Dopamine D4 receptor gene exon III polymorphism associated with binge drinking attitudinal phenotype

Michael G. Vaughn[a,*], Kevin M. Beaver[b], Matt DeLisi[c], Matthew O. Howard[d], Brian E. Perron[e]

[a]School of Social Work, Department of Community Health, Division of Epidemiology, School of Public Health, Saint Louis University, 3550 Lindell Boulevard, St. Louis, MO 63103, USA
[b]College of Criminology and Criminal Justice, Florida State University, Tallahassee, FL, USA
[c]Department of Sociology, Iowa State University, Ames, IA, USA
[d]School of Social Work, University of North Carolina, Chapel Hill, NC, USA
[e]School of Social Work, University of Michigan, Ann Arbor, MI, USA

Abstract

Although binge drinking is a serious public health problem, relatively few studies have investigated the relationship between specific dopaminergic genes such as the dopamine D4 receptor (*DRD4*) and binge drinking attitudinal phenotypes. This study used the DNA subsample ($N = 233$, mean age 19.8, standard deviation, 0.89) of the National Longitudinal Study of Adolescent Health to investigate the association between a 48 base-pair variable number of tandem repeats in the *DRD4* gene and a measure of binge drinking. Multivariate regression models indicated that the 7-repeat (7R) allele of the exon III polymorphism is significantly positively associated ($\beta = 0.16$, $P < .05$) with binge drinking while controlling for low self-control and demographic variables. Findings were sturdy across race and gender. The present study provides unique evidence to the genetic underpinnings of binge drinking. Results suggest that the 7R allele may be an important contributor to the liability to binge drinking.   © 2009 Elsevier Inc. All rights reserved.

Keywords: Binge drinking; *DRD4*; Alcohol abuse; Self control; Alcohol; Genes and alcohol

Introduction

Binge drinking constitutes a serious public health threat. According to the National Institute on Alcohol Abuse and Alcoholism, binge drinking is a pattern of drinking that brings a person's blood alcohol concentration to 0.08 g percent or above, which typically occurs when males consume five or more drinks and females consume four or more drinks over a two-hour span. Like most forms of antisocial behavior, binge drinking is more prevalent among males than females and among those in late adolescence and early adulthood. A national epidemiologic study found that males accounted for 81% of binge drinking episodes and young adults between the ages of 18 and 25 accounted for nearly one-third of all binge drinking (Naimi et al., 2003). The national lifetime prevalence of binge drinking in the United States is estimated to be 17% (Town et al., 2006) and affects more than six million college students in the United States (Wechsler et al., 1995).

Binge drinking has been linked to a range of antisocial behaviors and other forms of psychopathology, including early-onset alcohol use (Burek and Wright, 2005) and co-occurring tobacco and marijuana use (Tucker et al., 2005). Using data from Russian respondents, Pridemore (2004) found links between binge drinking and violent criminal offenses, including homicide. The co-occurrence of binge drinking with other substance abuse and antisocial behaviors is suggestive of a general propensity that likely has a partially genetic etiology.

A number of genes have been linked to alcohol dependence (Batel et al., 2008; Covault et al., 2004; Devor and Cloninger, 1989; Dick et al., 2004; Edenberg et al., 2008; Fehr et al., 2006; Lappalainen et al., 2005; Reich et al., 1998; Wetherill et al., 2008; Xuei et al., 2006), but fewer candidate genes have been associated with binge drinking. Treutlein et al. (2006) found an association between two haplotype tagging single nucleotide polymorphisms (htSNPs) of the corticotropin-releasing hormone receptor 1 gene (*CRHR1*) and binge drinking, lifetime prevalence of alcohol use, and lifetime prevalence of alcohol intoxication. Herman et al. (2003) found a significant association between the serotonin transporter promoter polymorphism *5-HTTLPR* (*SLC6A4*) and frequency of binge drinking, frequency of drinking to intoxication, and greater quantity

* Corresponding author. Tel.: +1-314-977-2718.
E-mail address: mvaughn9@slu.edu (M.G. Vaughn).

of alcoholic drinks consumed during drinking occasions among a Caucasian college student sample. Severity of alcohol dependence has also been linked to the 3′ Taq1 A1 allele of the D2 dopamine receptor gene (*DRD2*) (Blum et al., 1993).

