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## Gene-Lifecourse Interaction for Alcohol Consumption in Adolescence & Young Adulthood: Five Monoamine Genes

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### Abstract

Association analysis has suggested that common sequence variants of genes that affect monoamine function can affect substance use and abuse. Demonstration of these associations has been inconsistent because of limited sample sizes and phenotype definition. Drawing on the life course perspective, we predicted a stronger association between the polymorphisms in *5HTT*, *DAT1*, *DRD4*, *DRD2*, and *MAOA* and alcohol consumption in young adulthood than adolescence. This analysis tested for the gene-lifecourse interaction for the frequency of alcohol consumption in a nationally representative non-alcohol dependent sample of 2,466 individuals that were visited during adolescence and young adulthood for four times between 1994 and 2002. All five genes are significantly associated with the frequency of alcohol consumption, with the genotype effects ranging 7–20% of the mean score of alcohol consumption and their P-values being 0.014, 0.0003, 0.003, 0.007, 0.005, and 0.003, respectively. The association is only observed in the life stage of young adulthood and not in adolescence. This analysis has demonstrated the potential usefulness of the life course perspective in genetic studies of human behaviors such as alcohol consumption.

### Keywords

alcohol use; *DRD4*; *DRD2*; *5HTT*; *DAT1*; *MAOA*; life course

## INTRODUCTION

The life course approach attempts to understand human behavior in a social context that changes continually throughout one's life span (Elder 1974, 1999; Elder 1998). The changing social context can result from either a regular life-cycle transition such as leaving home and entering college or an irregular historical event such as the Great Depression. Peer influence is considered among the most important forces in shaping adolescents' behavior (Harris 1995). Adolescents spend twice as much of their time with peers outside the family as do they with parents (Brown 1990). Peer influence was often found critical for the initiation and maintenance of risk behavior such as substance use, drinking, and smoking (Brown and Theobald 1999; Billy, Rodgers, and Udry 1984; Billy and Udry 1985; Ennett and Bauman 1994; Yamaguchi and Kandel 1987; Rose 1998). The intensity of peer

influence seems to change over the life course. The presence of strong peer influence in adolescence contrasts with relatively weakened peer influence in young adulthood. The critical importance of peer influence in adolescence suggests that genotype effects on alcohol use in adolescence may be less prominent than in young adulthood.

Twin studies have also lent support for the gene-lifecourse hypothesis. Twin studies carried out in Australia, Finland, the Netherlands, and the United States consistently demonstrate that the initiation of alcohol use in mid-adolescence is associated predominantly with environmental rather than genetic factors and that genetic influences on alcohol use are increasing in importance starting in late adolescence (Heath and Martin, 1988; Koopmans and Boomsma, 1996; Prescott et al., 1994; Rose et al., 1999; Rose et al., 2001).

Monoamine neurotransmitters are released by a small fraction of neurons that typically have processes that extend throughout the nervous system. Monoamines act on receptors through complex signal transduction processes to modulate the function of neurons both transiently and through long-term changes in gene expression. Many genes code for proteins that directly and indirectly play a role in monoamine neurotransmission, including synthetic enzymes, receptors and transporters. The drugs that bind to some of these gene products modulate behavior and are frequently abused. Implicit in this work and for many other studies is the hypothesis that the polymorphisms in genes that play a role in monoamine neurotransmission could affect behavior including drinking. Table 1 lists 5 genes and one polymorphism for each of the 5 genes that have been previously implicated as affecting alcohol use (*e.g.*, Herman et al. 2005; Limosin et al. 2004; Munafo et al. 2005; Noble et al. 1994; Hutchison et al. 2002) and other risky behaviors and that were genotyped for this study. These polymorphisms are thought to affect gene expression or be in disequilibrium with variation that affects gene expression (*DAT1*, Mill et al. 2002; *MAOA*, Sabol et al. 1998; *5HTT*, Lesch et al. 1996; *DRD2*, Noble et al. 1994).

