



An examination of the association between DRD4 and DRD2 polymorphisms and personality traits

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Received 1 June 2001; received in revised form 1 October 2001

Abstract

To date, evidence supporting a positive association between the 7-repeat allele of the D4 dopamine receptor (DRD4) exon III 48 bp polymorphism and Novelty Seeking (NS) has been mixed, with some studies confirming and others refuting the association. A positive association between NS and the minor *Taq1* A allele (A1) of the D2 dopamine receptor (DRD2) has also been reported. In the present study, we sought to replicate the associations between the DRD4 and DRD2 polymorphisms and various personality traits, as measured by the Multidimensional Personality Questionnaire. The sample consisted of 137 families ($n = 348$) assessed as part of the ongoing Minnesota Twin Family Study. The data were analyzed at both the individual-level, to maximize comparability with previous studies, and at the family-level, to control for population stratification. The DRD4 and DRD2 polymorphisms were not associated with MPQ measures related to NS, results that may cast doubt on the generalizability of previous positive findings. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: DRD4; DRD2; Personality; Molecular; MPQ

Decades of biometric family, twin, and adoption research have demonstrated that genetic factors play an important role in normal range personality differences, typically accounting for 40–50% of the variance (Bouchard, 1994). Only recently however, have investigators sought to identify the specific genetic polymorphisms influencing personality variation. In 1996, both Ebstein et al. and Benjamin et al. reported a positive association between a variable number of tandem repeat (VNTR) polymorphism in exon III of the D4 dopamine receptor (DRD4) and

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novelty-seeking (NS), a personality trait characterized by impulsivity, exploration, fickleness, excitability, quick-temper, and extravagance. In both cases, individuals carrying at least one copy of the 7-repeat allele had higher NS scores than individuals not carrying this allele. Subsequent studies have both supported (Benjamin et al., 2000, Strobel, Wehr, Michel, & Brocke, 1999) and refuted (Gebhardt et al., 2000; Jönsson et al., 1997, 1998; Mitsuyasu et al., 2001; Persson et al., 2000; Pogue-Geile, Ferrell, Deka, Debski, & Manuck, 1998; Sullivan et al., 1998; Vandenberg, Zonderman, Wang, Uhl, & Costa, 1997) these findings (see McGue, in press).

The minor *Taq I A* allele (A1) of the D2 dopamine receptor (DRD2) has also been found to be associated with high NS scores (Noble et al., 1998). Moreover, the DRD2 and DRD4 polymorphisms may interact, accounting for more of the variance in NS when examined in combination than expected based on the additive effects of each polymorphism (Noble et al., 1998). The present study sought to replicate the reported associations between personality traits related to the NS construct and the DRD4 VNTR and the DRD2 *Taq I A* polymorphisms.

1. Methods

1.1. Participants

The sample consisted of 17-year-old twins and their parents who participated in the Minnesota Twin Family Study (MTFS). The MTFS is a population-based, longitudinal study of adolescent twins and their parents. Twin families were ascertained from Minnesota birth records and located using public databases. The participating families were broadly representative of the Minnesota population at the time the twins were born; approximately 98% were Caucasian. A thorough description of the design, recruitment procedures, and participation rates of the MTFS is given in Iacono, Carlson, Taylor, Elkins, and McGue (1999). Families ($n = 137$) were included in the analyses if DNA was available for both parents and at least one child, and the child had a valid personality measure. Two mothers and two fathers were dropped from the individual-level analyses because of elevated scores on the validity scales from the personality measure. This resulted in a total sample of 348 individuals, of which 40.4% were 17-year-old twins, 29.8% were the twins' mothers, and 29.8% were the twins' fathers. Eight individuals omitted more than two items on at least one of the primary personality scales, and thus do not have scores for those particular scales, but were otherwise included in the sample.

1.2. Measures

Personality was assessed using the 198-item version of the Multidimensional Personality Questionnaire (MPQ; Tellegen, 2000). The MPQ contains two validity scales, Variable-Response Inconsistency (VRIN) and True-Response Inconsistency (TRIN), which assess inconsistent responding and the tendency to answer items indiscriminately true or false, respectively. As mentioned, only those individuals with valid TRIN and VRIN scores were included in the analyses. The MPQ measures 11 primary personality traits, which in turn form three higher-order factors. Only those MPQ scales that were maximally related to the personality measure used in the original studies (Benjamin, Li, Patterson, Greenberg, Murphy, & Hamer, 1996; Ebstein et al.,

