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Brief Research Communication

Antisociality, Substance Dependence, and the *DRD5* Gene: A Preliminary Study

Michael M. Vanyukov,[1,3]* Howard B. Moss,[1] Barry B. Kaplan,[2] Galina P. Kirillova,[1] and Ralph E. Tarter[1]

[1]*Center for Education and Drug Abuse Research (CEDAR), University of Pittsburgh, Pittsburgh, Pennsylvania*
[2]*Molecular Neurobiology and Genetics Program, University of Pittsburgh, Pittsburgh, Pennsylvania*
[3]*Departments of Pharmaceutical Sciences, Psychiatry, and Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania*

A pilot population-based study of a microsatellite polymorphism at the *DRD5* locus in adult European-Americans showed its association with childhood symptom counts for oppositional defiant disorder (ODD) in males and females and adult antisocial personality disorder (ASPD) in females. No association with childhood conduct disorder symptom count was observed. ODD mediated the genotype-ASPD relationship in females. Neither ODD nor ASPD significantly mediated the relationship between the genotype and the liability to substance dependence (SD). The data suggest involvement of the *DRD5* locus in the variation and sexual dimorphism of SD liability and antisociality and in the developmental continuity of antisociality. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 96:654–658, 2000.

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INTRODUCTION

Liability [Falconer, 1965] to substance dependence (SD) is a multifactorially inherited trait whose variation in the population is significantly contributed by genotypic differences [e.g., Grove et al., 1990; van den Bree et al., 1998]. The heritability of SD liability is based on polymorphisms at the genes likely to be related to the function of the central nervous system and, possibly, the biotransformation of xenobiotics. We have recently shown the dopamine D5 receptor gene's (*DRD5*) associations with liability to SD and novelty seeking [Vanyukov et al., 1998]. These relationships were moderated by sex (stronger in females). Hypothesizing that the possible contribution of this gene to variation in SD liability is nonspecific (i.e., polymorphisms at this gene may underlie individual differences in personality/temperament traits related to this liability), we tested mediation of the *DRD5*-liability relationship by novelty seeking. The results indicated that the *DRD5* contributions to variation in the two traits are independent. It is possible that *DRD5* polymorphisms directly contribute to drug response, e.g., by mediating reduction in drive to seek drug reinforcement, as shown for the D1 receptor, the other receptor from the D1-like group [Self et al., 1996]. It is also likely, however, that other personality/temperamental variables underlie this relationship between receptor properties and the complex behavior that develops as a result of the long process of organism-environment interaction [Tarter and Vanyukov, 1994].

The strong relationship between liability to substance use disorders (SUD) and antisociality is well documented. For instance, men with antisocial personality disorder (ASPD) are five times more likely to abuse drugs than those without it, and the risk of drug abuse for women is 12 times higher in the presence of ASPD than in its absence [Robins et al., 1991]. Twin studies have provided evidence for common genetic mechanisms of variation in liability to SUD and antisociality [Grove et al., 1990]. Due to the expression of the *DRD5* gene in the limbic system, which is integral to emotion regulation, cognition, and goal-directed motivation, this gene could be one of the loci underlying this genetic commonality. To address this issue, we tested the relationship between liability to SD, antisociality, and a microsatellite polymorphism at the *DRD5* gene in the sample of adult males and females used in the previous study [Vanyukov et al., 1998].

Subjects were participants in a family/high-risk study of SUD (Center for Education and Drug Abuse Research, CEDAR) where probands are adult males with or without a DSM-III-R (*Diagnostic and Statisti-*

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*Correspondence to: Michael M. Vanyukov, Ph.D., University of Pittsburgh, 707 Salk Hall, Pittsburgh, PA 15261.
E-mail: mmv@pitt.edu

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cal Manual of Mental Disorders, third edition, revised) diagnosis of SUD. The diagnosis of SUD is based on an expanded version of the Structured Clinical Interview for DSM-III-R, outpatient version [Spitzer et al., 1987] and finalized at a consensus conference according to the best estimate procedure [Kosten and Rounsaville, 1992].

In CEDAR, DNA samples were collected from the members of the probands' nuclear families. From this DNA collection, we selected samples of 28 adult males (mean age ± SEM, 38.8 ± 0.65) and 14 females (36.6 ± 1.16) with a lifetime DSM-III-R diagnosis of SD, as well as 57 males (41.6 ± 0.76 years of age) and 57 females (40.6 ± 0.53) without any DSM-III-R axis I or II disorder. To lessen the potential influence of stratification bias in this pilot study, the sample was circumscribed to European-Americans. To maximize phenotypic differences for SD liability between the affected and unaffected subsamples, the control subjects were selected to be older than 35 years (males' age range, 35–64; females', 35–52), and thus predominantly had been beyond the modal age of risk for SUD [Warner et al., 1995]. The distribution of SD diagnoses in the sample, the procedure, and the DNA analyses are described elsewhere [Vanyukov et al., 1998].