The serotonin transporter (*5HTT*, locus symbol *SLC6A4*) moves released serotonin back into presynaptic terminals and is the site of action of selective serotonin reuptake inhibitors (SSRIs). The association of *5HTT* promoter VNTR alleles with alcohol and abuse of other drugs has been inconsistent (Dick and Foroud 2003; Munafo et al. 2004; Herman et al. 2003; Nilsson et al. 2005; Hopfer et al 2005). The dopamine transporter (*DAT1* known by the locus symbol *SLC6A3*) acts to take released dopamine back up into presynaptic terminals and is inhibited by cocaine. Polymorphisms in this gene have been associated with alcohol withdrawal seizures or delirium (Sander et al. 1997) and may lead to more severe withdrawal symptoms in chronically intoxicated alcoholics (Schmidt et al. 1998). The 48-base-pair exon-3 dopamine-D4-receptor (*DRD4*) polymorphism affects binding properties for ligands for the receptor (Van Tol et al. 1992). The *DRD4* coding sequence has been extensively examined since the studies by Benjamin et al (1996) and Ebstein et al (1996) who reported the association with novelty seeking behavior. Dozens of papers have reported associations and non-replications with aspects of personality, psychiatric diseases (Lopez et al. 2005), attention deficit disorder (Faraone et al. 2001) and substance abuse (reviewed in Paterson et al. 1999). The dopamine D2 receptor (*DRD2*) is a G-coupled receptor. Blum et al (1990) reported an association between a 3' non-coding sequence polymorphism, called TaqIA (dbSNP ID rs112594) and alcoholism. Others have not been able to replicate these

results (Buckland 2001; Gelernter et al. 1993). The X-linked Monoamine Oxidase A (*MAOA*) is an important enzyme in the monoamine degradation pathway. Several investigators have found suggestive associations with alcohol use disorders (Herman et al. 2005; Parsian et al. 1995; Parsian et al. 2003; Saito et al. 2002; Samochowiec et al. 1999).

The goal of this study is to examine the genes by life-course interactions for alcohol use in adolescence and young adulthood, using the DNA sample (N=2,466) of the National Longitudinal Study of Adolescent Health (Add Health). We hypothesize that the associations between the genetic variants and alcohol consumption tend to be stronger in young adulthood than in adolescence among the general or non-alcohol dependent population. Figure 1 illustrates our hypothesis. The curves in Figure 1 describe the typical age pattern of alcohol consumption in adolescence and young adulthood in the United States (Chen and Kandel, 1995; Kandel and Logan, 1984). The hypothesis of gene-lifecourse interaction suggests that the differential use of alcohol by genotype is likely to appear starting from early young adulthood.

## MATERIALS AND METHODS

### Subject

The data source for our analysis is the sibling sub-sample of about 2,466 participants in Add Health, a school-based study of the health-related behaviors of adolescents in grades 7–12 (aged 12–18) in 1994–5 (Harris et al. 2003). Add Health is based on a stratified sample of 132 high schools and middle schools in the United States; the schools were stratified by region, urban/rural, school type (public, private, parochial), ethnic mix, and size. The Add Health participants were interviewed four times during a 8-year period in 1994 (In-School), 1994–5 (Wave I In-Home), 1995–6 (Wave II In-Home), and 2001–2 (Wave III In-Home). Data on alcohol consumption was collected on each of the four occasions. Our analysis uses the sibling sample of Add Health because DNA measures are currently only available for this subset of the Add Health respondents. Our sibling sample is composed of monozygotic twins, dizygotic twins, and full biological siblings.

A total of 2,466 individuals contributed 1–4 observations of alcohol consumption. Of the 2,466 individuals, 1,527 contributed one observation at the In-School Wave; 2,430, 2,298, and 2,434 contributed one observation at the Waves I, II, and III surveys, respectively. Of the 2,466 individuals, about 60%, 18%, 14.3%, and 7.6% are White, African, Hispanic, and Asian Americans, respectively. Our data have measures on alcohol use taken at ages from 13 to 26 covering the life stages of adolescence and young adulthood. The Add Health Study has received written informed consent from all participants and the institutional IRB at the University of North Carolina, Chapel Hill, has approved this study.