1996), namely the NS scale of the Tridimensional Personality Questionnaire (TPQ; Cloninger, 1987), were used in the present study. Previous analyses by Waller, Lilienfeld, Tellegen, and Lykken (1991) explored the relationship between the TPQ and the MPQ, and found that the MPQ Constraint (CN) superfactor and the primary scales that compose CN, namely control (CON), harm avoidance (HA), and traditionalism (TR), had the strongest relationships with NS. Specifically, a rotated interbattery factor analysis of the TPQ-MPQ primary scales revealed that CON from the MPQ maximally loaded on the NS factor from the TPQ (-0.80). That CON and NS are maximally related is not unexpected, as both tap facets of behavioral disinhibition (Waller et al., 1991). The loadings of the other indicators of CN on the TPQ NS factor were lower, although they still indicate that CN is related to NS (-0.29 for HA and -0.38 for TR). Given the findings from the Waller et al. (1991) study, the CN superfactor, and the primary scales that compose it, were used in the present study. It should be noted, however, that because CN is negatively related to NS, low scores on the MPQ's CN, CON, HA, and TR scales are associated with high scores on the TPQ's NS. Scale scores for all four scales were adjusted to a T-score metric (mean = 50, standard deviation = 10) within each age-sex cohort prior to analysis.

The DRD4 48 bp repeat alleles were determined by the PCR technique of Nanko, Hattori, Ikeda, Sasaki, Kazamatsuri, and Kuwata (1993). Comings et al. (1999) found that because of the GC rich nature of the polymorphic region, unless 5-azaguanidine completely replaced guanidine, some heterozygotes were missed, producing pseudohomozygosity. This required the identification of the alleles by silver staining (Budowle, Chakiaborty, Guisti, Eisenberg, & Allen, 1991). The DRD2 Taq I A1/A2 polymorphism was genotyped by the technique of Grandy, Zhang, and Ceveili (1993). All the genotyping was done in the Department of Medical Genetics at the City of Hope Medical Center.

1.3. Data analyses

1.3.1. Individual-level analyses

In order to maximize comparability with earlier studies, the present study looked for associations at the individual-level employing three distinct DRD4 genotype groupings: those with at least one 7-repeat allele were compared to those without a 7-repeat allele, those with the 4,4 genotype were compared to those with the 4,7 genotype, and those with only short (2-, 3-, 4-, 5-repeat) alleles (SS) were compared to those with one or two long (6-, 7-, 8-repeat) alleles (SL and LL). For DRD2, those with at least one A1 allele were compared to those without an A1 allele. Two-factor (sex \times genotype) analyses of variance (ANOVA) were used to compare the MPQ scale scores between groups. A three-factor (sex \times DRD4 \times DRD2) ANOVA was used to analyze the interaction between DRD4 and DRD2. In the three-factor ANOVA, DRD2 (A1 present vs. A1 absent) and DRD4 (7 absent vs. 7 present) were both investigated at two levels. Each of these genotypic groupings replicates groupings used in previous studies (Benjamin et al., 1996; Ebstein et al., 1996; Noble et al., 1998).

1.3.2. Family-level analyses

Though individual-level analyses are necessary to detect small effect sizes, they should be complemented with analyses at the family-level. Family-level analyses are important because ethnic

stratification effects, which can confound genetic association studies, can be controlled via within-family controls. This approach seems especially germane here as there is marked ethnic variation in the allele frequencies of the DRD4 and DRD2 polymorphisms we are exploring (Barr & Kidd, 1993; Chang, Kidd, Livak, Pakstis, & Kidd 1996), and personality scores have been shown to vary by ethnicity (Davis, Hoffman, & Nelson, 1990; Hall, Bansal, & Lopez, 1999). The discordant sibling approach (Eaves & Meyer, 1994), which would be appropriate to control for ethnic stratification, was not feasible in the present analyses. Of the 32 complete pairs of dizygotic twins, only nine were genetically-discordant. Thus, we have used the transmission disequilibrium test for quantitative traits (Q-TDT) proposed by Allison (1997) to control for the possibility of ethnic stratification.

The sampling unit for the Q-TDT consists of the biological mother, biological father, and at least one offspring. The Q-TDT looks for an association between the offspring's personality score and the genetic marker conditional on parental mating type. By conditioning on parental mating type, the Q-TDT controls for ethnic stratification effects. At least one parent must be a heterozygote (i.e. have one short and one long allele at DRD4) for the family to be informative for the Q-TDT. As a consequence, in our sample of 137 families, only 68 were informative for DRD4 and 61 were informative for DRD2.