The 7-repeat (7R) allele in the third exon of the dopamine D4 receptor gene (*DRD4*) is hypothesized to be associated with the binge drinking phenotype based on its relationship with novelty seeking. Novelty seeking is a specific domain of the temperament model developed by Cloninger (1987) (Cloninger et al., 1993) that represents a dopaminergically modulated tendency toward exploratory activity and excitement in response to novelty. The personality traits associated with high novelty seeking are impulsiveness, fickleness, quick-tempered, excitability, and propensity to risk-taking. The profile of persons scoring high on novelty seeking is isomorphic to the profile of Type 2 alcoholics (Cloninger, 1987) and is hypothesized to be associated with the binge drinking phenotype. Research has yielded mixed findings vis-à-vis linkages between the *DRD4* variable number of tandem repeat (VNTR) and novelty seeking (cf. Ebstein et al., 1996; Sander et al., 1997); however, Laucht et al. (2007) recently found that males carrying the 7R allele consumed more alcohol per occasion and had greater lifetime rates of heavy drinking consistent with binge drinking. The present study is unique in that it evaluates the association between the 48 base-pair (bp) VNTR in exon III of the *DRD4* gene and binge drinking using data from a nationally representative sample of youth in the United States.

Methods

Data

Data for this study come from the DNA subsample of the National Longitudinal Study of Adolescent Health (Add Health; Udry, 2003). Detailed information about the data, including the sampling design, has been published elsewhere (Resnick et al., 1997). Briefly, Add Health is a study of a nationally representative sample of youths assessed across three waves of follow-up. The first wave of data was collected in 1994−1995 and included more than 20,745 participants. Approximately one-and-a-half-years later, the second wave of questionnaires was administered to 14,738 respondents. Finally, during 2001−2002, the third wave of data was collected. In total, 15,197 subjects completed the wave three surveys. Overall the Add Health data span seven years of adolescent and young adult development (Harris et al., 2003).

The Add Health data contain a rich array of items that measure the respondent's behavioral patterns, social relationships, and psychologic functioning. During wave three interviews, a subsample of respondents was selected to submit buccal cells for genotyping. To be eligible for this part of the study, the respondent had to have a sibling who was also an Add Health participant. More than 2,500 subjects were included in the DNA component to the Add Health study (Harris et al., 2003).

Measures

Binge drinking

At wave three, a subsample of all Add Health respondents was asked a series of questions pertaining to their binge drinking behaviors. Binge drinking was defined as consuming five or more drinks in a row at one time in the past 12 months on one or more occasions. This item used a gated question to identify a subgroup ($N = 233$) of add health participants as binge drinkers. Several items asked respondents about their attitudes pertaining to binge drinking. These items were used to construct a binge drinking phenotype. The introduction to these questions was as follows: ''The next questions are about 'binge drinking.' This is when a person drinks with the idea of getting drunk.'' Respondents were then queried about how favorably they feel about binge drinking, whether binge drinking allows them to have fun, whether binge drinking helps them relax, how positive they feel about their binge drinking, and how excited they get when thinking about binge drinking, how positive or negative it would be if you had lost your inhibitions as a result of binge drinking, if thinking about binge drinking how aroused and pumped up would that feel, how positive it would feel to lose control of yourself as a result of binge drinking, it would be pleasing to go out and binge drink. In total, nine items were included in the binge drinking scale (1 = strongly agree, 2 = agree, 3 = neither agree nor disagree, 4 = disagree, and 5 = strongly disagree). All of the items were standardized before constructing the scale. Higher scores on this scale reflected greater involvement in binge drinking and more favorable attitudes toward binge drinking ($\alpha = 0.89$). Table 1 displays descriptive statistics for all of the variables and scales.

