Impact of Psychosocial Adversity on Alcohol Intake in Young Adults: Moderation by the LL Genotype of the Serotonin Transporter Polymorphism

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Background: Evidence from animal studies supports a role for serotonin transporter gene promoter polymorphism (*5-HTTLPR*) gene-environment interaction (G × E) in the development of excessive alcohol intake. Few studies in humans have been conducted on this topic, yielding inconsistent results. The present study aims to further explore G × E between *5-HTTLPR* and exposure to psychosocial adversity on alcohol consumption in a high-risk community sample of young adults.

Methods: Data were collected as part of the Mannheim Study of Children at Risk, an ongoing epidemiological cohort study following the outcome of early risk factors from birth into young adulthood. At age 19 years, 309 participants (142 male participants, 167 female participants) were genotyped for the biallelic and triallelic *5-HTTLPR* and were administered a 45-day alcohol timeline follow-back interview, providing measures of the total number of drinks and the number of binge drinking days. Psychosocial adversity was assessed at birth (family adversity) and at age 19 (negative life events).

Results: In contrast to various previous reports, a significant G × E emerged, indicating that, when exposed to high psychosocial adversity, individuals with the LL genotype of *5-HTTLPR* exhibited more hazardous drinking than those carrying the S allele or those without exposure to adversity. This effect, which was confined to male participants, held both for different classifications of *5-HTTLPR* and different types of adversity.

Conclusions: One explanation for the discrepant results might be heterogeneity in alcohol phenotypes. While the L allele relates more strongly to early-onset alcoholism, the S allele may be linked more closely to alcohol use associated with anxiety and depression.

Key Words: Alcohol use, family adversity, gene-environment interaction, serotonin transporter gene, stressful life events, young adults

Alcohol use disorders (AUD) are common, complex disorders that constitute the leading cause of a wide variety of morbidity and mortality conditions in many developed countries. Behavioral genetic studies have amply demonstrated that both genetic and environmental factors contribute to the development of AUD, with heritability estimates ranging from 50% to 60% (1–4). Moreover, growing evidence suggests that genetic effects may be conditional on environmental factors, i.e., vulnerability to AUD may result from gene-environment interaction (G × E) (e.g., 5–8). Among the brain systems involved in mediating the psychoactive effects of alcohol, much attention has been placed on serotonergic (5-HT) neurotransmission as a potential contributor to vulnerability to AUD. A critical role in the regulation of serotonin function in the brain pertains to the serotonin transporter (5-HTT), making the gene encoding this protein a prominent candidate for genetic association studies. This locus contains a well-studied biallelic polymorphism in the promoter region (serotonin transporter gene promoter polymorphism [*5-HTTLPR*]) consisting of two common alleles, which appear to result in differential 5-HTT expression and function (9,10). Compared with the "long" (L) variant, the "short" (S) allele was found to exhibit significantly lower transcriptional activity of the 5-HTT gene in vitro. Recently, a third functional allele has been described, resulting from an A→G substitution in the long allele, which was reported to be equivalent in expression to the S allele (11). Failure to distinguish between these alleles may be one reason for inconsistency in previous research investigating effects of *5-HTTLPR*.

Numerous studies have examined a potential role of *5-HTTLPR* in determining a variety of personality traits and psychiatric disorders, including AUD (12). However, a consistent picture of the contribution of this polymorphism has not yet emerged. In a prior meta-analysis surveying 19 independent samples, evidence for a significant, albeit weak, association of the *5-HTTLPR* with AUD was confirmed, indicating that the S allele increased the risk of AUD (odds ratio [OR] = 1.18, confidence interval [CI] = 1.03–1.33) (13). However, although the majority of studies reported an association with the S allele, at least five of the samples showed the opposite effect. Since then, the number of studies providing evidence for an association with the L allele has increased, indicating that 1) compulsive craving was elevated in alcohol-dependent patients with the L allele (14), 2) the rates of AUD and heavy drinking were higher and the level of response to alcohol was

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lower among carriers of the L allele (15,16), 3) AUD was more likely in L allele carriers from a Korean population (17), and 4) binge drinking in adolescents from risk settings decreased with each additional copy of the S allele (18).

Several reasons for heterogeneity between studies have been discussed, such as sex, age, non-European ancestry, alcohol phenotype, and comorbidity. For example, it has been hypothesized that the comorbidity of AUD with depression may underlie the association with the S allele (19). Others have suggested that a specific phenotype of AUD, Type II alcoholism (20), which is associated with an earlier onset age and antisocial psychopathology, will be more likely to carry the LL genotype (21). However, evidence for both suppositions is sparse. In the meta-analysis of Feinn *et al.* (13), the association with the S allele was found to be most pronounced in samples with comorbid conditions, including both depressive and antisocial psychopathology. Among the five samples showing a stronger association with the L allele, there were at least three that had focused on early-onset alcoholics. Early age at onset also characterizes the above-mentioned samples of Bleich *et al.* (14), Olsson *et al.* (18), and Kweon *et al.* (17), with the latter revealing a significantly lower onset age in alcoholics carrying the L allele as compared with S allele homozygotes.

