GENE-ENVIRONMENT INTERACTION IN ALCOHOL PROBLEMS IN EMERGING AND YOUNG ADULTHOOD: THE DRD4 VNTR, DAT1 VNTR, AND 5-HTTLPR POLYMORPHISMS

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by

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IN EMERGING AND YOUNG ADULTHOOD:
THE DRD4 VNTR, DAT1 VNTR AND 5-HTTLPR POLYMORPHISMS

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이 박사논문을 저를 위해 헌신하신 할머니께 바칩니다.

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INTRODUCTION

Problematic alcohol use behaviors change over the course of the lifespan. To capture the dynamic nature of alcohol problems, they need to be characterized longitudinally within the developmental contexts (Plomin, 1986; Zucker, 2006). Emerging adulthood (from late teens to mid-twenties; Arnett, 2000) and young adulthood (late twenties to thirties) are critical developmental stages with respect to the development and subsequent persistence or remission of alcohol problems. For example, 50% and 75% of life-time alcohol dependence diagnoses were present by the ages of 23 and 31, respectively (Kessler et al., 2005). Rates of heavy drinking peaked in the late teens and early twenties and steadily decreased afterward (Johnston, O'Malley, & Bachman, 2001a, 2001b). However, 20% to 30% of adults departed from this normative trend – some maintained their previous alcohol problems or developed new alcohol problems in their late twenties or thirties (Fillmore, 1988; Jackson, Sher, Gotham, & Wood, 2001). Thus, emerging and young adulthood is an optimal period to characterize persistent versus developmentally-limited alcohol problems.

Susceptibility to alcohol problems is determined by both genetic and environmental influences, and the nature of those influences also changes as a function of developmental stages. During adolescence, genetic influence on alcohol use and abuse increased, whereas environmental influence decreased (Dick, Rose, & Kaprio, 2006). In addition, different risky genes (e.g., Guo, Wilhelmsen, & Hamilton, 2007; Hopfer et al., 2007) and environments (Masten, Faden, Zucker, & Spear, 2008) affect alcohol problems at different developmental stages. Therefore, a developmentally sensitive study design is needed to delineate how specific genes interact with high-risk environments to affect

persistent versus developmentally-limited alcohol problems during emerging and young adulthood.

Enduring and Time-Limited Effects of Social Environments

Alcohol use behaviors are influenced by social environments and those environmental influences vary widely in the persistence of their effects. Effects of some environments are more likely to be time-limited (e.g., spring break, pregnancy), whereas others are more enduring (e.g., religious upbringing). Childhood adversity – physical, sexual, and emotional abuse and neglect – has been associated with a higher rate of alcohol problems throughout adulthood (Koss et al., 2003; Simpson & Miller, 2002; Wilsnack, Vogeltanz, Klassen, & Harris, 1997). Childhood adversity has been shown to change brain structure and function via repeated over-activation of stress-response neural systems (Perry, Pollard, Blakely, Baker, & Vigilante, 1995). Given these enduring neurobiological changes, exposure to childhood adversity may increase alcohol problems throughout emerging and young adulthood even after the adversity is no longer present.

In contrast, harmful effects of college environments appear to be limited to emerging adulthood. College students tend to show higher rates of heavy drinking during college years than do their non-college age peers (Johnston, O'Malley, & Bachman, 2003; Slutske et al., 2004). However, after college graduation, they decrease to a level lower than that of non-college bound peers (B. Muthén & L. Muthén, 2000; White, Labouvie, & Papadaratsakis, 2005). Among college environments, fraternity/sorority organizations have been associated with heavy drinking (Knight et al., 2002; Jackson, Sher, & Park, 2004). For example, residence in a Greek house was the strongest correlate of heavy drinking in college out of 33 individual difference variables examined

(Wechsler, Dowdall, Davenport, & Castillo, 1995). However, involvement with the Greek system in college was not associated with continued high rates of heavy drinking after college graduation (Bartholow, Sher, & Krull, 2003). Diverse alcohol-conducive aspects of college/Greek environments – high levels of alcohol availability and peer influences and low levels of structure and supervision – may facilitate alcohol problems among college students (White & Jackson, 2004/2005).

Adult role transitions – full-time employment, marriage, and parenthood – are associated with decreases in alcohol problems after the mid-twenties (Bachman et al., 2002; Jessor, Donovan, & Costa, 1991). Because of high structure and demands, adoption of new responsibilities is not compatible with problematic alcohol use (Kandel, 1980). In response to these social environmental changes, young adults who assume those adult roles are more likely to "mature out" of alcohol problems (Bachman, Wadsworth, O'Malley, Schulenberg, & Johnston, 1997; Chilcoat & Breslau, 1996; Curran, Muthén, & Harford, 1998; Gotham, Sher, & Wood, 1997) in comparison to their peers who are yet to assume such roles. Taken together, it is important to identify developmentally specific risky environments and to model the persistence of their effects to better understand their interaction with genetic susceptibility in alcohol problems.