### Measures of Adolescent Alcohol Use

At the In-School as well as the three subsequent Home interviews, respondents were asked about their frequency of alcohol use. At the In-School interview, respondents were asked, “During the past twelve months, how often did you drink beer, wine, or liquor?” In the Home interviews, respondents answered the question, “During the past twelve months, on

how many days did you drink alcohol?" In all Waves, respondents' answers were recorded as 0, never; 1, one or two days in the past twelve months; 2, once a month or less; 3, two or three days a month; 4, one or two days a week; 5, three to five days a week; or 6, everyday or almost everyday. This seven point scale is simplified in the analysis to a six point scale in which categories 1 and 2 of the original measure are collapsed. Thus, the drinking score of an individual is recorded as 0, 1, 2, 3, 4, or 5 for never, once in a month or less, 2–3 times in a month, 1–2 times a week, 3–5 times a week, or almost everyday, respectively. At the In-School Wave, the responses were obtained via self-administered paper-and-pencil survey. To protect confidentiality and reduce non-responses, this section of the interview was self-administered by audio-CASI (Computer Assisted Self Interview) at the three Home interviews. The sensitive questions were read to respondents by means of audio headphones. Respondents were given instructions on how to complete their answers on the computer.

### DNA Preparation and Genotyping

At Wave III in 2002, in collaboration with the Institute for Behavioral Genetics (IBG) in Boulder, Colorado, Add Health collected, extracted, and quantified DNA samples from the sibling sub-sample. Genomic DNA was isolated from buccal cells using a modification of published methods (Lench et al. 1988; Meulenbelt et al. 1995; Spitz et al. 1996; Freeman et al. 1997). All of the methods employed Applied Biosystems instruments and reagents. Microsatellite and VNTR polymorphisms were done using fluorescent primers that were analyzed on an ABI capillary electrophoresis instrument. Single nucleotide polymorphisms were analyzed using an ABI Sequence Detection System and 5'-nuclease (Taqman®) methodology. The additional details on DNA collection and genotyping are at Add Health website (Smolen and Hewitt, <http://www.cpc.unc.edu/projects/addhealth/>).

A series of  $\chi^2$  tests for each polymorphism and for each self-reported ethnic group (European, African American, Hispanic, and Asian) reveals no deviation from the Hardy-Weinberg equilibrium.

### Analytical Strategies

To test the hypothesis of gene-lifecourse interaction for alcohol consumption in adolescence and young adulthood, a three-step analytical strategy is adopted. The first step is a contingency table analysis in which the means of alcohol consumption across genotypes and life stages (adolescence vs. young adulthood) were compared. The second step is a mixed regression model (Searle 1971; Searle, Casella, and McCulloch 1992) that adjusts for race/ethnicity and gender and for correlation among siblings and repeated measures in the data. The third step addresses potential bias from population stratification.

In the rest of this section, we elaborate on the second and third steps. Our sample consists of twins and siblings as well as the repeated observations of the same individual over different Add Health Waves and these observations are not independent. The mixed model has long been established in the statistical literature for the analysis of data that are not independent. Several major statistical packages (e.g., SAS and STATA) include the mixed model as a standard procedure. The following equation describes the mixed model of alcohol consumption

$$Alcohol_{jii(s)} = \beta'X_{ji} + \beta_1 genotype_{ji} + \beta_2 adult_{jii} + \beta_3 (genotype_{ji} * adult_{jii}) + u_{j0(s)} + v_{ji} + e_{jii(s)} \quad (1)$$

where  $j, i$ , and  $t$  index sibling cluster or pair, individual, and Add Health Waves, respectively;  $s=m, d, \text{ or } f$  indicates whether the sibling cluster or pair are MZ twins, DZ twins, or full biological siblings; *adult* is a dummy variable taking the value of one when the measure of alcohol consumption is taken at age 19 or older and the value of zero when the measure is taken at age younger than 19; and  $(genotype_{ji} * adult_{jii})$  is an interaction term between genotype and life stage. The size and significance level of the coefficient for the interaction term is a direct test of the gene-lifecourse hypothesis. The model allows the random effect at the sibling cluster level and the measure level to vary by type of sibling cluster because the strength of the correlation varies considerably by type of sibling clusters ( $s$ ). Conditional on the three random intercepts at the level of sibling clusters and one random intercept at the individual level, the siblings and repeated measures are assumed to be independent. The models were estimated by SAS (SAS Institute 1965–2005).