Risk-taking propensity and low self-control

Risk-taking propensity and associated low self-control is a robust correlate of a wide range of antisocial behaviors (Pratt and Cullen, 2000), including binge drinking (Piquero et al., 2006). As a result, we included a nine-item low self-control scale that has been used previously (Vaughn et al., 2009). During wave three interviews, respondents were asked a series of questions that tapped their risk-taking propensity. Respondents were asked questions about whether they try things just for fun or thrills, whether they do things based on how they feel at the moment, and whether they often get so excited that they lose control, among others. Responses to each question were summed together to form the low self-control scale ($\alpha = 0.88$). Higher scores indicated lower levels of self-control.

Table 1
Descriptive statistics for add health sample variables and scales ($N = 233$)

	Mean	S.D.	Min.–Max.
Binge drinking	0.28	6.60	−8.01–9.40
Low self-control	25.55	8.80	9–45
Socioeconomic status	5.08	1.78	3–12
Age	19.80	0.89	18–23
	Frequency		Percentage
DRD4			
≥7R/≥7R	149		63.9
≥7R/<7R	71		30.5
<7R/<7R	13		5.6
Gender			
Male	126		54.1
Female	107		45.9
Race			
Caucasian	162		69.5
Nonwhite	71		30.5

Abbreviations: S.D., standard deviation; Min., minimum; Max., maximum; *DRD4*, dopamine D4 receptor; 7R, 7-repeat allele.

Socioeconomic status

To take into account the effects of socioeconomic status vis-à-vis the binge drinking phenotype, we created a 10-item socioeconomic status scale. During wave three interviews, respondents were asked about their financial and economic well-being. Specifically, they were asked whether they had a checking account, whether they had a credit card, whether they had a savings account, whether they had phone service in the past 12 months, whether they had not paid their rent or mortgage in full in the past 12 months, whether they had been evicted from their house in the past 12 months, whether they had not paid their gas, electric, or oil bill in full in the past 12 months, whether they had their utilities turned off in the past 12 months, whether they were unable to go to the doctor or hospital in the past 12 months because they could not afford it, and whether they could not go to the dentist in the past 12 months because they could not afford it. All of the items were coded dichotomously and responses to the 10 items were summed together to form the socioeconomic status scale ($\alpha = 0.65$). Higher scores on this scale corresponded to lower socioeconomic status.

Demographics

Three control variables were included in the statistical models to help prevent model misspecification. First, given that alcohol consumption varies across the life course, age was included in all models. Age was a continuous variable measured in years. Second, a dichotomous measure of gender (0 = female, 1 = male) was included to take into account gender differences in alcohol consumption. Third, race was measured as a dichotomous dummy variable (0 = Caucasian, 1 = nonwhite).

DRD4 polymorphism

Respondents who were part of the DNA subsample had their buccal cells genotyped for a polymorphism found in the *DRD4* gene. This polymorphism is 48 bp VNTR found on chromosome 11p15.5 in exon III of the gene encoding for the *DRD4*. The two proceeding primer sequences were used to amplify this polymorphism—forward, 5′-AGGACCCTCATGGCCTTG-3′ (fluorescently labeled), and reverse, 5′-GCGACTACGTGGTCTACTCG-3′. This genotyping process produced polymerase chain reaction products of 379, 427, 475, 523, 571, 619, 667, 715, 763, and 811 bps. Consistent with extant research (Hopfer et al., 2005), two groups were created by pooling together the 379 (2R), 427 (3R), 475 (4R), 523 (5R), and 571 (6R) bp alleles and by pooling together the 619 (7R), 667 (8R), 715 (9R), and 763 (10R) bp alleles. This polymorphism was then coded co-dominantly; Table 1 shows the distribution of alleles using this nomenclature. No deviations from Hardy–Weinberg equilibrium were detected ($\chi^2 = 1.33$, degree of freedom = 1, $P > .05$).