We studied a dinucleotide repeat polymorphism (DRP) at the *DRD5* gene, D5(CT/GT/GA)$_n$ [Sherrington et al., 1993]. The genotype coded in accordance with the dose (0, 1, or 2) of the modal allele (148 bp, allele 9) [Vanyukov et al., 1998] was used for testing the statistical relationships with the DRP. Counts of symptoms for the lifetime DSM-III-R diagnoses of ASPD (adult symptoms) and, retrospectively assessed, childhood conduct disorder (CD) and oppositional defiant disorder (ODD) were used as indices of antisociality. The categorical diagnoses of these disorders were not used in the analyses because they are generally less informative than dimensional indices and because of their low prevalence in this sample (e.g., only five males [6%] and 1 female [1.4%] had a diagnosis of ASPD).

Association analyses had to be performed for male and female subsamples separately, because of sex-related heterogeneity found in the *DRD5* associations in the previous report (e.g., the association with the SD risk was much stronger in females) [Vanyukov et al., 1998], and because of prior data indicating sex differences in liability to substance abuse and the composition of its phenotypic variance [e.g., van den Bree et al., 1998]. Correlation and regression analyses (linear regression for continuous dependent variables and logistic regression for dichotomous dependent variables) were used for detecting and testing statistical relationships between the genotype and behavioral traits. Mediation was tested using regression analysis [Baron and Kenny, 1986]. A mediational hypothesis can be accepted if (1) the independent variable (in this case, the DRP genotype) affects the mediator (antisociality index) when the mediator is regressed on the independent variable; (2) the independent variable affects the dependent variable (the dichotomously defined SD liability: affected/nonaffected) when the latter is regressed on the independent variable; and (3) the mediator affects the dependent variable when the latter is regressed on both the mediator and independent variable, and the effect of the independent variable is less than that in the second regression equation.

TABLE I. *DRD5* Genotype-Symptom Count Correlations

	Symptoms[a]		
Sex	ODD	CD	ASPD
Male	0.25*	0.11	0.06
Female	0.25*	0.14	0.30*

*$p < 0.05$.
[a]ODD = oppositional defiant disorder; CD = conduct disorder; ASPD = antisocial personality disorder.

The correlations between the indices of antisociality and the DRP genotype (Table I) suggest that the polymorphism is associated with ODD severity in both males and females.

There is no significant relationship between the genotype and CD symptoms. The relationship between the genotype and the adult ASPD symptoms is moderated by sex: there is a positive correlation in females but no association in males.

Temporal continuity is observed among the indicators of antisociality: correlations between the ODD and ASPD symptoms in males and females are 0.46 and 0.30 ($P < 0.001$), respectively. Since ODD symptoms occur earlier than ASPD symptoms, it is plausible that ODD symptoms mediate the relationship between the genotype and the adult antisocial symptoms. Such mediation may be possible only in females because of the absence of the genotype-ASPD correlation in males.

A test of the mediational hypothesis in females (Table II) shows that the conditions for mediation are satisfied: The genotype contributes to variation in both the mediator (ODD) and the dependent variable (ASPD), and its relationship with the latter is weaker when the mediator is present in the regression equation.

Both ODD and ASPD symptom counts are associated with the diagnosis of SUD (logistic regression coefficients are b = 1.24, $P < 0.01$, and b = 1.19, $P < 0.001$, respectively). Since genetic correlation has been found between SUD problem severity and both childhood and adult antisocial problems [Grove et al., 1990], we tested the possibility that the *DRD5* gene may partly underlie this correlation. Tests of mediation of the genotype-SUD liability relationship by ODD and ASPD symptom counts (Tables III and IV, respectively) do not suggest a considerable effect of either potential mediator.

TABLE II. Mediation of the Genotype-ASPD Symptom Count Relationship by ODD Symptom Count*

Predictor	b	SE_b	Constant	P_b
Mediation condition 1 test (dependent: ODD)				
Genotype	0.50	0.061	1.48	<.001
Mediation condition 2 test (dependent: ASPD)				
Genotype	0.83	0.322	0.59	.01
Mediation condition 3 test (dependent: ASPD)				
Genotype	0.54	0.302	0.48	.08
ODD	1.07	0.274		<.001

*ASPD = antisocial personality disorder; ODD = oppositional defiant disorder.