We used three strategies to address the potential impact of population structure. First, we adjusted for self-reported race/ethnicity in all regression analysis so that comparisons across genotypes are made within each race/ethnicity. Tang et al. (2005) showed a near-perfect correspondence between the four self-reported ethnic categories (European Americans, African Americans, East Asians, and Hispanics) and the categories determined by 326 microsatellite markers.

The second strategy addressed this concern by re-estimating the models after eliminating individuals who reported belonging to more than one racial category. In keeping with the new Census policy, Add Health respondents were allowed to mark as many ethnicity categories as they felt applied to them (Harris et al. 2003). About 7.5%, 3.5%, and 0% of African, Hispanic, and White participants marked more than one category, respectively. Of those who marked more than one ethnic category, the large majority (86%) marked two ethnic categories and 12% marked three ethnic categories.

As a third strategy, we applied Allison et al. (1999)'s procedure to test for possible population stratification. Following the idea used in the development of sibship tests of linkage and association (Curtis 1997; Boehnke and Langefeld 1998; Spielman and Ewens 1998), Allison et al. reasoned that the probabilities of genotypes of siblings depended entirely on parental genotypes and that controlling for the effects of sibship would be equivalent to controlling for parental genotypes. Indexing sibships by  $j$ , individuals by  $k$ , and genotypes by  $i$ , they proposed a procedure that can be written as a mixed model

$$Y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + e_{ijk}, \quad (2)$$

Where  $\alpha_i$ , or the effect of genotype  $i$ , is assumed to be fixed;  $\beta_j$ , or the effect of sibship  $j$ , is assumed to be random; and  $(\alpha\beta)_{ij}$  is an interaction term specifying the dependence of the

random effect of sibship on genotype. The conditioning on sibship in the model eliminates the possible confounding of population stratification. This model is a special case of the mixed model (Searle 1971; Searle, Casella, and McCulloch 1992).

## RESULTS

### Contingency Table Analysis

Table 2 shows the mean score of alcohol use by genotype and life stage. The two life stages of adolescence and young adulthood are defined as the age range of 13–18 and 19–26, respectively. Table 2 provides comparisons of mean alcohol consumption across genotypes within each life stage. The Table also gives genotype frequency in proportion for each polymorphism examined and number of observations used for each comparison. Alcohol consumption appears to be associated with all the five monoamine genes considered in this analysis; however, the association consumption seems to mainly exist in young adulthood and not in adolescence.

In adolescence, of the six comparisons across genotypes, only the 3R allele of the *DRD4* gene seems to be associated with alcohol use (1.236 vs. 1.038). In young adulthood, the mean alcohol use seems to differ by genotype in all comparisons except the one concerning *MAOA* among the females. The comparison with regards to *MAOA* was carried out separately for males and females because of the X-linked *MAOA*. The genotype effect on alcohol consumption ranges from 0.104 for serotonin transporter (*5HTT*) to 0.414 for the dopamine D4 receptor (*DRD4*), representing about 5–20% of the mean score of alcohol use. When a rare genotype was not the focus of comparison, it would be included in the category that was used as the reference category in the regression analysis. Because of the sibling clustering and repeated observations in the data, standard *t* tests are not valid for these comparisons. In the next section, results are presented from significance tests conducted within the mixed-model framework that has taken into consideration the correlation in the data.

### Regression Analysis

Table 3 presents the coefficients and their P-values in eight separate regression models. Except for the first “No genes” model and the last “All genes” model, each of these models includes a main genotype effect and an interaction term between genotype and the dummy variable (Age = 19) for young adulthood. *MAOA* is again analyzed separately for males and females separately. The last “All genes” model includes simultaneously the main effects and the interaction effects of all the polymorphisms under consideration in this analysis except *MAOA*.