Statistical analysis

The analyses for this study were carried out in a series of linked steps. First, the association between the 7R allele of *DRD4* and binge drinking was examined by calculating ordinary least-squares (OLS) regression models. OLS regression is appropriate because the binge drinking scale is normally distributed. These models also tested the possibility that low self-control and socioeconomic status mediated the relationship between the 7R allele and binge drinking. The models were then estimated separately for males and females and for Caucasians and nonwhites to determine whether the effect of the 7R allele on binge drinking varied across different racial and gender categories. Following prior researchers analyzing the Add Health data (Beaver et al., 2007), all of the models used Huber/White standard errors to correct for nonindependence in some of the observations.

The final analytical sample consisted of $N = 233$ respondents. This sample size was arrived at because of three different criteria. First, only a subsample of respondents was genotyped ($N = 2,574$). Second, only a subsample of respondents was asked the binge drinking questions. Third, in some cases two monozygotic (MZ) twins from the same MZ twin pair were included in the sample. To provide conservative parameter estimates, one MZ twin from each MZ twin pair was randomly removed from the sample (Haberstick et al., 2005).

Results

The analysis began by examining the effects of the 7R allele, age, gender, and race on the binge drinking scale. Model 1 of Table 2 shows that the 7R allele maintained a positive and statistically significant association with binge drinking. This finding can be interpreted to mean that respondents who possess alleles of 7R or greater also have greater scores on the binge drinking scale. In the subsequent models, we examine whether the association between *DRD4* and binge drinking is mediated by low self-control and/or

Table 2
OLS regression models predicting binge drinking attitudinal phenotype for the full sample

Predictors	Model 1 b	Model 1 β	Model 2 b	Model 2 β	Model 3 b	Model 3 β	Model 4 b	Model 4 β
DRD4	1.65	.15*	1.79	.16*	1.68	.15*	1.78	.16*
	(0.63)		(0.59)		(0.64)		(0.60)	
Low self-control			0.29 (0.05)	.38*			0.28	.37*
	(0.05)	(0.05)						
Socioeconomic status					0.38	.10*	0.09 (0.05)	0.03
Age	−0.01	−0.00	0.08	0.01	−0.08 (0.15)	−.01	0.02 (0.16)	0.00
	(0.39)		(0.39)		(0.41)		(0.41)	
Gender	5.54	.42*	4.05	.31*	5.60	.42*	4.15	.31*
	(0.75)		(0.78)		(0.77)		(0.80)	
Race	−2.71	−.19*	−2.02	−.14*	−2.72	−.19*	−1.97	−.13*
	(0.84)		(0.81)		(0.85)		(0.83)	
N	233		229		228		224	

Abbreviations: OLS, ordinary least squares; *DRD4*, dopamine D4 receptor.
*$P < .05$, two-tailed tests.
Note: Huber/White standard errors in parentheses.

socioeconomic status. As can be seen, the association between the 7R allele and binge drinking remains statistically significant even when controlling for the effects of low self-control (Model 2), socioeconomic status (Model 3), and the combined effects of both of these measures (Model 4).

The next set of OLS models examined whether the relationship between the 7R allele and binge drinking was consistent between males and females and between Caucasians and nonwhites. All of these models (i.e., the models for males, females, Caucasians, and nonwhites) controlled for the effects of low self-control, socioeconomic status, and demographic characteristics. Table 3 displays the results of these models and shows that the 7R allele had a positive and statistically significant effect on males, Caucasians, and nonwhites. The association between binge drinking and the 7R allele for females was marginally significant ($P = .069$).