Role of Genes in the Monoamine Neurotransmitter Systems in Alcohol Problems

Genetic susceptibility to alcohol problems is determined by multiples genes in many neurotransmitter systems (Goldman, Orozi & Ducci, 2005). Among promising candidate genes for alcohol problems are genes involved in the monoamine neurotransmitter system. The dopamine system, especially in the mesolimbic pathway, is vital in reward association learning (Wise, 2004; Wise & Rompr, 1989), providing a

neurobiological basis of psychological dependence and craving (Wise, 1988). Among dopamine receptor genes, the gene encoding the dopamine D4 receptor (DRD4) on chromosome 11p15.5 has a functional polymorphism of two to ten 48-base-pair variable number tandem repeats (VNTR) in the third exon (Van Tol et al., 1992). Association and linkage studies of the DRD4 gene found its role in diverse phenotypes, with consistent findings of its role in attention-deficit hyperactivity disorders (ADHD; Kebir, Tabbane, Sengupta, & Joober, 2009) and major depressive disorder (López León et al., 2008). Association studies of the DRD4 gene effects on alcohol and substance dependence (Dick & Found, 2003; McGeary, 2009) and novelty seeking (Munafò, Yalcin, Willis-Owen, & Flint, 2008; Tochigi et al., 2006) have largely yielded null findings. However, findings on its association with urges – especially in response to alcohol and substance cues – appear robust (McGeary, 2009). Three linkage studies also found an association of alcohol dependence with a region on chromosome 11 close to the DRD4 gene (Ehlers et al., 2004; Long et al., 1998; Reich et al., 1998).

In addition to the dopamine receptors, the dopamine transporter plays a central role in the regulation of dopamine levels through dopamine reuptake from the synaptic cleft. The gene encoding the dopamine transporter (DAT1) on chromosome 5p15.3 has a 40-base-pair VNTR, with three to 11 repeats (Fuke et al., 2001). Recent meta-analyses found significant associations of the DAT1 gene with ADHD (Yang et al., 2007) and successful smoking cessation (Stapleton, Sutherland, & O'Gara, 2007). Family-based and case-control association studies showed inconsistent findings for the role of the DAT1 gene in alcohol dependence (Dick & Found, 2003; Li & Burmeister, 2009). However, a robust association between the DAT1 gene and severe withdrawal symptoms –

hallucinations, Delirium tremens, and seizures – has been found (van der Zwaluw et al., 2009).

Genes in the serotonin system also have been a focus of genetic studies for alcohol problems because the serotonin system regulates behaviors closely related to alcohol problems – mood, aggression, and impulsivity (Dick & Foroud, 2003). The serotonin system also modifies dopamine activity on reward pathways. The serotonin transporter plays a central role in regulating serotonergic nuerotransimission, through serotonin reuptake from the synaptic cleft. The gene encoding the serotonin transporter on chromosome 17q11.1–q12 has a functional polymorphism in the promoter region (5-HTT gene-linked polymorphic region: 5-HTTLPR). The short (S) allele in the 5-HTTLPR has been associated with lower transcription efficiency and thus decreased extracellular transporter availability and increased synaptic serotonin, compared to the long (L) allele (Heils et al., 1996). More recently, Hu et al. (2004) found a common functional A/G substitution (SNP rs25531) in the first of two extra 22 base-pair repeats of the L allele, which generates two forms (L_A and L_G). The L_G allele was associated with low mRNA expression, which was almost equivalent to the S allele, whereas the L_A allele was associated with high mRNA expression. Association and linkage studies of the 5-HTTLPR gene have focused on diverse phenotypes, with the most consistent findings of its role in anxiety-related traits (especially neuroticism; Munafò et al., 2009), ADHD (Faraone & Khan, 2006), and suicidal behaviors (especially violent attempts; Li & He, 2007). Research on the association between the 5-HTTLPR gene and alcohol problems have yielded mixed findings (Dick & Found, 2003; Higuchi, Matsushita, & Kashima, 2006; Tyndale, 2003), with both positive and negative associations reported. However, a

meta-analysis (Feinn, Nellissery, & Kranzler, 2005) found a significant association between the 5-HTTLPR short allele and alcohol dependence, especially with an early onset, severe form of alcohol dependence (a history of withdrawal seizures and delirium), or co-morbid psychopathology (e.g., suicidality, depression, antisocial personality disorder, or ADHD).

Accumulating evidence suggests that effects of specific genotypes change over time. For example, in one study, the DAT1 gene and the DRD4 gene accounted for alcohol quantity at age16 and 23, respectively, but not vice versa (Hopfer et al., 2005). Five polymorphisms that affect monoamine function, including the DRD4, DAT1, and 5-HTTLPR polymorphisms, were associated with the frequency of alcohol use at ages 19 to 26 but not at ages 13 to 18 (Guo et al., 2007). Thus, the use of samples aggregating individuals in different developmental stages may obscure the time-varying nature of genotyping effects. Prospective studies that model gene effects on alcohol problems within different developmental stages are necessary to resolve interactions between genes and stages of development.

Gene and Environment Interaction in Alcohol Problems

Despite the well-established role of the monoamine system on alcohol problems (Enoch, 2003), previous findings regarding associations of the genes in that system are inconsistent. This may be due to many factors, such as multiple genes being involved, typically small effect sizes of a single polymorphism, gene-gene interactions, and heterogeneity of alcohol problems and their diverse etiological mechanisms. Of particular interest, manifestation of genetic susceptibility differs depending on the presence versus absence of certain environments: that is, gene and environment interaction (G x E;

Plomin, DeFries, & Loehlin, 1977). Emerging evidence suggests that individuals with genetic susceptibility for alcohol problems are more affected by certain types of environments. First, environments differ in their adversity. For example, individuals with a low activity 5-HTTLPR showed greater alcohol use when they were exposed to childhood maltreatment (Kaufman et al., 2007), a low quality family relationship (Nilsson et al., 2005), and negative life events (Covault et al., 2007). This pattern was also observed in female rhesus macaque monkeys; peer-reared female monkeys with a low activity 5-HTTLPR gene showed a greater ethanol preference and increases in alcohol consumption over time, compared with mother-reared female monkeys with the same gene (Barr et al., 2004). A haplotype of DAT1 genes also was associated with severe nicotine dependence among women with trauma (Segman et al., 2007). Second, environments differ in alcohol-conduciveness. Behavioral genetic studies found genetic influences on alcohol use were greater in college-bound siblings (vs. non-college bound siblings; Timberlake et al., 2007), singles (vs. married individuals; Heath, Jardine, & Martin, 1989), women from a non-religious upbringing (vs. religious upbringing; Koopmans, Slutske, van Baal, & Boomsma, 1999), and adolescents in urban areas (vs. rural areas; Rose, Dick, Viken, & Kaprio, 2001; Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001). Thus, individuals with specific genetic susceptibility may be more affected by alcohol-conducive and/or adverse environments than are individuals without. However, there is a lack of studies on interactions between specific genotypes (as opposed to a latent genetic effect as a whole) and developmentally specific environmental risks.

