abuse and physical conflict), and these variables could not be included.

Analyses

A two-stage approach was used to elucidate relationships between predictors and outcome. First, the Young Adult Alcohol Symptom Scale was regressed separately on variables from the five domains described previously to identify the

Table 2. Outcome variable and predictor variables

Domains	Variable (*n*; Cronbach's α)		% or mean (SD) score
Outcome	Young Adult Alcohol Symptom Scale (141; .83)		2.11 (2.49)
Predictors			
1) Demographic Characteristics	Gender (141)		57.45% female
	Age at baseline (141)		15.06 (1.82)
	Age at follow-up (141)		20.58 (1.89)
2) Child/Adolescent Alcohol Involvement	No. of drinks consumed in a typical week (141)		2.28 (8.70)
	Child/adolescent alcohol symptom count (141; .88)		0.94 (1.93)
3) Biological Risk	*GABRA2* (number of high-risk alleles)	rs279826 (130)	18.46% 0 48.46% 1 3.08% 2
		rs279871 (126)	12.70% 0 57.14% 1 30.16% 2
	GABRG3 (number of high-risk alleles)	rs140679 (132)	24.24% 0 52.27% 1 23.49% 2
		rs3097493 (127)	24.41% 0 51.18% 1 24.41% 2
		rs3097490 (127)	25.20% 0 50.39% 1 24.41% 2
	SRE	Alcohol sensitivity (126)	4.17 (2.17)
4) Externalizing Behaviors	CD symptom scale (141; .64)		1.86 (1.86)
	ODD symptom scale (141; .69)		0.89 (1.28)
	ADHD symptom scale (141; .81)		1.89 (2.20)
5) Family Environment	Family type (high risk) (141)		56.03%
	Parent education (141)		13.77 (2.40)
	Household income (median range) (140)		$40,000-$49,999
	Religion prohibited alcohol (125)		12.80%
	Looked older as teen (141)		33.33%
	Mother worked outside home (141)		73.05%
	Father away from home frequently (123)		31.71%
	Relationship with mother (141)		13.48% fair/poor
	Relationship with father (123)		27.64% fair/poor

Notes: SRE = Self-Rating of the Effects of Alcohol; CD = conduct disorder; ODD = oppositional defiant disorder; ADHD = attention deficit-hyperactivity disorder.

TABLE 3. Single- and multiple-domain regression results for Young Adult Alcohol Symptom Scale (see also Figure 1)

Domain (*n*)	R^2	Variable	Estimated coefficient	Estimated SE
Demographic Characteristics (141)	.04	Gender*[a]	1.05	0.42
Child/Adolescent Alcohol Involvement (141)	.15	Ch/adol alcohol sx count‡	0.50	0.10
Biological Risk (115)	.19	SRE (alcohol sensitivity)‡	0.43	0.09
		GABRA2: rs279826*[b]	1.31	0.53
Externalizing Behaviors (141)	.18	CD symptom scale‡	0.56	0.10
Family Environment (123)	.18	Relationship with father‡[c]	1.81	0.46
		Family type*[d]	1.06	0.41
Multiple-domain (final model) (108)	.31	Relationship with father‡[c]	1.68	0.45
		Ch/adol alcohol sx count‡	0.39	0.10
		SRE (alcohol sensitivity)†	0.28	0.09

Notes: Ch/Adol = Child/Adolescent; sx = symptom; SRE = Self-Rating of the Effects of Alcohol; CD = conduct disorder. [a]Male gender was associated with more alcohol symptoms than was female gender; [b]dominant (at least one high-risk allele vs no high-risk alleles); [c]a fair/poor (negative) relationship with father was associated with more alcohol symptoms than was a good/excellent (positive) relationship; [d]membership in a high-risk family was associated with more alcohol symptoms than was membership in a comparison family.
*$p < .05$; †$p < .01$; ‡$p < .001$.

most prominent ($p < .05$) predictors, adjusted for the other variables, within each domain. In the second stage of analysis, all significant ($p < .05$) predictors that emerged in the previous single-domain analyses were combined and further examined, thereby identifying the most prominent predictors—adjusted for the other significant variables—across domains. Stepwise variable selection was used to determine which combination of predictors best accounted for variation in outcome in the single-domain analyses. Both stepwise variable selection and backward variable elimination were used to refine the initial combined multiple-domain model into the final multiple-domain model. Because the outcome variable was in the form of a symptom count, generalized linear regression was explored under three distributional assumptions: (1) normal, (2) Poisson, and (3) negative binomial. The identification of significant predictors was not sensitive to distributional assumptions; only results from the normal analysis will be reported herein because of its widespread familiarity and straightforwardness of interpretation.

