American Journal of Medical Genetics (Neuropsychiatric Genetics) 81:257–267 (1998)

D_2 and D_4 Dopamine Receptor Polymorphisms and Personality

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The relationship of various dimensions of temperament, measured by the Tridimensional Personality Questionnaire (TPQ), to polymorphisms of the D_2 dopamine receptor (DRD2) and D_4 dopamine receptor (DRD4) genes was determined in 119 healthy Caucasian boys who had not yet begun to consume alcohol and other drugs of abuse. Total Novelty Seeking score of the TPQ was significantly higher in boys having, in common, all three minor (A1,B1, and Intron 6 1) alleles of the DRD2 compared to boys without any of these alleles. Boys with the DRD4 7 repeat (7R) allele also had a significantly higher Novelty Seeking score than those without this allele. However, the greatest difference in Novelty Seeking score was found when boys having all three minor DRD2 alleles and the DRD4 7R allele were contrasted to those without any of these alleles. Neither the DRD2 nor the DRD4 polymorphisms differentiated total Harm Avoidance score. Whereas subjects having all three minor DRD2 alleles had a significantly higher Reward Dependence 2 (Persistence) score than subjects without any of these alleles, no significant difference in this personality score was found between subjects with and without the DRD4 7R allele. In conclusion, DRD2 and DRD4 polymorphisms individually associate with Novelty Seeking behavior. However, the combined DRD2 and DRD4 polymorphisms contribute more markedly to this behavior than when these two gene polymorphisms are individually considered.

Contract grant sponsor: Adele C. Smithers and The Christopher D. Smithers Foundation; Contract grant sponsor: NIAAA; Contract grant number: AA-08020.

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Received 30 September 1997; Revised 30 December 1997

Am. J. Med. Genet. (Neuropsychiatr. Genet.) 81:257–267, 1998. © 1998 Wiley-Liss, Inc.

KEY WORDS: D_2 dopamine receptor gene; D_4 dopamine receptor gene; polymorphism; personality; novelty seeking; reward

INTRODUCTION

Family, twin, and adoption studies have provided convergent evidence for the importance of hereditary factors in a variety of human traits and disorders [Plomin et al., 1994]. The specific nature of these factors have remained elusive until the recent advent of molecular genetic techniques, the application of which has led to spectacular identification of single genes in rare disorders with simple Mendelian patterns of inheritance. However, it has been a great challenge to identify genes in human behavioral traits and disorders where no simple patterns of inheritance are known, and wherein minor genes in various combinations may conspire with environmental factors to produce a variety of phenotypes.

Neurotransmitter genes are among key candidates for evaluation in complex behaviors and behavioral disorders. In this regard, the dopaminergic system has received a great deal of attention since a large body of knowledge implicates this system in brain reward mechanisms [Wise and Rompre, 1989; Koob, 1992; Schultz et al., 1995]. That dopaminergic genes are involved in behavioral disorders was first revealed when the D_2 dopamine receptor (DRD2) gene was found to be involved in alcoholism [Blum et al., 1990]. Specifically, the minor *Taq*I A allele (A1) of the DRD2 was observed to be associated with a severe form of alcoholism. Whereas controversy has arisen because some studies found a lack of significant association of the DRD2 allele with this disorder, more recent investigations have revealed that the type of controls and alcoholics used [Noble et al., 1994d; Neiswanger et al., 1995; Lawford et al., 1997] are important determinants in this association [for recent review, see Noble, 1997]. It should, however, be noted that besides alcoholism, the DRD2

gene has also been implicated in a spectrum of dopamine related disorders, including cocaine dependence [Noble et al., 1993], polysubstance abuse [O'Hara et al.,1993; Comings et al., 1994a], nicotine dependence [Noble et al., 1994c; Comings et al., 1996a], obesity [Comings et al., 1993; Noble et al., 1994b; Blum et al., 1996], and Tourette's Syndrome [Comings et al., 1996b]. If a commonality, through the DRD2 gene, exists among these disorders, does the DRD2 A1 allele express itself as a unique CNS phenotype? Indeed, studies have shown the A1 allele is characterized by reduced brain D_2 dopamine receptor numbers [Noble et al., 1991; Pohjalainen et al., 1996], diminished CNS dopaminergic activity [Noble et al., 1994a; Berman and Noble, 1995], and enhanced response to stress [Berman and Noble, 1997]. Moreover, positron emission tomography studies have shown reduced glucose metabolism [Noble et al., 1997] in brains of subjects carrying the A1 allele. Given that, in some CNS measures, phenotypic expression differentiates subjects with and without the DRD2 A1 allele, does this differentiation also extend to personality dimensions?