Another possible source of inconsistency may be that the effect of *5-HTTLPR* is conditional on environmental factors. Considering that serotonin is a critical modulator of the stress response, several researchers have suggested that the influence of the 5-HTT genotype may be moderated by the presence of stressful experiences. In a seminal study, Caspi *et al.* (22) reported an interaction between *5-HTTLPR* and depression, demonstrating that the S allele was associated with depression only among individuals exposed to stressful life events. These findings have attracted a large number of replication attempts, the majority of which have provided results consistent with the initial reports (23). However, in a most recent meta-analysis, Munafo *et al.* (24) concluded that the effects of *5-HTTLPR* and its interaction with stressful life events on the risk of depression were negligible and positive results were compatible with chance findings. Following the G × E evidence reported, researchers have tried to find a similar relationship for alcohol use. The link between stressful experiences and alcohol use has long been discussed (25,26), with the stress-coping model of addiction proposing that alcohol use serves to regulate negative affect. Findings in humans and in experimental animals have demonstrated that exposure to stress is closely related to the initiation and continuation of heavy drinking, as well as to relapse in alcohol dependence.

Evidence from animal studies supports a role for *5-HTTLPR* G × E in the development of excessive alcohol intake. In studies with nonhuman primates, Barr *et al.* (27) demonstrated that the effects of early stress on alcohol use in later life were conditional on variation in *5-HTTLPR*, with higher consumption only in carriers of the S allele. So far, only few studies in humans have been conducted, yielding inconsistent results. While Covault *et al.* (28) and Kaufman *et al.* (29) provided evidence for earlier and heavier alcohol use only among carriers of the S allele following stressful life events, Olsson *et al.* (18) reported a decrease in binge drinking in risk settings with each additional copy of the S allele. Dick *et al.* (30) failed to establish G × E in a large subset of individuals from the Collaborative Study on the Genetics of Alcoholism (COGA) sample. Nilsson *et al.* (31) found that adolescents with poor family relations had an increased risk of alcohol intoxication when carrying the heterozygous LS genotype of *5-HTTLPR* instead of the homozygous LL or SS genotypes.

The present study reports on research designed to further explore G × E between *5-HTTLPR* and exposure to psychosocial adversity on alcohol consumption in a high-risk community sample of young adults. Due to the longitudinal design of this study, both early family adversity and current stressful life events were considered as potential moderators of genetic vulnerability to AUD.

Methods and Materials

Participants

Participants were members of the Mannheim Study of Children at Risk, an ongoing epidemiological cohort study following the outcome of early risk factors into adulthood (32). The initial sample comprised 384 children born between 1986 and 1988 of predominantly (>99.0%) European descent. Infants were recruited from two obstetric and six children's hospitals of the Rhine-Neckar Region of Germany and were included consecutively into the sample according to a two-factorial design intended to enrich and control the status of the sample regarding obstetric and psychosocial risks (33) (for more details, see Supplement 1).

Assessment

The first part of the 19-year assessment was a postal survey concerning drug-related behavior and problems, as well as psychosocial functioning. For the second part, the young adults were invited to our laboratory to participate in a standardized interview administered by trained clinical psychologists and to undergo a social stress test. To assess current drinking behavior, a 45-day timeline follow-back (TLFB) interview (34) was conducted, providing estimates of the distribution of drinking days and the amount of daily alcohol consumption (for details, see Supplement 1).

Early psychosocial adversity according to an enriched family adversity index as proposed by Rutter and Quinton (35) and Blanz *et al.* (36) was derived from a standardized parent interview conducted at the 3-month assessment (details appear in Supplement 1).

Current stressful life events were assessed by questionnaire and confirmed by interview using a modified and shortened version of the Munich Events List (MEL) (37). Details of the MEL are in Supplement 1.

Genotype Analysis

Details are available in Supplement 1.

Data Analysis

Scores in genotype groups were compared with *t* tests or analyses of variance. Chi-square tests examined genotypic frequencies between groups. Linear regression analyses were conducted to examine whether *5-HTTLPR* genotype moderated the effect of early or current adversity on drinking measures. Details are presented in Supplement 1.

Results[1]

5-HTTLPR Genotype and Exposure to Early Family Adversity

The results of linear regression models testing for the impact of *5-HTTLPR* genotypes and early adversity on young adult

[1]Demographic and clinical features of the study sample are presented in Supplement 1.