To evaluate the four hypotheses, results from the two-stage regression analyses, as well as bivariate relationships, were examined. Both Pearson and Spearman correlation coefficients—in conjunction with either Fisher's exact or Mantel-Haenzsel test—were used in estimating and testing the significance of bivariate relationships (Agresti, 2002). All analyses were conducted using SAS release 9.1 (SAS Institute, Inc., Cary, NC).

Results

Descriptive statistics of all variables, as well as Cronbach's alphas of symptom scales, are presented in Tables 1 and 2.

Single-domain regression analyses

Table 3 displays the five domain-specific regression models for the Young Adult Alcohol Symptom Scale (also see boldfaced predictors in Figure 1). In the Demographic Domain, male gender (β [SE] = 1.05 [0.42]) explained 4% of the variability in young adult symptom count. Within the Child/Adolescent Alcohol Involvement Domain, baseline alcohol symptom count (β = 0.50 [0.10]) was the only significant predictor, accounting for 15% of the variance. From the Biological Risk Domain, initial sensitivity to alcohol (SRE; β = 0.43 [0.09]) and at least one high-risk allele on *GABRA2* SNP rs279826 (β = 1.31 [0.53]) together explained 19% of the variance in young adult alcohol symptoms. Number of CD symptoms (β = 0.56 [0.10]) was the sole significant Externalizing Behaviors predictor, accounting for 18% of the variance. Finally, two significant predictors were identified in the Family Environment Domain, together explaining 18% of young adult alcohol symptoms: negative (fair/poor) child/adolescent relationship with father (β = 1.81 [0.46]) and membership in a high-risk family (β = 1.06 [0.41]).

Multiple-domain regression analyses

The initial multiple-domain model included all seven domain-specific significant predictors. Both stepwise variable selection and backward variable elimination procedures generated a final model with the same three jointly significant predictors ($p < .05$, in order of entering): relationship with father (β = 1.68 [0.45]), alcohol sensitivity (SRE; β = 0.28 [0.09]), and number of child/adolescent alcohol symptoms (β = 0.39 [0.10]). The four nonsignificant predictors were (in order of being removed): (1) CD symptom score, (2) family

type, (3) gender, and (4) *GABRA2:* rs279826 (dominant). The final multiple-domain model (Table 3) was based on a sample size of 108 after pair-wise deletion because of missing values and explained 31% of the variation in the Young Adult Alcohol Symptom Scale. The multiple-domain box in Figure 1 lists the seven domain-specific significant predictors, with three predictors in the final model boldfaced.

Bivariate correlations

GABRA2 was not significantly correlated with the CD Symptom Scale or with SRE score (alcohol sensitivity).

Discussion

In this exploratory article, we obtained a final, multiple-domain regression model that accounted for nearly one third of the variance in the number of alcohol symptoms endorsed at follow-up. In contrast, no single-domain model explained more than one fifth of the variance, supporting the utility of multiple-domain prediction in our sample. Baseline alcohol symptoms were, as anticipated, powerful risk factors, bringing to mind the maxim that the best predictor of future behavior is current behavior and reflecting likely continuity of genetic and environmental influences across time (Malone et al., 2004). Above and beyond this anticipated finding, a negative relationship with father and early low sensitivity to alcohol each contributed additional predictive information.

Results from the single-domain regression analyses were largely in line with previous studies. In the Demographic Domain, consistent with prevalence studies of alcohol disorders (Grant et al., 2004), male gender was associated with more young adult alcohol symptoms. In future investigations with larger samples, it would be appropriate to conduct separate regression analyses for each gender, because their respective predictors may differ to some degree (Gogineni et al., 2006; Heath et al., 2001; King et al., 2005; Wodarz et al., 2003).