The Q-TDT procedure was implemented using hierarchical regression analysis. Specifically, our first regression model involved predicting offspring personality from parental mating type and offspring sex. Our next model involved adding offspring genotype. If offspring genotype added significantly to the prediction of personality beyond parental mating type, then there is evidence of a genetic association not due to ethnic stratification effects. Our third model involved adding in an interaction term for offspring genotype by sex. The genotype-by-sex interaction term was used to determine whether genetic effects varied by gender. Our final regression model involved adding a non-linearity term (i.e. genotype squared) to capture any non-additive genotypic expression. Specifically, squaring the genotype gives a non-linear function that, when added to the linear function, will capture any additional non-additive variance.

2. Results

The allele frequencies for DRD4 closely replicate the results from prior association studies of mixed European samples in which the 4- and the 7-repeat DRD4 alleles were the most common (Benjamin et al., 1996; Ebstein et al., 1996; Pogue-Geile et al., 1998). Specifically, the 2-, 3-, 4-, 5-, 6-, 7-, and 8-repeat alleles accounted for 10.8%, 5.6%, 65.5%, 2.2%, 0.1%, 18.4%, and 0.4% of alleles, respectively. Similarly, the frequencies of the DRD2 A1 and A2 alleles, 20.4 and 79.6%, respectively, closely replicate those reported in Noble et al. (1998).

The mean CN, CON, HA, and TR scores for each genotype are reported in Table 1. The individual-level analyses of DRD4 were largely non-significant, finding no significant main effects of DRD4 for any of the personality scales. The only significant finding was a sex by DRD4 interaction for the HA scale across the SS, SL, and LL grouping, the 7-absent vs. 7-present grouping, and the 4,4 vs. 4,7 grouping ($P < 0.05$). Specifically, the presence of a long allele was associated with higher HA scores in males and lower HA scores in females.

The individual-level analyses for DRD2 were also largely non-significant. Analyses of HA, TR, and CN did not reveal any significant main effects for DRD2, nor did they reveal any significant

sex by DRD2 interactions. However, there was a significant main effect of DRD2 on CON ($P < 0.05$), with the A1 allele associated with higher CON scores.

Individual-level analyses of the joint effect of DRD2 and DRD4 were also largely non-significant (Table 2). A three-way ANOVA of the presence and absence of DRD2×DRD4×sex did not reveal any significant main effects or interactions for HA, TR, CON, or CN.

To assess whether the positive findings at the individual level were artifactual (i.e. a result of ethnic variability or population stratification), analyses were also conducted at the family level using Q-TDT (Table 3). Of the 68 informative families for DRD4, 51 were in the SL×SS grouping, 16 were in the SL×SL grouping, and 1 was in the SL×LL grouping. As the SL×LL mating type contained only one family, that group was dropped from the analyses. The DRD4 by sex interactions that were found for Harm Avoidance at the individual level were not supported at

Table 1
Effects of the DRD2 and DRD4 genotypes on MPQ scores^a

Sex	Genotypes	HA	TR	CON	CN	<i>n</i>
		M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	
Male						
	7-absent	48.8 (10.0) ^b	50.4 (9.7)	49.9 (10.6)	49.4 (10.1)	124–126
	7-present	52.8 (9.7) ^b	50.3 (10.0)	51.0 (8.9)	51.5 (9.4)	54–55
	4,4	48.6 (10.9) ^b	50.3 (9.7)	51.4 (9.8)	50.5 (9.7)	69–71
	4,7	51.3 (9.1) ^b	50.9 (9.5)	51.2 (8.7)	52.2 (9.2)	64–65
	Short short	48.8 (10.0) ^b	50.3 (9.8)	49.9 (10.7)	49.3 (10.1)	122–124
	Short long	51.6 (9.3) ^b	50.1 (9.2)	50.9 (9.2)	51.8 (8.9)	47–48
	Long long	58.1 (11.1) ^b	53.4 (14.1)	51.6 (4.7)	56.0 (10.9)	9
	1-absent	49.7 (10.7)	50.0 (9.3)	49.6 (9.9) ^c	49.7 (10.1)	124–126
	1-present	50.8 (10.0)	50.1 (10.9)	51.8 (9.9) ^c	51.9 (8.8)	52–53
Female						
	7-absent	50.5 (10.1) ^b	50.6 (10.2)	49.6 (9.9)	50.4 (10.1)	109–110
	7-present	49.0 (10.3) ^b	49.4 (10.3)	50.8 (10.7)	49.3 (10.2)	53–57
	4,4	52.0 (9.9) ^b	50.5 (9.9)	49.0 (10.5)	51.1 (10.5)	64–65
	4,7	48.7 (9.9) ^b	49.4 (10.6)	49.4 (11.8)	49.2 (10.3)	37–40
	Short short	50.6 (10.0) ^b	50.2 (10.0)	49.7 (9.8)	50.4 (10.1)	107–108
	Short long	49.7 (9.9) ^b	50.2 (10.5)	50.6 (11.1)	49.4 (9.9)	48–52
	Long long	42.1 (12.7) ^b	46.9 (9.8)	50.0 (8.9)	45.8 (11.8)	7
	1-absent	50.0 (10.9)	49.4 (10.0)	49.1 (11.0) ^c	49.4 (10.4)	100–102
	1-present	50.0 (8.8)	51.0 (10.0)	51.6 (8.4) ^c	51.2 (9.4)	62–65