Discussion

Analysis of the Add health data indicated a robust association between the 48 bp VNTR in exon III of the *DRD4* gene and a measure of binge drinking while controlling for self-control and relevant demographic variables. Findings were stable across gender and race with one caveat; socioeconomic status was significantly associated with the full sample when low self-control was left out of the models. When low self-control was entered into the models socioeconomic status became nonsignificant, indicating that impulse-control possessed a stronger effect on binge drinking attitudes than socioeconomic status. Current findings suggest that *DRD4* may contribute to liability to binge drinking. Whether this susceptibility operates through a personality trait such as novelty seeking is unresolved. Caution regarding this potential association is in order given the conflicting findings in

Table 3
OLS regression models predicting binge drinking attitudinal phenotype by gender and by race

Predictors	Males b	Males β	Females b	Females β	Caucasians b	Caucasians β	Nonwhites b	Nonwhites β
DRD4	1.95	.18*	1.42	0.16[a]	1.43	.14*	2.86	.24*
	(0.92)		(0.77)		(0.67)		(1.35)	
Low self-control	0.30	.38*	0.26	.41*	0.31	.42*	0.21	.26*
	(0.08)		(0.07)		(0.06)		(0.11)	
Socioeconomic status	0.27	0.07	−0.07	−0.03	.07	.02	.10	0.02
	(0.23)		(0.23)		(0.19)		(0.35)	
Age	−0.17	−.03	0.31	0.05	−.07	−.00	0.18	0.03
	(0.55)		(0.59)		(0.52)		(0.70)	
Gender					4.06 (0.95)	.31*	4.80 (1.61)	.37*
Race	−1.94	−.13	−2.08	−.19*				
	(1.31)		(1.03)					
N	122		102		156		68	

Abbreviations: OLS, ordinary least squares; *DRD4*, dopamine D4 receptor.
*$P < .05$, two-tailed tests.
[a] $P = .069$.
Note: Huber/White standard errors in parentheses.

previous studies of the 7R allele, novelty seeking, and addiction (e.g., Lusher et al., 2001).

The present study results, however, should be considered in light of several study limitations. First, the measure of binge drinking was based on self-reports. Accompanying response bias of self-reports is important given disagreements about what constitutes binge drinking. In a related study, Laucht et al. (2007) found in a sample of 303 adolescents that a significant association between the 7R allele of *DRD4* and heavy drinking. However, this relationship was mediated by a measure of novelty seeking but only in male participants. Our findings are convergent with Laucht and colleagues with the limitation that our measure of binge drinking, although broadly similar, was clearly not identical. Furthermore, no measure of the personality dimension of novelty seeking was available to assess its mediating effect. Another limitation is that only a subsample of respondents was genotyped, which necessarily raises questions regarding the generalizability of the findings. Last, we should note that our subsample of "nonwhites" included respondents from a range of different racial and ethnic heritages. As a result, it is possible that the association between the 7R allele and binge drinking is the result of population stratification. Future research should explore this possibility in greater detail.

The impact of the 7R allele on binge drinking behavior remains to be determined. Future research elucidating the relationship between binge drinking and genetic polymorphisms such as the VNTR in the third exon of *DRD4* should use theoretically meaningful personality measures that capture intermediate traits that increase the susceptibility to binge drinking. As binge drinking is a major health concern, identifying the causal mechanisms that underpin it may improve prevention efforts.

Acknowledgments

References

Batel, P., Houchi, H., Daoust, N., Ramoz, M., Naassila, M., and Gorwood, P. (2008). A haplotype of the DRD1 gene is associated with alcohol dependence. Alcohol. Clin. Exp. Res. *32*, 567–572.

Beaver, K. M., Wright, J. P., DeLisi, M., Walsh, A., Vaughn, M. G., Boisvert, D., et al. (2007). A gene x gene interaction between DRD2 and DRD4 is associated with conduct disorder and antisocial behavior in males. Behav. Brain Funct. *30*, 3–30.

Blum, K., Noble, E. P., Sheridan, P. J., Montgomery, A., Ritchie, T., Ozkaragoz, T., et al. (1993). Genetic predisposition in alcoholism: association of the D2 dopamine receptor Taq1 B1 RFLP with severe alcoholics. Alcohol *10*, 59–67.