In the Biological Risk Domain, alcohol sensitivity emerged as a significant predictor of young adult alcohol-related symptoms, consistent with previous studies (e.g., Schuckit et al., 2007). *GABRA2* SNP rs279826 also was significantly associated with outcome, indicating that this SNP, originally linked to adult alcohol dependence in adults (Edenberg et al., 2004), also signals risk for early problems among individuals in their 20s. *GABRG3,* a less extensively studied risk factor, did not emerge as significant. The joint predictive significance of SRE and *GABRA2* suggests that these two biological variables explained different sources of variation. Our finding for alcohol sensitivity is consistent with other multiple-domain regression studies in which sensitivity has remained in the final model as a significant predictor of average monthly alcohol intake among adolescents (Hinckers et al., 2006) and number of alcohol symptoms in adults (Heath et al., 2001). Although alcohol sensitivity was the only biological risk predictor retained in our final model, this does not diminish the potential importance of *GABRA2.* Rather, it suggests that the source of variation in young adult symptoms explained by rs279826 may have been more fully accounted for by predictors from other domains.

In the Externalizing Behaviors Domain, CD symptoms accounted for almost as much variance in outcome (18%) as did the two Biological Risk variables (19%). After adjusting for CD symptoms, ADHD and ODD symptoms revealed no significant correlations with problematic alcohol use, in part owing to significant correlations among the three scales, possibly reflecting shared disinhibitory traits (Begleiter and Porjesz, 1999; Martin et al., 2006; Young et al., 2000). In addition, the connection between ADHD and problematic alcohol use may manifest itself primarily among older adolescents rather than young adults (Molina et al., 2007). In the final multiple-domain model, baseline CD symptoms were no longer a significant predictor of young adult alcohol symptoms. This suggests that other risk factors were correlated both with child/adolescent CD and with young adult outcome, thereby preempting CD as a significant predictor. As with rs279826, the multiple-domain model does not negate the role of CD symptoms; instead, it suggests the need for additional research to reveal relationships (e.g., mediation and redundancy) between predictors from different domains.

In the Family Environment domain, a negative child/adolescent relationship with father emerged as a significant precursor of young adult alcohol symptoms, in line with other research (e.g., Castro et al., 2006). Furthermore, this predictor was retained in the final model, along with baseline problematic alcohol use and alcohol sensitivity. Another study incorporating both biological and familial variables found that a similar variable, Quality of Family Relationships, also was retained in addition to a biological variable (5-HTT) in the prediction of adolescent alcohol intoxication (Nilsson et al., 2005). Our observed link between a negative baseline paternal relationship and follow-up problematic alcohol use might be attributable to a causal process flowing from deviant parenting behaviors to offspring substance use, the effect of deviant offspring behavior on the parent-child relationship, and/or inherited risk factors that influence both parenting and offspring substance use. The latter two are examples of, respectively, evocative and passive gene-environment correlations (Reiss, 2005).

In sum, the current analyses suggest that at least one *GABRA2* SNP identified in conjunction with adult alcohol dependence also predicts early alcohol problems in young adults. Furthermore, three of our hypotheses were supported. First, problematic alcohol use in young adulthood was significantly associated both with child/adolescent problematic alcohol use and biological risk (early sensitivity to alcohol). In addition, sensitivity predicted problematic alcohol use even after adjusting for psychosocial predictors. Finally,

parent-child (paternal) relationships remained significant predictors after controlling for biological risk factors. However, the fourth hypothesis—significant correlations between *GABRA2* and CD symptoms or between *GABRA2* and alcohol sensitivity—was not supported. Thus, we were not able document mechanisms through which *GABRA2* might influence risk for problematic alcohol use in young adulthood.

The current project has several strengths. COGA participants are a highly characterized and demographically diverse national sample, assessed with reliable and valid procedures and instruments. Information on externalizing behaviors and some of the home environment predictors were collected during childhood or adolescence, thereby reducing distortions associated with long-term recall (Mannuzza et al., 2002). Parental informants potentially increased further the accuracy of ODD and ADHD symptom counts (Loeber et al., 1989).