^a HA, TR, CON, and CN represent the primary personality scales of Harm Avoidance, Traditionalism, Control, and the higher-order factor of Constraint, respectively. The genotype groupings 7-absent vs. 7-present, 4,4 vs. 4,7, and short short vs. short long, vs. long long are different permutations of the 7-repeat DRD4 allele. The genotype grouping 1-present vs. 1-absent indicates the presence or absence of the DRD2 A1 allele.

^b Significant DRD4 by sex interaction ($P < 0.05$).

^c Significant main effect of the DRD2 A1 allele ($P < 0.05$).

the family level ($P=0.24$). For additive and non-additive main effects of the DRD4 7-repeat allele, the family-based method confirmed the insignificant findings of the individual-level analyses for all of the MPQ scales ($0.30 \leq P \leq 0.95$). In no case did offspring genotype contribute significantly to the prediction of offspring personality once parental mating type had been taken into account.

Of the 61 informative families for DRD2, six were in the 1,2×1,1 grouping, nine were in the 1,2×1,2 grouping, and 46 were in the 1,2×2,2 grouping. As the offspring in the 1,2×1,1 grouping all had the 1,1 genotype, this mating type was not informative on the differential effect of a 1 versus a 2 allele and so this mating type was dropped from the analyses. Similarly, among the nine offspring of the 1,2×1,2 mating type, seven had a 1,2 genotype, leaving insufficient genotypic variability among offspring in this group to permit meaningful statistical analysis. Thus, the analyses were performed only on the offspring from the 1,2×2,2 mating type. As both linear and quadratic terms cannot be entered into a model with only one mating type, the non-additive quadratic term (i.e. genotype squared) was not added into this model. None of the effect sizes reached a statistically significant level ($0.25 \leq P \leq 0.87$). The main effect of DRD2 on CON found at the individual level was not replicated at the family level ($P=0.54$). Again, offspring genotype did not contribute significantly to the prediction of offspring personality once parental mating type had been taken into account.

3. Discussion

The purpose of the present study was to try to replicate positive associations between DRD4 and DRD2 polymorphisms and the personality traits encompassed in novelty seeking. Analyses

Table 2
Effects of the DRD2 by DRD4 genotypes on MPO scores^a

Sex	Genotypes	HA	TR	CON	CN	<i>n</i>
		M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	
Male	1-A×7-A	48.2 (9.7)	50.5 (9.1)	49.6 (10.4)	49.0 (10.3)	83–84
	1-A×7-P	52.5 (10.1)	49.2 (9.9)	49.6 (9.0)	51.2 (10.0)	39–40
	1-P×7-A	50.3 (10.5)	50.3 (10.9)	51.1 (10.5)	50.8 (9.0)	40–41
	1-P×7-P	52.6 (8.4)	52.9 (11.0)	54.3 (7.4)	55.5 (7.3)	12
Female	1-A×7-A	50.8 (10.4)	50.0 (9.5)	49.6 (10.5)	50.6 (10.3)	74–75
	1-A×7-P	47.1 (12.1)	47.0 (11.4)	47.5 (12.8)	45.5 (10.0)	24–25
	1-P×7-A	49.5 (9.3)	50.6 (11.0)	49.9 (8.4)	50.0 (9.4)	33
	1-P×7-P	50.5 (8.4)	51.5 (8.9)	53.3 (8.2)	52.5 (9.4)	29–32