Burek, M. W., and Wright, J. M. (2005). Imported and inherent factors in relation to drinking, deviance, and crime: a new way of examining old behaviors of college students. J. Crim. Justice *28*, 107–137.

Cloninger, C. R. (1987). Neurogenetic adaptive mechanisms in alcoholism. Science *236*, 410–416.

Cloninger, C. R., Svrakic, D. M., and Przybeck, T. R. (1993). A psychobiological model of temperament and character. Arch. Gen. Psychiatry *50*, 975–990.

Covault, J., Gelernter, J., Hesselbrock, V., Nellissery, M., and Kranzler, H. R. (2004). Allelic and haplotype association of GABRA2 with alcohol dependence. Am. J. Med. Genet. B Neuropsychiatr. Genet. *129*, 104–109.

Devor, E. J., and Cloninger, C. R. (1989). Genetics of alcoholism. Annu. Rev. Genet. *23*, 19–36.

Dick, D. M., Edenberg, H. J., Xuei, X., Goate, A., Kuperman, S., Schuckit, M., et al. (2004). Association of GABRG3 with alcohol dependence. Alcohol. Clin. Exp. Res. *28*, 4–9.

Ebstein, R. P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., et al. (1996). Dopamine D4 receptor exon III polymorphism associated with the human personality trait of novelty seeking. Nat. Genet. *12*, 78–80.

Edenberg, H. J., Wang, J., Tian, H., Pochareddy, S., Xuei, X., Wetherill, L., et al. (2008). A regulatory variation in OPRK1, the gene encoding the k-opiod receptor, is associated with alcohol dependence. Hum. Mol. Genet. *17*, 1783–1789.

Fehr, C., Sander, T., Tadic, A., Lenzen, K. P., Anghelescu, I., Klawe, C., et al. (2006). Confirmation of association of the GABRA2 gene with alcohol dependence by subtype-specific analysis. Psychiatr. Genet. *16*, 9–17.

Haberstick, B. C., Lessem, J. M., Hopfer, C. J., Smolen, A., Ehringer, M. A., Timberlake, D., et al. (2005). Monoamine oxidase A (MAOA) and antisocial behaviors in the presence of childhood and adolescent maltreatment. Am. J. Med. Genet. *135B*, 59–64.

Harris, K. M., Florey, F., Tabor, J., Bearman, P. S., Jones, J., and Udry, J. R.. The national longitudinal study of adolescent health: research design [www document]. Available at. http://www.cpc.unc.edu/projects/addhealth/design. Accessed August 12, 2008.

Herman, A. I., Philbeck, J. W., Vasilopoulos, N. L., and Depetrillo, P. B. (2003). Serotonin transporter promoter polymorphism and differences in alcohol consumption behavior in a college student population. Alcohol Alcohol. *38*, 446–449.

Hopfer, C. J., Timberlake, D., Haberstick, B., Lessem, J. M., Ehringer, M. A., Smolen, A., et al. (2005). Genetic influences on quantity of alcohol consumed by adolescents and young adults. Drug Alcohol Depend. *78*, 187–193.

Lappalainen, J., Krupitsky, E., Remizov, M., Pchelina, S., Taraskina, A., Zvartau, E., et al. (2005). Association between alcoholism and gamma-amino butyric acid alpha2 receptor subtype in a Russian population. Alcohol. Clin. Exp. Res. *29*, 493–498.

Laucht, M., Bekcer, K., Blomeyer, D., and Schmidt, M. H. (2007). Novelty seeking involved in mediating the association between the dopamine D4 receptor gene exon III polymorphism and heavy drinking in male adolescents: results from a high-risk community sample. Biol. Psychiatry *61*, 87–92.