However, several factors placed limits on the generalizability of our results. High-risk families with multiple affected sib pairs were more likely to be genotyped because they were genetically informative; as a result, our findings may be most relevant to densely affected families (this selection bias did not apply to comparison family subjects, of whom 94.4% were genotyped). Confining the analyses to white subjects provided a more genetically homogeneous sample, but it also potentially limited the scope of our findings. We included a small number of subjects who were children rather than adolescents at baseline (n's = 15 and 126, respectively). Because it is possible that relationships between predictors and outcome might differ for the two age groups, future analyses should target a more restricted age range. Attrition owing to missing variables and to follow-up may have skewed our findings. Comparisons between our 141 subjects and all 649 offspring genotyped at baseline (see the Method section) revealed a higher baseline alcohol symptom count in the latter (0.9 vs 0.5, $p < .0001$) but no differences in weekly consumption or in baseline CD, ODD, and ADHD symptom counts. Finally, stepwise regression in small samples may have introduced bias through inflated multiple correlations and significance tests. Thus, the possibility of spurious results must be tested in other, larger investigations.

As a step in this direction, COGA investigators are prospectively assessing a sample of adolescents and young adults from both types of families every 2 years. These analyses will provide larger and older samples, with more extensive alcohol use and additional risk factors. A more fine-grained exploration of the interplay between biological predisposition and environment can be attained through structural equation modeling and latent variable construction (Schuckit et al., 2006). We anticipate that these studies will more fully illuminate the broad spectrum of risk factors that foreshadow the development of AUDs and other substance disorders.

Acknowledgments

COGA (co-principal investigators: L. Bierut, H. Edenberg, V. Hesselbrock, and B. Porjesz) includes nine different centers where data collection, analysis, and storage take place. The nine sites and principal investigators and co-investigators are the University of Connecticut (V. Hesselbrock); Indiana University (H. Edenberg, J. Nurnberger, Jr., P.M. Conneally, and T. Foroud); University of Iowa (S. Kuperman and R. Crowe); The State University of New York Downstate Medical Center (B. Porjesz); Washington University in St. Louis (L. Bierut, A. Goate, and J. Rice); University of California at San Diego (M. Schuckit); Howard University (R. Taylor); Rutgers University (J. Tischfield); and Southwest Foundation (L. Almasy). Zhaoxia Ren serves as the National Institute on Alcohol Abuse and Alcoholism staff collaborator.

This research is dedicated to the memories of Henri Begleiter and Theodore Reich, principal and co-principal investigators, respectively, of COGA since its inception. We are indebted to their leadership in the establishment and nurturing of COGA and acknowledge with great admiration their seminal scientific contributions to the field.

References

Agresti, A. Categorical Data Analysis, 2nd Edition, New York: John Wiley & Sons, 2002.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R), Washington, DC, 1987.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR), Washington, DC, 2000.

Begleiter, H. and Porjesz, B. What is inherited in the predisposition toward alcoholism? A proposed model. Alcsm Clin. Exp. Res. **23:** 1125-1135, 1999.

Begleiter, H., Reich, T., Hesselbrock, V., Porjesz, B., Li, T.-K., Schuckit, M.A., Edenberg, H.J., and Rice, J.P. The collaborative study on the genetics of alcoholism. Alcohol Hlth Res. World **19:** 228-236, 1995.

Bird, H.R., Gould, M.S., and Staghezza, B. Aggregating data from multiple informants in child psychiatry epidemiological research. J. Amer. Acad. Child Adolesc. Psychiat. **31:** 78-85, 1992.

Bucholz, K.K., Cadoret, R.J., Cloninger, C.R., Dinwiddie, S.H., Hesselbrock, V.M., Nurnberger, J.I., Jr, Reich, T., Schmidt, I., and Schuckit, M.A. A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. J. Stud. Alcohol **55:** 149-158, 1994.

Castro, F.G., Brook, J.S., Brook, D.W., and Rubenstone, E. Paternal, perceived maternal, and youth risk factors as predictors of youth stage of substance use: A longitudinal study. J. Addict. Dis. **25:** 65-75, 2006.

Catalano, R.F., Kosterman, R., Hawkins, J., and Newcomb, M.D. Modeling the etiology of adolescent substance use: A test of the social development model. J. Drug Issues **26:** 429-455, 1996.