^a HA, TR, CON, and CN represent the primary personality scales of Harm Avoidance, Traditionalism, Control, and the higher-order factor of Constraint, respectively. 1-A and 1-P represent the absence and presence of the A1 DRD2 allele, respectively. 7-A and 7-P represent the absence and presence of a 7-repeat DRD4 allele, respectively. None of the effect sizes reached a statistically significant level.

were conducted both at the individual-level, to maximize comparability with earlier studies, and at the family-level, to control for ethnic variability. The results indicate that the MPQ scales that maximally load on the TPQ NS scale, specifically HA, TR, CON, and CN (Waller et al., 1991), were largely unrelated to the 7-repeat allele and the A1 allele. There were some exceptions, however. There was a significant sex by DRD4 interaction at the individual level across all three genotype groupings. There was also a significant main effect of DRD2 on CON. However, these associations were not replicated at the family level.

The positive associations that were uncovered do not provide support for previous findings of associations between DRD4 and DRD2 polymorphisms and novelty seeking personality traits. Previous studies have found that NS scores increase with the addition of a 7-repeat allele. As the MPQ personality scales used herein are negatively correlated with NS, MPQ scores should decrease with the addition of a 7-repeat allele. However, HA scores were found to decrease only for females. HA scores for males were found to increase with the addition of a 7-repeat allele, a result that is very much at odds with previous positive findings for males (Benjamin et al., 1996; Ebstein et al., 1996; Strobel et al., 1999). Similarly, the positive association between the DRD2 A1 allele and CON, in which the presence of an A1 allele was associated with higher CON scores, directly contradicts the findings in previous analyses (Noble et al., 1998). Moreover, neither the sex by DRD4 interaction for HA nor the main effect of DRD2 on CON were replicated when ethnic variability was controlled, further decreasing confidence in the results.

Table 3
Means of Q-TDT family-level multiple regressions on DRD4 and DRD2^a

Mating type	No. of long or A-1 alleles	Sex	HA	TR	CON	CN	<i>n</i>
			M (S.D.)	M (S.D.)	M (S.D.)	M (S.D.)	
SL×SS	0	M	48.2 (8.0)	49.9 (6.0)	50.6 (11.4)	49.3 (9.7)	13
	0	F	50.9 (8.7)	52.5 (12.0)	9.7 (12.1)	51.2 (10.9)	15
	1	M	48.1 (10.9)	51.6 (10.7)	52.8 (11.4)	52.0 (9.4)	11
	1	F	47.6 (9.0)	46.2 (9.2)	49.7 (8.3)	46.4 (9.2)	11–12
SL×SL	0	M	61.9 (n/a)	80.2 (n/a)	64.0 (n/a)	68.2 (n/a)	1
	0	F	57.3 (n/a)	51.9 (n/a)	57.4 (n/a)	56.0 (n/a)	1
	1	M	57.0 (8.5)	47.6 (7.8)	52.7 (13.3)	55.9 (9.1)	5
	1	F	43.8 (n/a)	– (n/a)	66.0 (n/a)	– (n/a)	1
	2	M	58.7 (10.3)	56.0 (15.5)	51.1 (5.5)	57.0 (11.0)	6
	2	F	53.7 (2.2)	52.0 (2.0)	48.1 (1.0)	51.1 (1.4)	2
1,2×2,2	0	M	51.0 (7.2)	48.6 (10.9)	50.3 (13.5)	49.7 (13.8)	8–10
	0	F	52.2 (11.3)	49.3 (13.4)	52.2 (5.6)	51.7 (11.5)	12–14
	1	M	49.2 (9.8)	54.4 (10.7)	54.8 (11.3)	53.9 (10.2)	11–12
	1	F	48.0 (5.6)	51.6 (11.5)	51.8 (9.7)	50.3 (7.0)	9–10

^a HA, TR, CON, and CN represent the primary personality scales of Harm Avoidance, Traditionalism, Control, and the higher-order factor of Constraint, respectively. The mating types of SS and SL correspond to the DRD4 genotype, while the mating types of 1,1 and 1,2 correspond to the DRD2 genotype. n/a indicates that the standard deviation could not be calculated for that cell. – indicates that *n* = 0 for that cell. None of the genotypic main effects or sex by genotype interactions reached statistical significance.