Overview of the Current Study

Using the prospective data of 454 individuals followed up at ages 18 through 34, the current study examined interaction effects between monoamine gene polymorphisms and developmental environments on alcohol problems during emerging and young adulthood. A developmental perspective was taken via modeling persistent and developmentally-limited alcohol problems and modeling enduring and time-limited effects of genes and environments. Specifically, first, a longitudinal hierarchical factor model was estimated to decompose variability in alcohol problems into one trait-like persistent alcohol problem factor and two state-like developmentally-limited alcohol problem factors specific to emerging adulthood and to young adulthood. Second, interactions between monoamine gene polymorphisms (DRD4 VNTR, DAT1 VNTR, and 5-HTTLPR) and adverse and alcohol-conducive environmental risks were modeled to account for the persistent and developmentally-limited alcohol problem factors. Persistence of environmental risks was modeled as an enduring effect of childhood adversity and time-limited effects of college involvement and delayed adult role transition. It was hypothesized that individuals with susceptible genotypes would show more alcohol problems when they were exposed to alcohol-conducive and/or adverse environments.

METHOD

Participants

Data were derived from a prospective study, in which 489 incoming first year students at a large Midwestern university were followed up and assessed on alcohol and health behaviors over 16 years at the mean ages of 18, 19, 20, 21, 25, 29, and 34. Initially, 3,156 first-time incoming first year students (80% of entire incoming freshmen,

N = 3,944) were screened for family history of alcohol use disorders using the adapted versions (Crews & Sher, 1992) of the Short Michigan Alcoholism Screening Test (Selzer, Vinokur, & van Rooijen, 1975) and the Family History-Research Diagnostic Criteria interview (Endicott, Andreasen, & Spitzer, 1978). Based on the screening, 489 participants (53% female, 94% Caucasian) were retained for the prospective study, consisting of roughly equal numbers of high-risk participants (whose biological fathers met diagnostic criteria for alcoholism; *n* = 250, 53% female) and low-risk participants (none of whose biological first-degree relatives met criteria for alcoholism and substance abuse or antisocial personality disorder and none of whose biological second-degree relatives met criteria for alcoholism or substance abuse; *n* = 237, 52% female). Data from one male participant and one female participant were treated as missing on the family history of alcoholism variable because they were found to have been adopted and to have no information about their biological parents. By the time of the last assessment at the mean age of 34, 383 participants (78% of baseline sample) participated in the study. Further details of participant recruitment and screening procedures are available in Sher, Walitzer, Wood, and Brent (1991). The baseline sample of 489 participants was contacted and invited to take part in the new genetic component of this study at the mean age of 35. A tube for blood sampling and instructions for phlebotomists were sent to those interested in participating (*n* = 435; 89% of the baseline sample). A total of 255 blood samples drawn at participants' preferred locations were sent back to us via mail. Written assent/consent was obtained from each participant and written parental consent was obtained for all participants under the age of 18. All measures and procedures were reviewed and approved by a human subjects institutional review board.

For the current study, 35 participants were excluded from the baseline sample. First, 30 non-Caucasian participants were excluded to control for potential confounds from population stratification. To determine participants' race, self-reported ancestry was used, which has been shown as a reasonable measurement to control for the potential threat of population stratification (e.g., Hutchison, Stallings, McGeary, & Bryan, 2004; Wacholder, Rothman, & Caporaso, 2000; 2002). Second, among 459 Caucasian participants, five participants who reported no alcohol consumption throughout the seven assessments of the study were also excluded, because genetic and environmental influences on abstinence (versus drinking) have been shown to differ from those influences on alcohol problems (Rhee et al., 2003). As a result, the final sample of the current study consisted of 454 Caucasian individuals who had consumed alcohol at some point in the 17-year study (mean age = 18.6 years [*SD* = 0.98] at the first assessment, 52% female, 51% with positive family histories of alcoholism). In the final sample, 233 – 234 participants (51% of the final sample) provided their genotyping data.

Measures

Alcohol problems

The Young Adult Alcohol Problems Screening Test (YAAPST; Hurlbut & Sher, 1992) was used to measure negative alcohol consequences during the past year at all seven assessment points. The YAAPST covers a range of alcohol problem areas (including interpersonal problems, legal problems, physically hazardous use, problems in role obligations) and severity (including hangover, withdrawal symptoms and getting professional help for alcohol problems). A sum of 27 dichotomously scored items (0 = did not experience; 1 = did experience) was used for data analyses. Means of alcohol

problems decreased from the age of 18 (4.23, *SD* = 3.41) to the age of 34 (1.28, *SD* = 1.99). The YAPPST scale was shown to have a single-factor structure and moderate Pearson correlations (r = .43 – .60) with diverse alcohol consumption measures in the original study (Hurlbut & Sher, 1992). High internal consistency across seven assessments, as measured by coefficient alpha (α = .87 – .90), was found in the final sample of the current study. Out of 27 items of the YAPPST scale, 13 items measured alcohol dependence symptoms of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994). Analyses with these 13 items of alcohol dependence symptoms yielded very similar results to the results of all 27 items reported here.