TABLE III. Mediation of the Genotype-SUD Relationship by ODD*

Predictor	b	SE_b	Constant	P_b
Mediation condition 1 test (dependent: ODD)				
Genotype	0.50	0.061	1.48	<.001
Mediation condition 2 test (dependent: SUD diagnosis)				
Genotype	1.59	0.537	−3.37	<.005
Mediation condition 3 test (dependent: SUD diagnosis)				
Genotype	1.54	0.620	−3.91	<.05
ODD	1.10	0.439		<.05

*SUD = substance use disorders; ODD = oppositional defiant disorder.

Nevertheless, in contrast to the ODD symptom count that does not influence the relationship, the regression coefficient for genotype decreases somewhat when the ASPD count is entered in the regression equation, from 1.59 to 1.12, and 95% confidence interval for the genotype odds ratio deteriorates from 1.7–14.1 to 0.9–11.6.

In this pilot study we analyzed the relationship between the genotype for a polymorphism at the *DRD5* gene, antisociality, and the risk for SD. The dopamine D5 receptor, together with the D1 receptor, belongs to the family of D1-like receptors that stimulate adenylate cyclase. This receptor family may mediate a reduction in drive to seek cocaine reinforcement, in opposition to the reward and reinforcement effects ascribed to the D2-like receptors [Self et al., 1996]. The D5 receptor has been shown to have 10 times higher affinity to dopamine than the D1 receptor [Sunahara et al., 1991]. Importantly, a high D5 receptor density is found in the limbic brain structures, which suggests its putative role in emotional regulation and, perhaps, the hostility and anger that typify ODD.

Because of the sample size limitations, to avoid empty cells, we chose to test associations with the modal allele (allele 9) of the polymorphism studied, predominant in both cases and controls, pooling other alleles in the non-9 group. This procedure was also justified by a higher *a priori* likelihood for a functional mutation in the *DRD5* gene to be in allelic association with the predominant marker allele than with any minor allele. The reduction of a multiallelic marker polymorphism to two alleles has been described as a practical approach to allelic association studies [Collins and Morton, 1998; these authors suggest merging associated alleles through a stepwise process]. Whereas it is unlikely that the DRP studied herein has functional significance, it has been shown to be a highly informative marker of the *DRD5* gene [Sherrington et al., 1993], used as such in a number of studies of psychiatric disorders [e.g., Barr et al., 1997; Kalsi et al., 1996], and may be in allelic association (linkage disequilibrium) with a functional *DRD5* polymorphism. We have previously shown association of this DRP with SD liability in males and females [Vanyukov et al., 1998]. We are not aware of other studies of this or other *DRD5* gene polymorphisms in SUD. The only additional indication that the region where this gene is located is involved in these disorders has been obtained in a genome scan for genes involved in liability to alcohol dependence (the data suggesting linkage to D4S244 and D4S2393 markers) [Reich et al., 1998]. It would be important to reproduce associations detected in this pilot study as well as to show the existence of a functional variation that underlies them.

TABLE IV. Mediation of the Genotype-SUD Relationship by ASPD*

Predictor	b	SE_b	Constant	P_b
Mediation condition 1 test (dependent: ASPD)				
Genotype	0.83	0.322	0.59	<.05
Mediation condition 2 test (dependent: SUD diagnosis)				
Genotype	1.59	0.537	−3.37	<.005
Mediation condition 3 test (dependent: SUD diagnosis)				
Genotype	1.16	0.655	−4.84	>.05
ASPD	1.12	0.320		<.001

*SUD = substance use disorders; ASPD = antisocial personality disorder.

The associations with the *DRD5* DRP genotype we observed for SD liability and ASPD symptoms were stronger in females, consistent with the notion that affected females—the less affected sex for both disorders—have higher genetic predisposition to these disorders than affected males. No sex difference was observed in the strength of the DRP association with ODD symptoms, which, in turn, is consistent with the fact that ODD affectedness in males and females does not differ [Simonoff et al., 1997].

Males and females also did not differ in their lack of significant association between the DRP genotype and CD symptom count. This finding in males is consistent with the low heritability of juvenile symptoms of ASPD found in males [Lyons et al., 1995]. The absence of the association with adult ASPD symptoms indicates that the moderate heritability of these symptoms in males is not contributed by the *DRD5* variation.