The “No genes” model shows that the alcohol consumption in the life stage of young adulthood is up 1.09 relative to that in adolescence, that the males tend to consume more alcohol than the females, and that African, Hispanic, and Asian Americans consume considerably less alcohol than White Americans. These non-gene effects generally hold in the “genetic” models. In the “*5HTT*” model, those with one or two copies of the short allele (Any S) do not differ (P=0.22) in alcohol consumption from those with the L/L (long/long)

genotype in adolescence; in contrast, in young adulthood, those with the Any-S genotype score 0.144 points higher than those with the L/L genotype ( $P=0.014$ ). This pattern of gene-lifecourse interaction is observed in every polymorphism examined in this analysis.

In the “*DAT1*” model, only in young adulthood do individuals with the Any-9R genotype score significantly higher (0.206;  $P=0.0003$ ) than individuals with the 10R/10R genotype. The “*DRD4*” model compares two relatively rare genotypes (Any 3R and 7R/7R) against the by-far the most frequent genotype of Any 4R; both Any 3R and 7R/7R consume more alcohol than Any 4R only in young adulthood (0.47,  $P=0.003$ ; 0.46,  $P=0.007$ , respectively). The models of “*DRD2*” and “*MAOA* (male)” reveal the same pattern of genotype effects. In the model of “*MAOA* (female)”, Any 3R is not related to alcohol use in either adolescence or young adulthood. These regression results are remarkably consistent with those from the contingency table analysis in Table 2. In the “All-genes” model in which the four polymorphisms are considered simultaneously, all the interaction coefficients and their P-values remain similar to those in the models that consider only one gene at a time, suggesting little correlation among these genetic polymorphisms with respect to alcohol use. To test for the gene-gene interactions more formally, we estimated a number of models containing the 2-way gene-gene interactions. These tests yielded a possible interactive effect between the 7R/7R of *DRD4* and Any A1 of *DRD2* ( $P=0.02$ ). Given the large number of tests carried out, however, we consider this result suggestive.

To address population stratification, we carried out the three strategies described earlier. Race/ethnicity was added as a control in all regression models estimated (Table 3). The set of models were re-estimated after eliminating individuals who designated themselves as multi-racial/ethnic. The results remained essentially unchanged (data not shown). We estimated Allison models (1999) that include one random effect at the sibling level and a second random effect at the individual level plus the required interaction parameters; our results in these models do not differ substantively from those presented in Table 3 (data not shown).

## DISCUSSION

The contingency table analysis has yielded exploratory evidence for the gene-lifecourse interaction hypothesis from all the five polymorphisms examined. The frequency of alcohol consumption seems to differ by genotype primarily in the life stage of young adulthood, in which all the five genetic variants appear to have an effect on alcohol consumption with the genotype effects ranging 5–20% of the mean alcohol consumption. The mixed model regression analysis further tests the hypothesis after adjusting for the effects of life stage, gender, and race/ethnicity and after taking into account the correlation among the siblings and repeated observations in the sample. The regression results have proved to be quite consistent with those from the analysis of contingency table. While none of the genetic variants are related to alcohol consumption in adolescence, all of them are associated with alcohol consumption in young adulthood, with the genotype effects of 0.144, 0.20, 0.47, 0.46,  $-0.15$ , and  $-0.25$ , respectively, ranging 7–20% of the mean score of alcohol consumption. The corresponding P-values are 0.014, 0.0003, 0.003, 0.007, 0.005, and 0.003, respectively. These results remain essentially unchanged when all the polymorphisms

(except *MAOA*) are included in one single model, implying little correlation among them. The last 'all genes' model suggests that genotypes can make substantial differences in alcohol consumption because a single individual can possess a number of higher-risk alleles. The effect of these higher-risk alleles can add up.

All the five polymorphisms in the five monoamine genes have been previously implicated in alcohol-use related measures. The studies of Herman et al. (2003) and Munafó et al. (2005) are two of the few that have investigated the role of the *5HTT* gene in alcohol consumption in non-alcohol dependent populations. Herman et al. reported an association between the short form of the *5HTT* gene and elevated alcohol consumption in a general college student population (mean age=19.1). Using a general adult population (aged 33–73), Munafó et al. showed that the short allele of the *5HTT* gene was significantly associated with increased alcohol consumption. This analysis demonstrates an increase in alcohol consumption among young adults with at least one copy of the short allele of the *5HTT* gene.