Childhood adversity

To measure experiences of verbal, physical, emotional, and sexual abuse, abandonment and neglect prior to the age of 18, 15 items were administered retrospectively at the mean age of 25 as part of a structured interview of the Childhood Life Events (Sher, Gershuny, Peterson, & Raskin, 1997). Trained, Masters-level clinical interviewers used strategies to improve accuracy of retrospective self-reports, such as providing recognition cues and responding sensitively to respondents' emotional status (Brewin et al., 1993). A sum score of the dichotomously scored 15 items (0 = did not experience; 1 = did experience) was used for data analyses (*M* = 1.95, *SD* = 2.32, range = 0 – 12). Appropriate internal consistency, as indicated by coefficient alpha of .77, was found in the final sample of the current study.

College involvement

At the mean ages of 18, 19, 20, and 21, two items were administered to measure the degree of college involvement. College student status was determined dichotomously as full-time (1) versus part-time or non-college student status (0). Fraternity/sorority affiliation status was also dichotomously coded as members (1) versus nonmembers (0). A sum score of these two items over the four assessments, potentially ranging from 0 to 8, was used for data analyses (M = 5.03, SD = 2.03).

Delayed adult role transition

At the mean ages of 25, 29, and 34, each participant's delay in adult role transition was assessed in terms of employment, marital, and parenthood status. Employment status was determined dichotomously as full-time (0) versus part-time or unemployed (1). Being a full-time housemaker was coded as employed full-time. Marital status was dichotomized into currently married (0) versus not currently married (i.e., widowed, separated, divorced, engaged, or never married; 1). Parental status was also coded dichotomously as raising any child (including any biological, adopted, foster, or step child; 0) or not raising any child (1). A sum score of these three items over the three assessments, potentially ranging from 0 to 9, was used for data analyses (M = 4.01, SD = 2.27).

Dopamine D4 receptor (DRD4) gene polymorphism

Genotyping the DRD4 polymorphism of 48-base pair Variable Number of Tandem Repeat (VNTR) in exon 3 was performed as described by LaHoste et al. (1996). The observed numbers of repeats per allele were 2 (n = 55), 3 (n = 23), 4 (n = 285), 5 (n = 3), 6 (n = 4), 7 (n = 93), 8 (n = 4), and 10 (n = 1) repeats. Those numbers of repeats were dichotomized into short (i.e., 2- to 6-repeats) or long (i.e., 7 to 10-repeats) alleles. For

data analyses, participants were dichotomized into carriers of one or two long alleles (1; *n* = 85) versus carriers of two short alleles (0; *n* = 149). Parallel analyses excluding participants with rare alleles (i.e., 2, 3, 5, 6, 8, and 10 repeats) were conducted, which yielded essentially the same results as those reported below.

Dopamine transporter gene (DAT1) polymorphism

Genotyping the DAT1 polymorphism of 40-base pair Variable Number of Tandem Repeat (VNTR) in the 3' untranslated region was performed as described by Cook et al. (1995). The observed numbers of repeats per allele were 3 (*n* = 2), 6 (*n* = 1), 9 (*n* = 122), 10 (*n* = 338), and 11 (*n* = 3) repeats. Those numbers of repeats were dichotomized into short (i.e., 3- to 9-repeats) or long (i.e., 10 to 11-repeats) alleles. For data analyses, participants were dichotomized into carriers of two long alleles (1; *n* = 125) versus carriers of one or two short alleles (0; *n* = 108). Parallel analyses excluding participants with rare alleles (i.e., 3, 6, and 11 repeats) were conducted, which yielded essentially the same results as those reported below.

Serotonin transporter-linked polymorphic region (5-HTTLPR) polymorphism

Genotyping of the triallelic 5-HTT polymorphisms was performed as described in Chorbov et al. (2007). In short, a 44-base pair insertion/deletion polymorphism in the promoter region of serotonin transporter gene was dichotomously determined as short (S; *n* = 181) or long (L) alleles. The L allele was further divided based on its single nucleotide variant: the A variant (L_A; *n* = 253) and the G variant (L_G; *n* = 32). Then, the S and L_G alleles were combined as a low-activity genotype, as compared to the L_A allele as a high-activity genotype. For data analyses, participants were dichotomized into carriers of two low-activity alleles (1; *n* = 50) or carriers of one or two high-activity alleles (0; *n*

= 183). Parallel analyses using the old genotypes of S versus L alleles without considering the A/G substitution, which yielded essentially the same results as those reported below.

Analyses

Mplus version 5.01 (L. Muthén & B. Muthén, 1998 - 2007), a structural equation modeling package, was used. To accommodate missing data, full-information maximum likelihood (FIML) estimation was used. FIML generates excellent estimates and reasonable standard errors through estimating a likelihood function for each individual based on all the available data (Graham et al., 2003). We note that analyses only with participants who provided genotyping data (n = 234 for the DRD4 gene and n = 233 for the DAT1 and 5-HTTLPR genes) showed essentially the same results as those reported here. Given difficulties in detecting interaction effects in general (McClelland & Judd, 1993), we tried to improve the power of analyses by using quantitative alcohol problem outcome measures, latent models to control for unreliability of measures, and FIML estimator to retain partially missing data.

RESULTS

Factor Models of Alcohol Problems

To model seven assessments of alcohol problems at the mean ages of 18 through 34, three factor models were fit. First, a single-factor model was fit, where all seven observed alcohol problem variables loaded to an alcohol problems trait factor. The single-factor model showed a poor fit to the data, $\chi^2(14, n = 454) = 245.53$, $p < .001$, Comparative Fit Index (CFI) = .83, Tucker Lewis Index (TLI) = .75, Root Mean Square Error of Approximation (RMSEA) = .19 (95% confidence interval [CI] = .17, .21),

Standardized Root Mean Square Residual (SRMR) = .09. Second, a correlated two-factor model was fit, where four alcohol problem variables assessed at ages 18 to 21 loaded to a factor of alcohol problems in emerging adulthood and the remaining three alcohol problem variables assessed at ages 25 to 34 loaded to a factor of alcohol problems in young adulthood. The two-factor model also showed a poor fit to the data, $\chi^2(13, n = 454) = 127.42$, $p < .001$, CFI = .92, TLI = .86, RMSEA = .14 (95% CI = .12, .16), SRMR = .06.