Covault, J., Tennen, H., Armeli, S., Conner, T.S., Herman, A.I., Cillessen, A.H., and Kranzler, H.R. Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. Biol. Psychiat. **61:** 609-616, 2007.

Curran, G.M., Stoltenberg, S.F., Hill, E.M., Mudd, S.A., Blow, F.C., and Zucker, R.A. Gender differences in the relationship among SES, family history of alcohol disorders and alcohol dependence. J. Stud. Alcohol **60:** 825-832, 1999.

Dick, D.M., Agrawal, A., Schuckit, M.A., Bierut, L., Hinrichs, A., Fox, L., Mullaney, J., Cloninger, C.R., Hesselbrock, V., Nurnberger, J.I., Jr., Almasy, L., Foroud, T., Porjesz, B., Edenberg, H., and Begleiter, H. Marital status, alcohol dependence, and *GABRA2*: Evidence for gene-environment correlation and interaction. J. Stud. Alcohol **67:** 185-194, 2006a.

Dick, D.M., Aliev, F., Wang, J.C., Grucza, R.A., Schuckit, M., Kuperman, S., Kramer, J., Hinrichs, A., Bertelsen, S., Budde, J.P., Hesselbrock, V., Porjesz, B., Edenberg, H.J., Bierut, L.J., and Goate, A. Using dimensional models of externalizing psychopathology to aid in gene identification. Arch. Gen. Psychiat. **65:** 310-318, 2008.

Dick, D.M., Bierut, L., Hinrichs, A., Fox, L., Bucholz, K.K., Kramer, J., Kuperman, S., Hesselbrock, V., Schuckit, M., Almasy, L., Tischfield, J., Porjesz, B., Begleiter, H., Nurnberger, J., Jr., Xuei, X., Edenberg, H.J., and Foroud, T. The role of *GABRA2* in risk for conduct disorder and alcohol and drug dependence across developmental stages. Behav. Genet. **36**: 577-590, 2006b.

Dick, D.M., Edenberg, H.J., Xuei, X., Goate, A., Kuperman, S., Schuckit, M., Crowe, R., Smith, T., Porjesz, B., Begleiter, H., and Foroud, T. Association of *GABRG3* with alcohol dependence. Alcsm Clin. Exp. Res. **28:** 4-9, 2004.

Dick, D.M., Li, T.-K., Edenberg, H.J., Hesselbrock, V., Kramer, J., Kuperman, S., Porjesz, B., Bucholz, K., Goate, A., Nurnberger, J., Jr., and Foroud, T. A genome-wide screen for genes influencing conduct disorder. Mol. Psychiat. **9:** 81-86, 2004.

Dick, D.M., Rose, R.J., Pulkkinen, L., and Kaprio, J. Measuring puberty and understanding its impact: A longitudinal study of adolescent twins. J. Youth Adolesc. **30:** 385-400, 2000.

Disney, E.R., Elkins, I.J., McGue, M., and Iacono, W.G. Effects of ADHD, conduct disorder, and gender of substance use and abuse in adolescence. Amer. J. Psychiat. **156:** 1515-1521, 1999.

Edenberg, H.J., Dick, D.M., Xuei, X., Tian, H., Almasy, L., Bauer, L.O., Crowe, R.R., Goate, A., Hesselbrock, V., Jones, K., Kwon, J., Li, T.-K., Nurnberger, J.I., Jr., O'Connor, S.J., Reich, T., Rice, J., Schuckit, M.A., Porjesz, B., Foroud, T., and Begleiter, H. Variations in *GABRA2*, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations. Amer. J. Human Genet. **74:** 705-714, 2004.

Elkins, I.J., McGue, M., and Iacono, W.G. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. Arch. Gen. Psychiat. **64:** 1145-1152, 2007.

Feighner, J.P., Robins, E., Guze, S.B., Woodruff, R.A., Jr., Winokur, G., and Munoz, R. Diagnostic criteria for use in psychiatric research. Arch. Gen. Psychiat. **26:** 57-63, 1972.