Two studies (Sander et al. 1997; Schmidt et al. 1998) reported a significant higher prevalence of the 9-repeat (9R) of the *DAT1* gene among alcoholics displaying withdrawal syndromes than among matched nonalcoholics. This analysis shows an approximate 10% increase ( $P=0.0004$ ) in the score of alcohol consumption among young adults with one or two copies of 9R allele of the *DAT1* gene.

The *in vitro* studies suggest that the exon III *DRD4* 7-repeat allele (7R) has decreased affinity for dopamine and transmits weaker intracellular signals in comparison to the most common 4R exon III allele (Asghari et al, 1995). A number of studies have reported the association of the 7R of *DRD4* with novelty seeking behavior, attention deficit disorder, and substance abuse. This analysis finds an approximate 20% increase in alcohol consumption among young adults with either two copies of 7R or one copy of 3R of the *DRD4* gene ( $P=0.007$  or  $0.003$ , respectively) relative to the 4R allele.

The *DRD2* gene has long been implicated in alcoholism (Blum et al. 1990). A meta-analysis of the published studies using Caucasians showed a significantly higher prevalence in the *DRD2* A1 allele among alcoholics than among the controls (Noble 2003). This analysis uses the A2/A2 genotype as the reference category and finds that young adults with the A1/A2 or A1/A1 genotype are associated with decreased alcohol consumption (about 8% reduction,  $P=0.006$ ). Hopfer et al. (2005), using Add Health Waves I-III data, reported a significant association between the usual number of drinks consumed per drinking episode (vs our measure of drinking frequency) and the same *DRD2* polymorphism at Wave III, but not at Waves I-II. The respondents were aged 12–18, 13–19, and 19–26 at Waves I-III, respectively.

Previous association studies concerning *MAOA* have produced inconsistent results regarding the direction of the associations. Samochowiec et al. (1999) reported a higher prevalence of the 3R allele (the *MAOA* low activity allele) among dissocial alcoholics. Saito et al. (2002), based on a Finnish male sample of alcoholics, detected no association between alcoholics and the *MAOA* alleles. Parsian et al. (2003) found a higher frequency of the 3R allele in their controls than alcoholics. The findings in this analysis are consistent with Parsian et



al.'s. This analysis uses a sample from the general population and detects a decrease in alcohol consumption among young adults for those with the 3R allele ( $P=0.0039$ ).

Our study has a number of limitations. Like gender and ethnicity, life course is a proxy variable under which a host of other factors could be operating. We briefly discussed the difference in the intensity of peer influence between adolescence and young adulthood as a possible explanation for the gene-lifecourse interactions. Other factors such as the degree of parental control and mental maturity across the two life stages could be important. Peer influence may not be as straightforward as it appears to be. Individuals may, to various extents, select friends; they and their friends may share certain genetic background (Guo 2006).

This study is only able to investigate one polymorphism in each of the five genes. An alternative explanation to these findings is that other functional variants within the five genes or in other genes on the same chromosome are in linkage disequilibrium with the genetic variants evaluated herein. However, it is biologically plausible that some of these genetic variants directly affect alcohol consumption. Because actual alcohol consumption is difficult to observe, this study relies on self-reported information, which can be biased or imprecise. This study is also limited because some of the genetic variants such as the 7R/7R and Any 3R of the *DRD4* gene are quite rare in spite of the reasonably large sample. It is possible that some of the findings related to the rare variants are attributable to chance. A follow-up study for the Add Health project (Wave IV of Add Health) is scheduled to collect DNA data from its entire sample of about 17,000 individuals, creating an opportunity to replicate these findings in an even much larger population based study.

In conclusion, our analysis of the 2,466 individuals has produced unambiguous evidence supporting the gene-lifecourse interaction hypothesis. Our data show that all the five genes examined (*5HTT*, *DAT1*, *DRD4*, *DRD2*, and *MAOA*) are significantly associated with the frequency of alcohol consumption; the association is only observed in the life stage of young adulthood and not in adolescence. Our analysis has demonstrated the potential usefulness of the life course perspective in genetic studies of human behaviors such as alcohol consumption.