Third, a hierarchical factor model was fit, which included one overarching factor alcohol problem trait spanning all measurement occasions and two residual factors corresponding to the emerging adulthood (the mean ages of ages 18 to 21) and young adulthood (the mean ages of 25 to 34). As shown in Figure 1, all seven observed alcohol problem variables loaded on the alcohol problem trait factor. In addition, the residual variances of observed alcohol problem variables, after accounting for the alcohol problem trait, were fit to two developmentally-limited alcohol problem factors: a residual factor of alcohol problems limited to emerging adulthood (loaded by the four alcohol problem variables assessed at ages 18 to 21) and a residual factor of alcohol problems limited to young adulthood (loaded by the remaining three alcohol problem variables assessed at ages 25 to 34). Correlations among these three alcohol problem factors were set to be zero. This unconditional hierarchical factor model showed an adequate fit to the data, $\chi^2(7, N = 454) = 31.43$, $p < .001$, CFI = .98, TLI = .95, RMSEA = .09 (95% CI = .06, .12), SRMR = .02. A non-significant loading of alcohol problem variable measured at age 21 on the residual alcohol problem factor limited to emerging adulthood, $\beta = .03$, $p = .81$, indicated that most of the variance of alcohol problems at 21 were accounted for by the

broad alcohol problems trait but not by alcohol problems unique to emerging adulthood. Modification indices suggested that a correlation between alcohol problem variables measured at 18 and at 34 would improve a model fit, $\chi^2(6, N = 454) = 12.11$, *ns*, CFI = 1.00, TLI = .98, RMSEA = .05 (95% CI = .00, .09), SRMR = .02. However, because it was data-driven with no prior theoretical rationale, this parameter was not added and the original hierarchical factor model was employed in all further analyses. Parallel analyses with that correlation between alcohol problem variables at ages 18 and 34 yielded essentially the same results as those reported below.

Gene and Environment Interactions (G x Es)

A separate structure equation model was estimated for each polymorphism to test its interaction effect with three environment variables on the three alcohol problem factors, resulted from the above hierarchical factor model. As shown in Figure 2, a main effect of a polymorphism was included as a manifest variable. Main effects of three environment variables also were included as manifest variables. An interaction effect of a polymorphism with each environment variable was included as a manifest variable, which was calculated by multiplying a polymorphism variable by an environment variable. All these main effects of a polymorphism and environments and their corresponding interaction effects were correlated to each other (paths are not shown in Figure 2) to account for gene-environment correlation (Plomin et al., 1977) as well as were correlation between main effects and cross-product terms. In Figure 2, standardized estimates in the models of the 5-HTTLPR, DAT1 VNTR, and DRD4 VNTR polymorphisms are presented on the first, second and third rows of each triad of parameters, respectively. To probe significant G x E effects, multiple group analyses

across two genotype groups were conducted to examine the effects of environments on alcohol problems as a function of genotypes. In addition, for descriptive purposes, factor scores of alcohol problem factors obtained from the hierarchical factor model are shown as a function of genotypes (those with a risky genotype vs. those without) and environments (those in the upper 30% vs. those in the lower 30% in a risky environment) in Figure 3. Note that a mean factor score of each alcohol problem factor was set to be zero. A standard deviation was based on the variance of each factor: 1.95 for the alcohol problem trait factor throughout emerging and young adulthood and 1.36 for the alcohol problem factor limited to emerging adulthood.

The DRD4 VNTR model showed a good fit to the data, $\chi^2(47, N = 454) = 108.04$, $p < .001$, CFI = .96, TLI = .94, RMSEA = .05 (95% CI = .04, .07), SRMR = .05. As shown in Figure 2 (numbers on the first row of each triad of parameters), a significant interaction effect between the DRD4 VNTR and childhood adversity on the alcohol problem trait factor was found, β (standardized estimate) = .25, $p = .04$. A multiple group analysis indicated that, among non-carriers of the long allele ($n = 149$), childhood adversity did not show a significant effect on the alcohol problem trait, b (unstandardized estimate) = -.03 (β = -.04), $p = .67$. Whereas, among carriers of the long allele ($n = 85$), childhood adversity significantly increased the alcohol problem trait, b = .23 (β = .25), $p = .03$. Constraining a path of childhood adversity on the alcohol problem trait to be invariant across the two DRD4 VNTR genotypes yielded a significant decrement in model fit, $\Delta\chi^2(1) = 4.12$, $p = .04$. This pattern is also shown in Figure 3, first panel, where a mean factor score of the alcohol problem trait factor was higher among carriers of the

long allele who were high in childhood adversity, compared to a mean factor score among carriers of the same genotype who were low in childhood adversity.