Foroud, T., Edenberg, H.J., Goate, A., Rice, J., Flury, L., Koller, D.L., Bierut, L.J., Conneally, P.M., Nurnberger, J.I., Bucholz, K.K., Li, T.-K., Hesselbrock, V., Crowe, R., Schuckit, M., Porjesz, B., Begleiter, H., and Reich, T. Alcoholism susceptibility loci: Confirmation studies in a replicate sample and further mapping. Alcsm Clin. Exp. Res. **24:** 933-945, 2000.

Gogineni, A., King, S., Jackson, K., Kramer, J., Bucholz, K., Chan, G., Iacono, W., Kuperman, S., Larkins, J.M., Longabaugh, R., McGue, M., Polgreen, L., Sher, K.J., Stout, R., Strong, D., and Woolard, R. Female offspring of alcoholic individuals: Recent findings on alcoholism and psychopathology risks: Symposium presented at the Research Society on Alcoholism, 2004, Vancouver, Aruna Gogineni, Chair. Alcsm Clin. Exp. Res. **30:** 377-387, 2006.

Grant, B.F., Dawson, D.A., Stinson, F.S., Chou, S.P., Dufour, M.C., and Pickering, R.P. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. Drug Alcohol Depend. **74:** 223-234, 2004.

Heath, A.C., Bucholz, K.K., Madden, P.A., Dinwiddie, S.H., Slutske, W.S., Bierut, L.J., Statham, D.J., Dunne, M.P., Whitfield, J.B., and Martin, N.G. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: Consistency of findings in women and men. Psychol. Med. **27:** 1381-1396, 1997.

Heath, A.C., Whitfield, J.B., Madden, P.P.F., Bucholz, K.K., Dinwiddie, S.H., Slutske, W.S., Bierut, L.J., Statham, D.B., and Martin, N.G. Towards a molecular epidemiology of alcohol dependence: Analyzing the interplay of genetic and environmental risk factors. Brit. J. Psychiat. **178** (Suppl. No. 40): s33-s40, 2001.

Hesselbrock, M., Easton, C., Bucholz, K.K., Schuckit, M., and Hesselbrock, V. A validity study of the SSAGA—a comparison with the SCAN. Addiction **94:** 1361-1370, 1999.

Hill, S.Y., Shen, S., Lowers, L., and Locke, J. Factors predicting the onset of adolescent drinking in families at high risk for developing alcoholism. Biol. Psychiat. **48:** 265-275, 2000.

Hinckers, A.S., Laucht, M., Schmidt, M.H., Mann, K.F., Schumann, G., Schuckit, M.A., and Heinz, A. Low level of response to alcohol as associated with serotonin transporter genotype and high alcohol intake in adolescents. Biol. Psychiat. **60:** 282-287, 2006.

Jensen, P.S., Rubio-Stipec, M., Canino, G., Bird, H.R., Dulcan, M.K., Schwab-Stone, M.E., and Lahey, B.B. Parent and child contributions to diagnosis of mental disorder: Are both informants always necessary? J. Amer. Acad. Child Adolesc. Psychiat. **38:** 1569-1579, 1999.

King, K.M. and Chassin, L. Mediating and moderated effects of adolescent behavioral undercontrol and parenting in the prediction of drug use disorders in emerging adulthood. Psychol. Addict. Behav. **18:** 239-249, 2004.

King, S.M., Burt, S.A., Malone, S.M., McGue, M., and Iacono, W.G. Etiological contributions to heavy drinking from late adolescence to young adulthood. J. Abnorm. Psychol. **114:** 587-598, 2005.

Koopmans, J.R., Slutske, W.S., vanBaal, G.C., and Boomsma, D.I. The influence of religion on alcohol use initiation: Evidence for genotype X environment interaction. Behav. Genet. **29:** 445-453, 1999.

Kuperman, S., Schlosser, S.S., Kramer, J.R., Bucholz, K., Hesselbrock, V., Reich, T., and Reich, W. Developmental sequence from disruptive behavior diagnosis to adolescent alcohol dependence. Amer. J. Psychiat. **158:** 2022-2026, 2001a.

Kuperman, S., Schlosser, S.S., Kramer, J.R., Bucholz, K., Hesselbrock, V., Reich, T., and Reich, W. Risk domains associated with an adolescent alcohol dependence diagnosis. Addiction **96:** 629-636, 2001b.