Lusher, J. M., Chnadler, C., and Ball, D. (2001). Dopamine D4 receptor gene (DRD4) is associated with novelty seeking (NS) and substance abuse: the saga continues. Mol. Psychiatry *6*, 497–499.

Naimi, T. S., Brewer, R. D., Mokdad, A., Denny, C., Serdula, M. K., and Marks, J. S. (2003). Binge drinking among U.S. adults. JAMA *289*, 1635–1636.

Pratt, T. C., and Cullen, F. T. (2000). The empirical status of Gottfredson and Hirschi's general theory of crime: a meta-analysis. Crime *38*, 931–964.

Piquero, A. R., Gibson, C. L., and Tibbetts, S. G. (2006). Does self-control account for the relationship between binge drinking and alcohol-related behaviors? Crim. Behav. Ment. Health *12*, 135–154.

Pridemore, W. A. (2004). Weekend effects on binge drinking and homicide: the social connection between alcohol and violence in Russia. Addiction *99*, 1034–1041.

Reich, T., Edenberg, H., Goate, A., Williams, J. T., Rice, J. P., Van Eerdewegh, P., et al. (1998). Genome-wide search for genes affecting the risk of alcohol dependence. Am. J. Med. Genet. *81*, 207–215.

Resnick, M. D., Bearman, P. S., Blum, R. W., Bauman, K. E., Harris, K. M., Jones, J., et al. (1997). Protecting adolescents from harm. Findings from the National Longitudinal Study on Adolescent Health. JAMA *278*, 823–832.

Sander, T., Harms, H., Dufeu, P., Kuhn, S., Rommelspacher, H., and Schmidt, L. G. (1997). Dopamine D4 receptor exon III alleles and variation of novelty seeking in alcoholics. Am. J. Med. Genet. *74*, 483–487.

Town, M., Naimi, T. S., Mokdad, A. H., and Brewer, R. D. (April 2006). Health care access among U.S. adults who drink alcohol excessively: missed opportunities for prevention. [serial online]. Prev. Chronic Dis. Available at. http://www.cdc.gov/pcd/issues/2006/apr/05_0182.htm. Accessed July 28, 2008.

Treutlein, J., Kissling, C., Frank, J., Wiemann, S., Dong, L., Depner, M., et al. (2006). Genetic association of the human corticotropin releasing hormone receptor 1 (*CRHR1*) with binge drinking and alcohol intake patterns in two independent samples. Mol. Psychiatry *11*, 594–602.

Tucker, J., Ellickson, P., Orlando, M., Martino, S., and Klein, D. (2005). Substance use trajectories from early adolescence to emerging adulthood: a comparison of smoking, binge drinking, and marijuana use. J. Drug Issues *35*, 307–332.

Udry, J. R. (2003). *The National Longitudinal Study of Adolescent Health (Add Health), Waves I and II, 1994–1996; Wave III, 2001–2002 [machine-readable data file and documentation]*. Chapel Hill, NC: Carolina Population Center. University of North Carolina at Chapel Hill.

Vaughn, M. G., Beaver, K. M., DeLisi, M., Perron, B. E., and Schelbe, L. (2009). Gene-environment interplay and the importance of self-control in predicting polydrug use and substance-related problems. Addict. Behav. *34*, 112–116.

Wechsler, H., Dowdall, G. W., Davenport, A., and Castillo, S. (1995). Correlates of college student binge drinking. Am. J. Public Health *85*, 921–926.

Wetherill, L., Schuyckit, M. A., Hesselbrock, V., Xuei, X., Liang, T., Dick, D. M., et al. (2008). Neuropeptide Y receptor genes are associated with alcohol dependence, alcohol withdrawal phenotypes and cocaine dependence. Alcohol. Clin. Exp. Res. *32*, 2031–2040.

Xuei, X., Dick, D., Flury-Wetherill, L., Tian, H. J., Agarwal, A., Beirut, L., et al. (2006). Association of the kappa-opioid system with alcohol dependence. Mol. Psychiatry *11*, 1016–1024.