A significant interaction effect between the DRD4 VNTR genotype and college involvement on alcohol problems limited to emerging adulthood also was found, $\beta = .77$, $p = .01$. A multiple group analysis indicated that, college involvement increased alcohol problems limited to young adulthood in a greater degree among carriers of the long allele, $b = .18$ ($\beta = .44$), $p = .01$, than among non-carriers, $b = .05$ ($\beta = .11$), $p = .21$. Constraining a path of college involvement on alcohol problems limited to emerging adulthood to be invariant across the two DRD4 VNTR genotypes yielded a significant decrement in model fit, $\Delta\chi^2(1) = 4.41$, $p = .04$. This pattern is also shown in Figure 3, second panel, where a mean factor score of the emerging adulthood alcohol problem factor was higher among carriers of the long allele who were high in college involvement, compared to a mean factor score among carriers of the same genotype who were low in college involvement. Although there was no significant interaction effect between the DRD4 VNTR and delayed adult role transition, delayed adult role transition significantly increased alcohol problems limited to young adulthood, regardless of the DRD4 VNTR genotype, $\beta = .37$, $p < .001$.

The DAT1 VNTR model showed a good fit to the data, $\chi^2(47, N = 454) = 82.01$, $p = .001$, CFI = .98, TLI = .96, RMSEA = .04 (95% CI = .03, .06), SRMR = .03. As shown in Figure 2 (numbers on the second row of each triad of parameters), no significant interaction effects of the DAT1 VNTR with childhood adversity, college involvement, or delayed adult role transition were found. Delayed adult role transition significantly

increased alcohol problems limited to young adulthood, regardless of the DAT1 VNTR genotype, β = .27, p = .01.

The 5-HTTLPR model showed a good fit to the data, $\chi^2(47, N = 454) = 87.90$, $p <$ .001, CFI = .97, TLI = .96, RMSEA = .04 (95% CI = .03, .06), SRMR = .03. As shown in Figure 2 (numbers on the third row of each triad of parameters), no significant interaction effects of the DAT1 VNTR with childhood adversity, college involvement, or delayed adult role transition were found. However, significant main environment effects on the three alcohol problem factors were found. That is, greater childhood adversity significantly increased alcohol problems persistent throughout emerging and young adulthood, regardless of the 5-HTTLPR genotype, β = .15, p = .04. Similarly, regardless of the 5-HTTLPR, college involvement and delayed adult role transition significantly increased alcohol problems limited to emerging adulthood, β = .20, p = .01, and young adulthood, β = .29, p < .001, respectively.

DISCUSSION

To date, most molecular genetic studies have failed to consider the changing nature of alcohol problems and their determinants as a function of developmental stages. However, aggregation of different developmental timings of alcohol problems (e.g., lifetime diagnosis of alcohol dependence) obscures potential roles of age-specific genetic and environmental risks. The current study represents a radical departure from the typical static approach and takes a developmentally sensitive strategy to studying gene-environment interactions. Specifically, a hierarchical factor model using the prospective data of a cohort assessed at the mean ages of 18 through 34 was estimated to distinguish persistent alcohol problems throughout emerging and young adulthood from time-limited

alcohol problems in emerging adulthood and in young adulthood. In addition, different developmental timings and varying persistence of environmental risks were taken into account through the modeling of both an enduring distal environmental risk persistent throughout the lifespan (i.e., childhood adversity) and situational environmental risks limited to emerging and young adulthood (i.e., college involvement and delayed adult role transition). Then, interaction effects of a genetic risk (i.e., each of the DRD4 VNTR, DAT1 VNTR, and 5-HTTLPR polymorphisms) with those developmentally relevant environmental risks on persistent and developmentally-limited alcohol problems were examined. This developmentally sensitive study design is critical, given that emerging and young adulthood – the highest risk periods for alcohol problems – is characterized by dramatic changes in social environments and alcohol use behaviors. Although we see our findings as preliminary due to the use of a small selected sample and the need for replication, we believe the current findings represent a "proof of concept" of a developmental perspective in both gene association studies and gene-environment studies.

Our findings suggest that carriers of the DRD4 VNTR long allele are more sensitive to childhood adversity and college involvement in alcohol problems, whereas non-carriers were not affected by them. Thus, the absence of the long allele appears to protect against detrimental effects of those environmental risks on alcohol problems. These findings may partially explain inconsistent findings of the DRD4 VNTR gene's association with alcohol problems (Dick & Found, 2003; McGeary, 2009). That is, the DRD4 VNTR gene appears to be associated with alcohol problems in emerging and

young adulthood only in the presence of environmental risks such as childhood adversity and college involvement.

Pathways by which those environmental risks increased alcohol problems among the DRD4 VNTR long-allele carriers are yet to be characterized. However, underlying mechanisms of gene-environment interactions are likely to differ as a function of persistence of environmental risk effects. For example, in the case of childhood adversity, prolonged changes in developing brain may mediate the increased susceptibility to alcohol problems later in life. There is considerable evidence of enduring neurobiological changes due to childhood adversity, leading to increased sensitization to drugs/alcohol effects (Zimmermann, Blomeyer, Laucht, & Mann, 2007). Of particular interest, stress-induced corticosteroid secretion has been shown to stimulate mesolimbic dopaminergic systems similar to the way that alcohol and drugs do (Berridge & Robinson, 1998; Piazza & Le Moal, 1997). However, specific roles of the DRD4 VNTR gene in the association between the neurobiological changes due to early stress and consequent alcohol problems later in life need to be further clarified.

While time-limited environments at later developmental stages are presumably less likely to lead to neurobiological changes that have chronic effects on susceptibility to alcohol problems, they may serve as facilitating milieus that permit individuals to actualize their inherited susceptibility. For example, college campuses are characterized by diverse alcohol-conducive factors, such as exaggerated perception of peers' drinking, easy access to alcohol, and low structure in life (Jackson et al., 2006). Embedded in highly alcohol-conducive environments, individuals with genetic susceptibility are more likely to develop alcohol problems than are those without such a predisposition. Given

the robust finding of the DRD4 gene's role in urges (McGeary, 2009), exposure to alcohol cues rampant in college campuses may lead carriers of the DRD4 VNTR long allele to experience greater and more frequent urges to drink, which eventually may lead to alcohol problems. The construct of college involvement may be an approximate measure of those alcohol conductive factors in college environments (White & Jackson, 2004/2005). Because these proximal, alcohol-conducive environmental risks do not involve persistent changes in individuals' neurobiological systems, their effects on alcohol problems may be time-limited, increasing alcohol problems at a specific time period but not beyond the immediate time period. Specific factors in college environments that interact with the DRD4 gene to increase alcohol problems in merging adulthood need to be identified.