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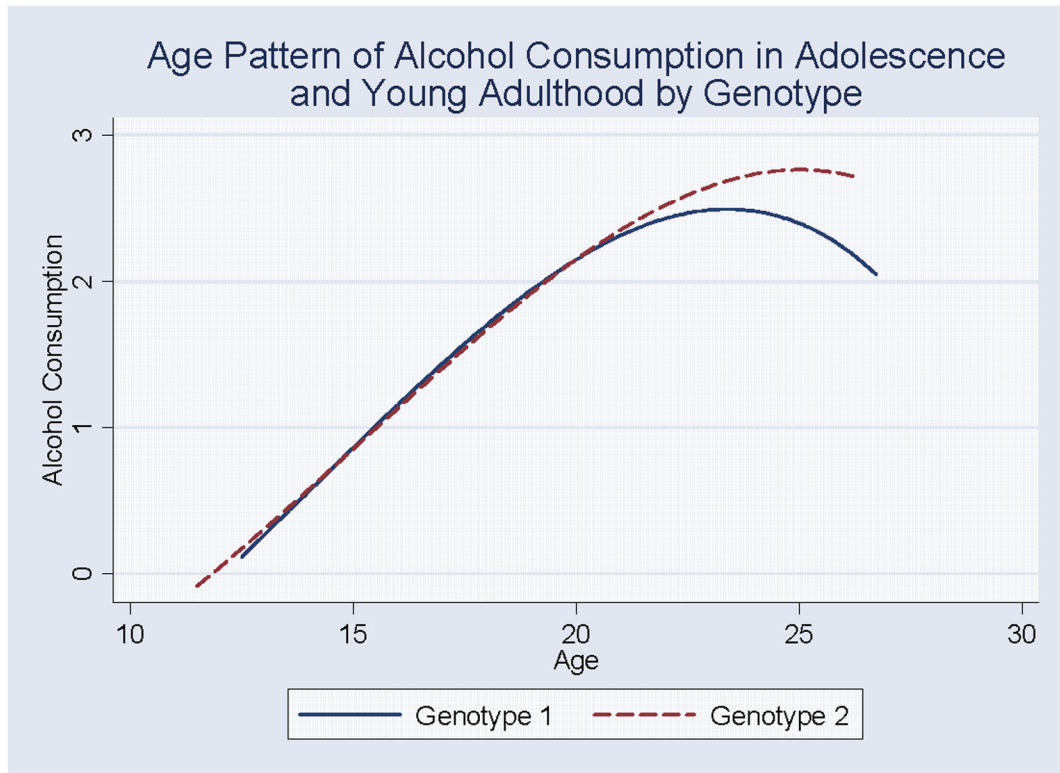
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**Figure 1.**  
Age pattern of alcohol consumption in adolescence and young adulthood by genotype.

Table 1.

Five genetic polymorphisms analyzed in the project

Gene	Description	Polymorphism	Association with alcohol-related & other behaviors	Selected References
<i>5HTT</i> (17q11.1–12)	Member of the 6 serotonin transporter family; limit level and duration of serotonin receptor activation	44 bp VNTR in 5' regulatory region	Association with alcohol use	Herman et al. (2003); Munafó et al. (2005)
<i>DAT1</i> (5p15.3)	Mediates uptake of dopamine into neurons; site of action of methylphenidate	3' UTR 40bp VNTR	Association with alcohol use	Sander et al. 1997; Schmidt et al. 1998
<i>DRD4</i> (11p15.5)	Member of the D2 receptor family; inhibits adenylylate cyclase, decreases C-AMP and is inhibitory	Exon 3 48-bp VNTR	Association with ADHD & substance abuse	Grady et al. (2003); Paterson et al. (1999)
<i>DRD2</i> (11q23)	Inhibits adenylyl cyclase, thereby down-regulating cAMP	3' TaqIA	Association with alcohol use	Noble 2003; Hopfer et al. 2005
<i>MAOA-u VNTR</i> (Xp11.3–11.4)	Responsible for degradation of dopamine, serotonin, and norepinephrine	30 bp VNTR in 5' regulatory region	Association with alcohol use	Herman et al. 2005; Parsian et al. 2003