Kuperman, S., Schlosser, S.S., Lidral, J., and Reich, W. Relationship of child psychopathology to parental alcoholism and antisocial personality disorder. J. Amer. Acad. Child Adolesc. Psychiat. **38:** 686-692, 1999.

Loeber, R., Green, S.M., Lahey, B.B., and Stouthamer-Loeber, M. Optimal informants on childhood disruptive behaviors. Devel. Psychopathol. **1:** 317-337, 1989.

Lonczak, H.S., Huang, B., Catalano, R.F., Hawkins, J.D., Hill, K.G., Abbott, R.D., Ryan, J.A., and Kosterman, R. The social predictors of adolescent alcohol misuse: A test of the social development model. J. Stud. Alcohol **62:** 179-189, 2001.

McGue, M. The behavioral genetics of alcoholism. Curr. Direct. Psychol. Sci. **8:** 109-115, 1999.

McGue, M., Iacono, W.G., and Krueger, R. The association of early adolescent problem behavior and adult psychopathology: A multivariate behavioral genetic perspective. Behav. Genet. **36:** 591-602, 2006.

Malone, S.M., Taylor, J., Marmorstein, N.R., McGue, M., and Iacono, W.G. Genetic and environmental influences on antisocial behavior and alcohol dependence from adolescence to early adulthood. Devel. Psychopathol. **16:** 943-966, 2004.

Mannuzza, S., Klein, R.G., Klein, D.F., Bessler, A., and Shrout, P. Accuracy of adult recall of childhood attention deficit hyperactivity disorder. Amer. J. Psychiat. **159:** 1882-1888, 2002.

Mannuzza, S., Klein, R.G., and Moulton, J.L., 3rd. Persistence of attention-deficit/hyperactivity disorder into adulthood: What have we learned from the prospective follow-up studies? J. Attent. Disord. **7:** 93-100, 2003.

Marshal, M.P. and Chassin, L. Peer influence on adolescent alcohol use: The moderating role of parental support and discipline. Appl. Devel. Sci. **4:** 80-88, 2000.

Marshal, M.P., Molina, B.S., Pelham, W.E., and Cheong, J. Attention-deficit hyperactivity disorder moderates the life stress pathway to alcohol problems in children of alcoholics. Alcsm Clin. Exp. Res. **31:** 564-574, 2007.

Martin, N.C., Levy, F., Pieka, J., and Hay, D. A genetic study of attention deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder and reading disability: Aetiological overlaps and implications. Int. J. Disab. Devel. Educ. **53:** 21-34, 2006.

Moffitt, T.E., Caspi, A., and Rutter, M. Strategy for investigating interactions between measured genes and measured environments. Arch. Gen. Psychiat. **62:** 473-481, 2005.

Molina, B.S. and Pelham, W.E., Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. J. Abnorm. Psychol. **112:** 497-507, 2003.

Molina, B.S., Pelham, W.E., Gnagy, E.M., Thompson, A.L., and Marshal, M.P. Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. Alcsm Clin. Exp. Res. **31:** 643-654, 2007.

Nilsson, K.W., Sjoberg, R.L., Damberg, M., Alm, P.O., Ohrvik, J., Leppert, J., Lindstrom, L., and Oreland, L. Role of the serotonin transporter gene and family function in adolescent alcohol consumption. Alcsm Clin. Exp. Res. **29:** 564-570, 2005.

Nurnberger, J.I., Jr., Wiegand, R., Bucholz, K., O'Connor, S., Meyer, E.T., Reich, T., Rice, J., Schuckit, M., King, L., Petti, T., Bierut, L., Hinrichs, A.L., Kuperman, S., Hesselbrock, V., and Porjesz, B. A family study of alcohol dependence: Coaggregation of multiple disorders in relatives of alcohol-dependent probands. Arch. Gen. Psychiat. **61:** 1246-1256, 2004.

Pierucci-Lagha, A., Covault, J., Feinn, R., Nellissery, M., Hernandez-Avila, C., Oncken, C., Morrow, A.L., and Kranzler, H.R. *GABRA2* alleles moderate the subjective effects of alcohol, which are attenuated by finasteride. Neuropsychopharmacology **30:** 1193-1203, 2005.