There are several possible reasons for this failure to replicate. One is the use of different measurement instruments. It is possible that the MPQ does not adequately measure the trait of Novelty-Seeking. While there is variance in the TPQ that is not accounted for by the MPQ (Waller et al., 1991), the predictive validity of this remaining variance is unclear. Specifically, both the Constraint scales of the MPQ and the Novelty-Seeking scales of the TPQ predict similar impulsive behaviors and behavioral disorders (Battaglia, Przybeck, Bellodi, & Cloninger, 1996; Cloninger, Sigvardsson, Przybeck, & Svrakic, 1995; Iacono et al., 1999; Krueger, 1999). Given this, it is noteworthy that the only studies that have found positive associations between DRD4 and NS have used the TPQ (Benjamin et al., 2000; Ebstein et al., 1996; Noble et al., 1998; Strobel et al., 1999). The primary exception is the 1996 study by Benjamin et al., in which the NEO-PI-R was used. However, none of the subsequent studies employing the NEO-PI replicated this result (Persson et al., 2000; Pogue-Geile et al., 1998; Vandenberg et al., 1997). Moreover, neither of the studies conducted with the Karolinska Scales of Personality have produced positive results (Jönsson et al., 1997, 1998). Even studies conducted with the Temperament and Character Inventory (TCI), which is an offshoot of the TPQ, have produced either conflicting (Ekelund, Lichtermann, Järvelin, & Peltonen, 1999; Ono et al., 1997) or negative results (Gebhardt et al., 2000; Mitsuyasu et al., 2001; Sullivan et al., 1998). This lack of generalizability to other personality inventories, which is supported by the present study, may act to further reduce confidence in the original positive associations between normal-range personality and DRD4.

Another possibility concerns differences among the studies' participants. The present sample differed from those in previous analyses on age, country of origin, ethnic group, and population representativeness. However, the personality data in the present study was age- and sex-corrected. Furthermore, allelic frequencies of DRD4 and DRD2 in the present study were consistent with those from previous studies, suggesting that differences between samples were not a function of differences in the distributions of alleles.

The variation in results may also reflect statistical power considerations. Both of the initial positive studies (Benjamin et al., 1996; Ebstein et al., 1996) reported effect sizes of approximately 0.5 standard deviations. The present study had an approximately 0.99 probability of detecting an effect of this magnitude in the individual-level analyses (effect size = 0.5, $n = 348$, $P < 0.01$, one-tailed). This suggests that the null findings herein are unlikely to represent a false negative result related to the effect sizes reported in previous studies. However, should the true effect size be 0.2 standard deviations as a recent meta-analysis suggested (McGue, in press), then the probability of detecting an effect in the present study drops to 0.55 (effect size = 0.2, $n = 348$, $P < 0.01$, one-tailed). This reduced power to detect effects of 0.2 standard deviations should be considered a limitation of this study, although this sample is one of the largest used to date. It may be that the effect of one gene within a polygenic phenotype is difficult to detect even within a sample of this size. Moreover, a small effect of each gene and genetic heterogeneity predicates that variation from study to study is the expected outcome (Comings, 1998).

A fourth possibility for the discrepant findings concerns the lack of control for ethnic variability. As noted previously, ethnicities can differ on both phenotypic frequencies and allelic frequencies, potentially resulting in spurious findings. All but one (Benjamin et al., 2000) of the positive associations were found in studies that only conducted individual-level analyses and did not control for ethnic variability. As there is evidence to suggest that personality traits may vary by ethnicity (Davis et al., 1990; Hall et al., 1999), these studies may have inadvertently reported

spurious associations. In the present study, the associations detected at the individual level (i.e. the sex by DRD4 interaction for HA, and the main effect of DRD2 on CON) were not detected at the family level, a result which may reflect either initial spurious associations or lack of power due to a reduced sample size.

The last explanation for the discrepant findings is that DRD4 and DRD2 are not functionally related to NS. Indeed, there is evidence that the DRD4 polymorphic repeat sequences are not functionally different (Asghari et al., 1994; Paterson, Sunohara, & Kennedy, 1999). Moreover, the base-pair sequences within the 48 base-pair repeat sequences can and do differ between people, leaving their biological relevance unclear (Paterson et al., 1999).

These results further reduce confidence in the functional role of the DRD4 exon III and Taq A 1 DRD2 polymorphisms in the personality trait of NS, although they do not preclude the role of other dopaminergic variation in NS. Future studies should use both individual-level and family-level analyses to examine other dopaminergic polymorphisms with more certain functional significance.

Acknowledgements

This research was funded in part by USPHS Grant Nos. DA05147, AA09367, and AA00175. S.A. Burt was supported by the NIMH Training Grant 2T32 MH17069-18.

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