**Table 2.**

Comparing mean score of alcohol use across genotypes and life course stages

Gene	Genotype	Genotype Frequency	Mean (age 13–18)	No. of Observations	Mean (age 19–26)	No. of Observations
<i>5HTT</i>	Any S	0.66	1.052	3942	<b>2.184</b>	1835
	L/L	0.34	1.050	2020	<b>2.08</b>	941
<i>DAT1</i>	Any 9R	0.38	1.036	2256	<b>2.269</b>	1051
	10R/10R	0.62	1.061	3706	<b>2.07</b>	1725
<i>DRD4</i>	7R/7R	0.043	1.004	265	<b>2.306</b>	121
	Any 3R	0.060	<b>1.236</b>	365	<b>2.548</b>	157
<i>DRD2</i>	Any 4R	0.83	<b>1.038</b>	4960	<b>2.134</b>	2318
	Any A1	0.45	1.055	2664	<b>2.07</b>	1266
	A2/A2	0.55	1.049	3298	<b>2.214</b>	1510
<i>MAOA (m)</i>	3R/Others	0.41	1.166	1125	<b>2.367</b>	545
	All else	0.59	1.122	1649	<b>2.54</b>	779
<i>MAOA (f)</i>	Any 3R	0.60	0.98	1894	1.864	889
	All else	0.40	0.96	1295	1.837	563



**Table 3.** Gene-Lifecourse interaction for alcohol use in adolescence and young adulthood: regression estimates using five monoamine genes

Predictors	No genes		5HTT		DAT1		DRD4		DRD2		MAOA (male)		MAOA (female)		All genes	
	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p
Intercept	1.087	0.0001	1.129	0.0001	1.125	0.0001	1.081	0.0001	1.051	0.0001	1.277	0.0001	1.082	0.0001	1.125	0.0001
Age 19	1.095	0.0001	0.999	0.0001	1.017	0.0001	1.086	0.0001	1.663	0.0001	1.455	0.0001	0.859	0.0001	0.985	0.0001
Male	0.319	0.0001	0.320	0.0001	0.321	0.0001	0.319	0.0001	0.320	0.0001					0.322	0.0001
Black	-0.522	0.0001	-0.527	0.0001	-0.525	0.0001	-0.514	0.0001	-0.53	0.0001	-0.588	0.0018	-0.183	0.028	-0.520	0.0002
Hispanic	-0.251	0.0019	-0.25	0.002	-0.253	0.0017	-0.242	0.0026	-0.259	0.0016	-0.245	0.0612	-0.232	0.131	-0.259	0.0017
Asian	-0.657	0.0001	-0.654	0.0001	-0.663	0.0001	-0.646	0.0001	-0.668	0.0001	-0.609	0.0057	-0.742	0.027	-0.660	0.0001
Any S			-0.063	0.2215											-0.062	0.22
Any S * Age 19			<b>0.144</b>	<b>0.0145</b>											<b>0.145</b>	<b>0.013</b>
Any 9R					-0.099	0.0464									-0.098	0.047
Any 9R * Age 19					<b>0.206</b>	<b>0.0003</b>									<b>0.198</b>	<b>0.0006</b>
Any 3R							0.063	0.642							0.066	0.62
Any 3R * Age 19							<b>0.470</b>	<b>0.003</b>							<b>0.456</b>	<b>0.0040</b>
7R/7R							-0.106	0.470							-0.107	0.46
7R/7R * Age 19							<b>0.461</b>	<b>0.007</b>							<b>0.466</b>	<b>0.0068</b>
Any A1									0.086	0.082					0.084	0.091
Any A1 * Age 19									<b>-0.156</b>	<b>0.005</b>					<b>-0.151</b>	<b>0.0069</b>
Any 3R											0.114	0.128	0.114	0.079		
Any 3R * Age 19											<b>-0.255</b>	<b>0.0039</b>	0.0383	0.596		
-2 Log likelihood	30173		30167		30160		30159		30165		14652		15314		30131	
N of persons	2466		2466		2466		2466		2466		1169		1297		2466	
N of observations	8739		8739		8739		8739		8739		4098		4641		8739	