Prescott, C.A. and Kendler, K.S. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. Amer. J. Psychiat. **156:** 34-40, 1999.

Reiss, D. The interplay between genotypes and family relationships: Reframing concepts of development and prevention. Curr. Direct. Psychol. Sci. **14:** 139-143, 2005.

Robins, L.N. Deviant Children Grown Up: A Social and Psychiatric Study of Sociopathic Personality, Philadelphia, PA: Lippincott Williams & Wilkins, 1966.

Robins, L.N. A 70-year history of conduct disorder: Variations in definition, prevalence, and correlates. In: Cohen, P., Slomkowski, C., and Robins, L.N. (Eds.) Historical and Geographical Influences on Psychopathology, Mahwah, NJ: Lawrence Erlbaum, 1999, pp. 37-56.

Schuckit, M.A., Smith, T.L., Danko, G.P., and Isacescu, V. Level of response to alcohol measured on the Self-Rating of the Effects of Alcohol questionnaire in a group of 40-year-old women. Amer. J. Drug Alcohol Abuse **29:** 191-201, 2003.

Schuckit, M.A., Smith, T.L., Danko, G.P., Pierson, J., Hesselbrock, V., Bucholz, K.K., Kramer, J., Kuperman, S., Dietiker, C., Brandon, R., and Chan, G. The ability of the Self-Rating of the Effects of Alcohol (SRE) scale to predict alcohol-related outcomes five years later. J. Stud. Alcohol. Drugs **68:** 371-378, 2007.

Schuckit, M.A., Smith, T.L., and Tipp, J.E. The Self-Rating of the Effects of Alcohol (SRE) form as a retrospective measure of the risk for alcoholism. Addiction **92:** 979-988, 1997.

Schuckit, M.A., Windle, M., Smith, T.L., Hesselbrock, V., Ohannessian, C., Averna, S., Bauer, L., Kramer, J., Bucholz, K., and Sher, K.J. Searching for the full picture: Structural equation modeling in alcohol research. Alcsm Clin. Exp. Res. **30:** 194-202, 2006.

Sher, K.J., Grekin, E.R., and Williams, N.A. The development of alcohol use disorders. Ann. Rev. Clin. Psychol. **1:** 493-523, 2005.

Slutske, W.S., Heath, A.C., Dinwiddie, S.H., Madden, P.A., Bucholtz, K.K., Dunne, M.P., Statham, D.J., and Martin, N.G. Common genetic risk factors for conduct disorder and alcohol dependence. J. Abnorm. Psychol. **107:** 363-374, 1998.

Stice, E., Barrera, M., Jr., and Chassin, L. Relation of parental support and control to adolescents' externalizing symptomatology and substance use: A longitudinal examination of curvilinear effects. J. Abnorm. Child Psychol. **21:** 609-629, 1993.

Wallace, J.M., Jr., Brown, T.N., Bachman, J.G., and Laveist, T.A. The influence of race and religion on abstinence from alcohol, cigarettes and marijuana among adolescents. J. Stud. Alcohol **64:** 843-848, 2004.

White, H.R., Xie, M., Thompson, W., Loeber, R., and Stouthamer-Loeber, M. Psychopathology as a predictor of adolescent drug use trajectories. Psychol. Addict. Behav. **15:** 210-218, 2001.

Winter, T., Karvonen, S., and Rose, R.J. Does religiousness explain regional differences in alcohol use in Fnland? Alcohol Alcsm **37:** 330-339, 2002.

Wodarz, N., Bobbe, G., Eichhammer, P., Weijers, H.G., Wiesbeck, G.A., and Johann, M. The candidate gene approach in alcoholism: Are there gender-specific differences? Arch. Womens Ment. Hlth **6:** 225-230, 2003.

Young, S.E., Stallings, M.C., Corley, R.P., Krauter, K.S., and Hewitt, J.K. Genetic and environmental influences on behavioral disinhibition. Amer. J. Med. Genet. **96:** 684-695, 2000.

Zhou, Q., King, K.M., and Chassin, L. The roles of familial alcoholism and adolescent family harmony in young adults' substance dependence disorders: Mediated and moderated relations. J. Abnorm. Psychol. **115:** 320-331, 2006.