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

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Background: *Previous research suggests that personality traits, particularly novelty seeking (NS), increase the risk of substance abuse. One possible explanation to account for this association relates to common genetic factors. The aim of this study was to examine whether allelic variants of the dopamine D4 receptor gene (DRD4) are associated with alcohol use in adolescents and to determine the extent to which these links are mediated by NS.*

Methods: *Three hundred three adolescents (144 male participants, 159 female participants, approximately 15 years old) from a high-risk community sample completed self-report questionnaires measuring alcohol intake and temperament (Junior Temperament and Character Inventory [JTCI]). DNA was genotyped for the DRD4 exon III polymorphism.*

Results: *Male participants carrying the 7-repeat allele of DRD4 drank higher maximum amounts of alcohol per occasion and had greater lifetime rates of heavy drinking than male participants without this allele. Higher levels of NS were associated with higher alcohol intake in both genders. Multiple regression analyses support the role of NS in mediating the relationship between DRD4 and heavy drinking in male adolescents but not in female adolescents.*

Conclusions: *These findings extend previous work highlighting the significance of personality traits as a mediating factor between genetic susceptibility and substance use during the period of early experimental use.*

Key Words: Dopamine D4 receptor gene (DRD4), drinking, novelty seeking, adolescence, genetics, substance use

Adolescence is a critical age period during which patterns of alcohol use are shaped. Experimentation with alcohol is highly prevalent among adolescents in Western countries (Hibell et al 2005; Johnston et al 2005). By the age of 18, more than 90% of German youths report having tried alcohol, with rates of regular use increasing from 1% in 12- to 13-year-olds up to 37% in 18- to 19-year-olds (BZgA 2001). Heavy drinking, defined as having five or more drinks on one occasion, rises steadily throughout adolescence, with 46% of 16- to 19-year-olds reporting heavy drinking during the last month (BZgA 2004). Patterns of heavy drinking in adolescents have been associated with diverse alcohol-related problems (Perkins 2002), including immediate consequences (e.g., blackouts, hangovers, academic problems, risk of injury, violence, unsafe sexual intercourse) as well as long-term effects such as alcohol abuse and dependence in adulthood (Guo et al 2000). Earlier initiation of alcohol use and younger age at first intoxication are among the strongest predictors of later dependence. Individuals who begin drinking before age 15 are four times more likely to develop dependence than those who begin at age 21 (Grant and Dawson 1997). Results of recent longitudinal studies underscore the unfavorable long-term prognosis of heavy drinking, demonstrating that risky drinking styles in adolescence directly predicted alcohol abuse and dependence 10 years later (e.g., Jennison 2004). These data highlight the importance of identifying predictive factors of early drinking initiation and maintenance in adolescents. A more refined understanding of these factors may contribute to the improvement of prevention and treatment strategies in adolescents.

Behavior and molecular genetics studies have convincingly demonstrated that genetic factors are involved in different stages of alcohol use and dependence, accounting for approximately 50% to 70% of the population variance. Many genes are thought to contribute to phenotypical variation in drinking behavior (Tyndale 2003). Evidence from neurobiological research points to genetic alterations in various neurotransmitter systems, including the dopamine, serotonin, norepinephrine, gamma-aminobutyric acid (GABA), glutamate, and opioid system, as possible explanations for these heritable influences. Several studies have examined the association between alcohol use and allelic variation in dopamine genes, with polymorphisms in the dopamine D2 receptor (DRD2) and the dopamine transporter (DAT1) being the most widely studied. Relatively little attention has been paid to the dopamine D4 receptor (DRD4) gene, which contains a highly polymorphic 48 base pair variable number of tandem repeats (48 bp VNTR) sequence in exon III. This polymorphism has been found to vary between 2 and 11 copies, with the 4-repeat (4r) being the most common in Caucasians, followed by the 7-repeat (7r) (Vallone et al 2000). The 7r variant appears to blunt the intracellular response to dopamine and to exhibit a lower affinity to antagonists in vitro as compared with the 4r variants (Oak et al 2000). The D4 receptors are highly expressed in limbic and prefrontal areas of the brain involved in cognition and emotion and have been shown to modulate exploratory behavior as well as drug sensitivity in experimental animals

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(Dulawa et al 1999; Rubinstein et al 1997). Research associating DRD4 with drinking yielded largely negative results (Tyndale 2003). One exception is recent studies that have focused on a specific alcohol phenotype, suggesting higher craving after consumption of alcohol in carriers of the 7r allele as compared with carriers of other alleles (Hutchison et al 2002, 2003).