In sum, we found two types of gene-environment interactions involved with the DRD4 gene: (1) an interaction with a distal environmental risk that affects susceptibility to persistent alcohol problems, which is more likely to be mediated by enduring neurobiological changes due to the early environmental adversity, and (2) an interaction with a proximal environmental risk that affects susceptibility to developmentally-limited alcohol problems, which is more likely to be mediated by time-limited alcohol-conducive factors. These different types of gene-environment interactions appear to be associated with different developmental subtypes of alcohol problems characterized by distinct etiological pathways (such as different types of environmental risks) and clinical presentations (such as persistence or desistence of alcohol problems). Although preliminary, these findings highlight the importance of modeling both distal and proximal

environments and their interplay with genetic susceptibility in alcohol problems at specific developmental stages.

Although there was no significant interaction of the DAT1 VNTR and the 5-HTTLPR genes with three environmental risks examined in the current study, because of their critical roles in alcohol related neurobiological pathways, those genes still remain potential candidate genes for the development of alcohol problems. Those genes may increase susceptibility to alcohol problems interacting with environmental risks other than those examined in the current study (e.g., sibling, peer or community factors). Those genes may be associated with different stages of alcohol use and abuse (e.g., alcohol use initiation or progression to abuse) or with certain subtypes of alcohol problems. Genetic influences and their interaction with environmental influences also may differ as a function of sample characteristics (gender, age, or social and cultural contexts; Li & Burmeister, 2009).

Several limitations and future directions of the current study are worthy of mention. First, we used a small sample from a selected population (incoming college students, half of whom were positive in family history of alcoholism), and thus, our findings should be regarded as preliminary. Clearly, our findings should be interpreted with consideration of sample characteristics and need to be replicated in independent samples. However, this study provides a good example of how we can exploit existing prospective studies by genotyping participants who had previously provided information regarding alcohol problems, environmental risks factors, and diverse psychological constructs (e.g., drinking motives, expectancies, and personality traits). Further, oversampling individuals positive in family history of alcoholism may have made it

easier to observe alcohol problems and genetic and environmental risk factors, compared with other college-based samples. Second, although it is beyond the scope of the current study, neurobiological and psychological mechanisms underlying the gene-environment interactions need to be characterized. Both human and animal studies of differential reactivity to childhood adversity and college environments as a function of the DRD4 VNTR gene would be helpful. Third, much work needs to be done before gene-environment interaction findings can provide direct implications for intervention and prevention strategies. However, accumulation of gene-environment interaction findings over time would lead to development of preventive strategies targeted for individuals with genetic susceptibility to reduce their exposure or reactivity to environmental risks.