In females, however, the association between the genotype and adult antisocial symptoms is significant and mediated by the ODD symptoms. This suggests that the *DRD5* gene partly underlies developmentally persistent variation in antisociality. Notably, a twin study in males has shown complete genetic overlap between adult and juvenile antisocial symptoms [Lyons et al., 1995]. Significant genetic continuity in antisocial behavior during adolescence also was shown in another twin study in which twins were not separated by sex [O'Connor et al., 1998]. Whereas our data do not support the possibility that this genetic correlation in males is contributed by the *DRD5* gene (the genotype is not associated with the adult symptoms), it is possible that the *DRD5* gene contributes to the developmental continuity of antisocial behavior in females. It should also be noted that the juvenile symptoms of ASPD are CD rather than ODD symptoms, and thus, considering their low heritability, unlikely to demonstrate a strong association with any single candidate gene. Another twin study, however, showed significant heritability of liability to a categorically defined conduct disorder (DSM-III-R diagnosis, with the exception of six-month symptom duration criterion) [Slutske et al., 1997]. This leaves open the possibility that other genetic polymorphisms than the one studied herein may be associated with this trait. A relationship between ODD and ASPD symptoms, genetically independent from the CD-ASPD connection, has been shown in an adoption study [Langbehn et al., 1998]. The authors suggest that "ge-

netically transmitted liability to sociopathy might manifest earlier in life as the personality-like symptoms of ODD rather than behaviorally oriented criteria for conduct disorder." Our data support both phenotypic and genetic relationships between ODD and adult ASPD symptoms, pointing to the *DRD5* gene as one possible determinant of this relationship.

The data obtained in this study do not support mediation of the relationship between the genotype and liability to SD by ODD or ASPD symptom counts. It is possible that a trend observed for ASPD count is reflective of the *DRD5* gene's role as a common cause of variation in the two traits. Nevertheless, even if the mediation effect exists, the direction of the cause-effect relationship involving the genotype, SD liability, and adult antisociality cannot be inferred with certainty from these cross-sectional data (except, of course, the unambiguous bivariate genotype-trait relationships). It is also conceivable that the genotype-antisociality association is secondary to the genotype-SD liability association, due to the antisociality-liability correlation, since the sample was ascertained based on the presence/absence of SD in the male proband. Our data, however, suggest independent contributions of the *DRD5* gene to antisociality and SD liability, a situation similar to that previously observed in the same sample for novelty seeking and SD liability [Vanyukov et al., 1998].

Although the associations detected in this study are unlikely to be spurious [see Vanyukov et al., 1998], they await confirmation in other studies, preferably using a family-based design in which case and control samples consist of alleles or haplotypes transmitted or not transmitted, respectively, from parents to the affected offspring. Whereas a case-control design is generally more efficient in detecting associations [Morton and Collins, 1998], a family-based approach [e.g., Spielman et al., 1993; Spielman and Ewens, 1996] ensures against spurious associations due to stratification bias (if cases and controls differ in the representation of groups with different base allelic frequencies). The likely effect of stratification in most populations, however, is more than two orders of magnitude less than association findings (where allelic association $\rho > 0.2$, as in this report) [Morton and Collins, 1998]. Regardless of the approach, it is important that the validation study sample be taken from the population of the original finding, because both genetic and environmental mechanisms of liability variation may differ in different populations (e.g., the *ALDH* gene's role in the risk for alcoholism among East Asians and Caucasians [Agarwal and Goedde, 1992]).

It should be emphasized that the *DRD5* gene is but one of the possible genetic determinants of variation in SUD liability and associated antisociality. These traits are characterized by polygenic (multifactorial) inheritance, i.e., the genetic component of their phenotypic variation is determined by polymorphisms at a number of loci. Both traits have been found to be associated with polymorphisms at other genes. Virtually all drugs of abuse stimulate dopaminergic neurons, and their rewarding effects are associated with dopamine release [Koob and Nestler, 1997; Wise, 1998]. Other dopamine receptor genes, as well as genes encoding other neurotransmitter receptors modulating reward, have been found to be associated with liability to SD [reviewed in Vanyukov and Tarter, in press]. Genes encoding enzymes involved in the neurotransmitter metabolism are also potential contributors to the heritability of SD liability. For instance, monoamine oxidases participate in the metabolism of dopamine, which is one of the possible ways of their influence on the risk for SUD. Studies of the monoamine oxidase A gene suggested its association with liability to SUD [Hsu et al., 1996; Parsian, 1999; Parsian et al., 1995; Vanyukov et al., 1995]. In addition, a number of candidate genes have been shown to be associated with personality characteristics related to the risk for SUD, such as novelty seeking [e.g., Ebstein et al., 1996; Vanyukov et al., 1998]. Moreover, genes encoding enzymes involved in the metabolism of xenobiotics—e.g., the *CYP2D6* gene encoding a cytochrome P-450 enzyme metabolizing opiates—also have been shown to be associated with the risk for SD [Tyndale et al., 1997]. Obviously, numerous other genes are potential candidates for SD-related association studies. Concurrent investigation of candidate genes, environmental factors, and their interactions within a developmental framework would be a desirable approach to resolving the complex system of SD liability determination.

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