Over the past years, research has discussed an association between the DRD4 gene and the personality trait of novelty seeking (NS), which has been implicated in alcohol abuse. According to the Cloninger et al (1993) model of personality, NS represents a dopaminergically modulated and heritable tendency toward frequent exploratory activity and intense excitement in response to novelty. Several studies have reported elevated substance use among individuals with a high level of NS (Etter et al 2003; Gabel et al 1999; Wills et al 1994). In particular, NS was related to an earlier initiation of use and predicted drug use in later life when assessed in early childhood (Masse and Tremblay 1997). Research on the genetic background of the Cloninger et al (1993) temperament model, examining the hypothesis that NS is mediated by genetic variability in dopamine transmission, has produced inconsistent evidence. Several groups have reported significant associations of DRD4 with NS, while others have failed to replicate these findings (Kluger et al 2002).

A number of reasons may account for the conflicting results. One limitation of previous research has been the use of rather crude assessments of drinking that failed to reflect the complex process of drinking development. However, the role of etiological factors may change in the progression of alcohol use from experimentation toward dependence. Several studies provided evidence suggesting that genetic and environmental factors predicting alcohol initiation may differ from those predicting the maintenance or cessation of the behavior (Rose 1998). Another limitation relates to the lack of attention to adolescent populations in research examining genetic influences on drinking behavior. The majority of studies conducted so far have neglected that genes may be expressed differentially at different stages of development. However, behavior genetics research has indicated that genes may be "switched on" or become especially penetrant at different time points during development (Rende and Plomin 1995). Adolescence may be viewed as a developmental period in which individuals are more likely to engage in risk-taking behavior and to explore unknown areas more actively than at either a younger age or in adulthood. Recently, we studied NS and smoking in adolescents from a high-risk community sample (Becker et al 2005; Laucht et al 2005). Our results indicated that male adolescents carrying the DRD4 7r allele exhibited higher smoking activity and higher scores on NS than those without this allele, while in females no association with smoking and NS was observed. This finding was interpreted as supporting the hypothesis that the phenotypic expression of a genetic susceptibility factor may be moderated by both developmental and gender specific characteristics. During a developmental period in which individual differences in exploring novel domains are particularly salient, the magnitude of genetic influences may become more evident or even more pronounced.

The present study aimed to clarify the nature of a possible genetic influence on adolescent drinking by 1) investigating the association of the DRD4 exon III polymorphism with alcohol use and novelty seeking in a birth cohort of adolescents aged 15 years; and 2) examining whether novelty seeking mediates a possible effect of DRD4 on adolescent drinking.

Methods and Materials

Participants

Data in this investigation are drawn from the Mannheim Study of Risk Children, an ongoing prospective study of the long-term outcome of early risk factors followed from birth onward. Detailed information about this study has been published elsewhere (Laucht et al 1997). The initial sample consisted of a cohort of 384 children born between 1986 and 1988, who were recruited from two obstetric and six children's hospitals of the Rhine-Neckar region of Germany. To be included in the study, parents and children had to meet well-defined criteria intended to enrich and to control the risk status of the sample. As a result, approximately two thirds of the study sample had experienced moderate to severe prenatal and perinatal complications such as preterm birth or neonatal asphyxia, while approximately two thirds of the families suffered from psychosocial adversities such as parental psychiatric disorder or chronic difficulties. To control for the confounding effects of family environment and infant medical status, only firstborn children with singleton births and German-speaking parents who had no severe physical handicaps, obvious genetic defects, or metabolic diseases were included in the sample. The participation rate at the time of recruitment was 64.5 %, with a slightly lower rate in families from psychosocially disadvantaged backgrounds. The participants were almost exclusively of European descent (> 99.0%). Assessments were conducted at the ages of 3 months and 2, 4.5, 8, and 11 years, and most recently at age 15 years.

The present investigation included 303 adolescents (144 male participants, 159 female participants) who participated in the 15-year assessment and for whom genetic data were available. Of the initial sample of 384 study members, 18 (4.7%) were excluded because of severe handicaps (neurological disorder or intelligence quotient [IQ] < 70), 28 (7.3%) were dropouts, and 35 (10.4%) refused to participate in blood sampling. The study was approved by the ethics committee of the University of Heidelberg, and written informed consent was obtained from all participants.

Assessment

Participants completed a drinking inventory including age at drinking initiation, lifetime alcohol use, and frequency of current (past month and past week) use. The inventory is part of the Substance Use Questionnaire (SUQ) designed by Müller and Abbet (1991) in collaboration with the World Health Organization (WHO). The total amount of alcohol intake during the last 6 months was measured using the Lifetime Drinking History (LDH) (Skinner and Sheu 1982). From this, three drinking variables were derived, indicating the average amount of alcohol consumed per month, the maximum amount of alcohol consumed per occasion, and lifetime presence of heavy drinking, defined as having drunk more than five (female participants: four) standard drinks (i.e., 8 g or 10 mL by volume of pure alcohol) in a row. To assess adolescent novelty seeking at age 15 years, an adolescent version of the Temperament and Character Inventory (TCI) (Cloninger et al 1994) was administered, which captured four temperament traits of adolescents. The psychometric characteristics of the instrument were confirmed for the German version (Junior Temperament and Character Inventory [JTCI]; Schmeck et al 2001). Satisfactory internal consistency of the NS scale (α = .80) was obtained in our sample.