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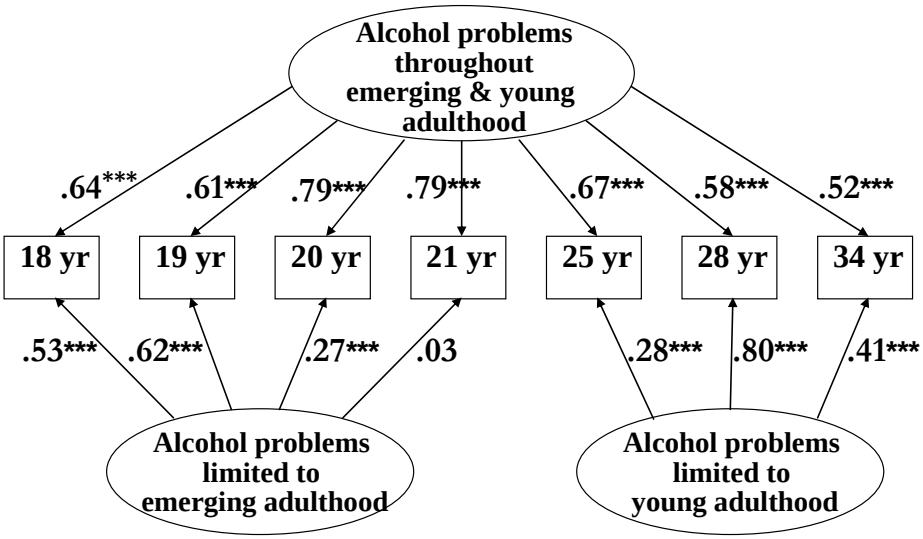
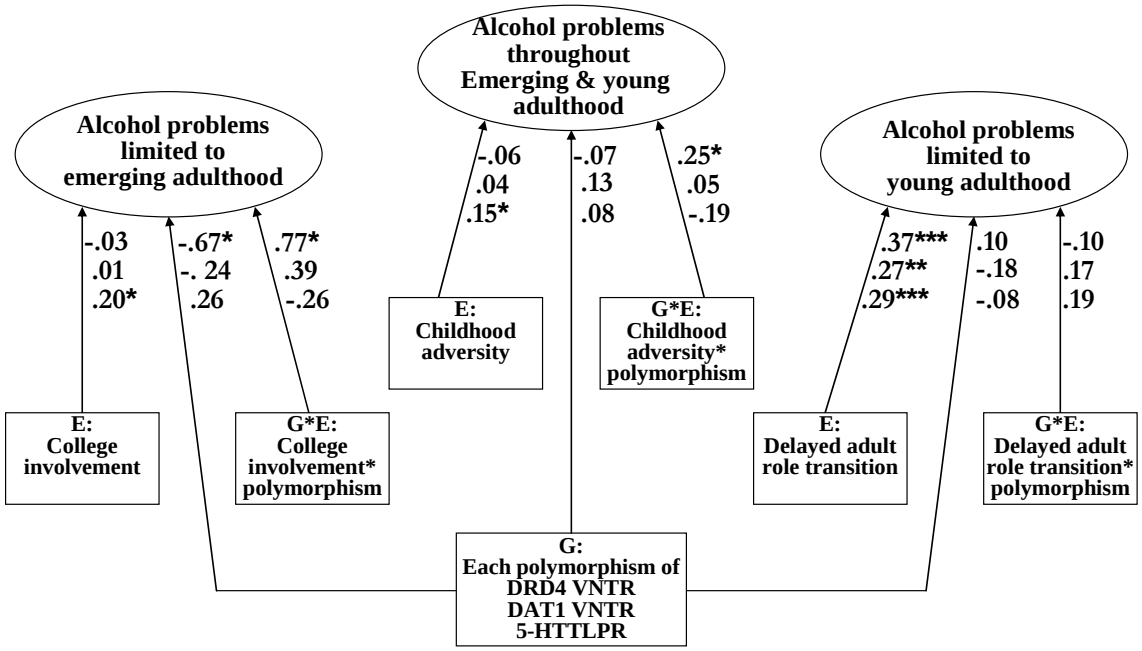
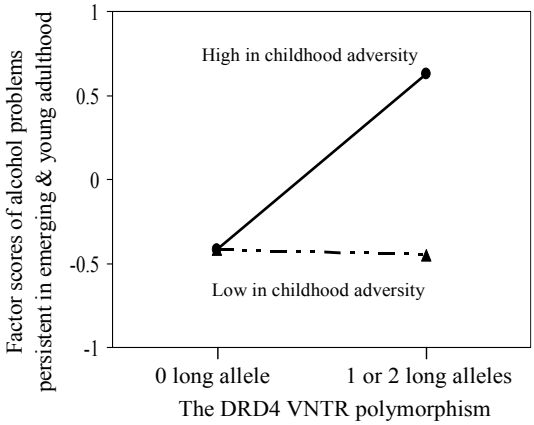
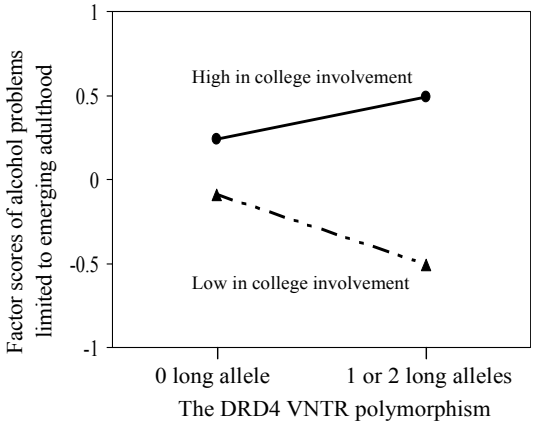

Alcohol problems throughout emerging & young adulthood
.64***
.61***
.79***
.79***
.67***
.58***
.52***
18 yr
19 yr
20 yr
21 yr
25 yr
28 yr
34 yr
.53***
.62***
.27***
.03
.28***
.80***
.41***
Alcohol problems limited to emerging adulthood
Alcohol problems limited to young adulthood


Alcohol problems throughout Emerging & young adulthood
Alcohol problems limited to emerging adulthood
Alcohol problems limited to young adulthood
-.06
.04
.15*
-.07
.13
.08
.25*
.05
-.19
-.03
.01
.20*
-.67*
-. 24
.26
.77*
.39
-.26
.37***
.27**
.29***
.10
-.18
-.08
-.10
.17
.19
E: College involvement
G*E: College involvement* polymorphism
E: Childhood adversity
G*E: Childhood adversity* polymorphism
E: Delayed adult role transition
G*E: Delayed adult role transition* polymorphism
G: Each polymorphism of DRD4 VNTR DAT1 VNTR 5-HTTLPR


Factor scores of alcohol problems persistent in emerging & young adulthood
1
0.5
0
-0.5
-1
High in childhood adversity
Low in childhood adversity
0 long allele
1 or 2 long alleles
The DRD4 VNTR polymorphism


Factor scores of alcohol problems limited to emerging adulthood
1
0.5
0
-0.5
-1
High in college involvement
Low in college involvement
0 long allele
1 or 2 long alleles
The DRD4 VNTR polymorphism

VITA

Aesoon Park, born in Daejeon in South Korea, earned a B.A. in Japanese language and literature at Korea University in South Korea. Then, she earned a M.A. in clinical psychology at Korea University and completed a post-masters internship training program at Young-In State Mental Hospital in South Korea. After working as a research associate at Ewha Women's University under the guidance of Dr. Young-Sook Park for two years, she came to the United State to join the doctoral program in clinical psychology at the University of Missouri. At the University of Missouri, she participated in two NIH-funded prospective studies on alcohol use and misuse among college students and young adults under the guidance of Dr. Kenneth J. Sher. Her research projects have primarily centered on characterizing reciprocal influences among personal and environmental factors on the longitudinal trajectories of problematic drinking in emerging and young adulthood. She has completed a predoctoral internship training program at the Division of Substance Abuse Clinical and Prevention Research unit at Yale University School of Medicine, Department of Psychiatry under the guidance of Drs. Samuel Ball and Stephanie O'Malley. After earning a Ph.D. in clinical psychology at the University of Missouri, she will join the Department of Psychology at Syracuse University, NY, as an assistant professor.