There are already some recent studies that have determined the role of neurotransmitter genes in personality dimensions. A positive association was first reported [Ebstein et al., 1996] between the 7-repeat (7R) allele of the D_4 dopamine receptor (DRD4) gene and the personality trait of Novelty Seeking (NS) of the Tridimensional Personality Questionnaire [TPQ, Cloninger et al., 1991]. In a simultaneous publication, another group [Benjamin et al., 1996], using another questionnaire [NEO-PI-R, Costa and McCrae, 1992], found a similar association. Subsequent studies have supported this association [Ono et al., 1997; Ebstein et al., 1997a], whereas others have not [Malhotra et al., 1996; Jönnson et al., 1997; Vandenbergh et al., 1997]. Indeed, one study [Malhotra et al., 1996] found a significant negative association between the NS score and the DRD4 7R allele, leading to the suggestion that a reevaluation of the DRD4 in personality variations is indicated. The DRD4 7R allele has also been studied in substance use disorders, again with mixed findings. A recent review [Ebstein and Belmaker, 1997] summarizes the extant association studies of DRD4 polymorphism in NS and substance use disorders.

Other gene variants have also been studied in personality characteristics. Lesch et al. [1996] reported an association between anxiety-related traits and polymorphism in the transcriptional control region of the serotonin transporter gene. Specifically, the short variant of this polymorphism was positively associated with the Neuroticism score of the NEO-PI-R, and with the Harm Avoidance (HA) score of the TPQ, using weighted regression equations. However, this finding has also not been confirmed in another population [Ebstein et al., 1997b] since no association was observed between individuals grouped by the long and short variants of the serotonin transporter gene and HA or any other TPQ dimension. Finally, a cysteine to serine substitution in the 5-HT_{2c} serotonin receptor gene has been reported to associate with lower Reward Dependence [RD2 (Persistence) and RD 1,3,4] score of the TPQ [Ebstein et al., 1997c]. However, another group [Hamer, cited in Ebstein et al., 1997c] has failed to observe an effect of the 5-HT_{2c} genotype on the RD score. It should be noted that even in studies where statistically significant results are obtained, the variance attributed to a specific gene variant is frequently less than 5% for the personality trait measured. This suggests that either a major gene variant for that personality trait has yet to be discovered or, and more likely, that different gene variants contribute incrementally to the trait in question.

In the present study, the relationship of DRD2 and DRD4 polymorphisms to various personality traits was examined in young alcohol- and other drug-naive males. Three alleles of the DRD2 (*Taq*I A, *Taq*I B, and Intron 6) were assessed individually and in combination, as well as repeat alleles of the DRD4, individually and in combination with DRD2 alleles on personality traits derived from the TPQ. This study was reported at a recent meeting of the Society for Neuroscience [Noble et al., 1996].

METHODS

Subjects

The sample consisted of 119 unrelated Caucasian (non-Hispanic) males with a mean age (± S.D) of 12.1 (± 1.2) years and mean IQ (± S.D.) of 112 (± 13). These volunteers were recruited from elementary and junior high schools in the Los Angeles area. Inclusion/exclusion criteria have been previously described [Noble et al., 1994a; Ozkaragoz and Noble, 1995]. Briefly, the children came from families with a positive or negative history of substance abuse. However, none had a positive family history of other psychiatric disorders (e.g., schizophrenia or affective disorders). All subjects were free of medical and psychiatric problems and none had yet begun to use alcohol, tobacco, or illegal drugs. Moreover, none of their mothers had consumed more than 4 drinks/week while pregnant with the proband. The research protocol was approved by the UCLA Human Subjects Protection Committee, and all subjects (parents and sons) gave written informed consent.

Personality Assessment The Tridimensional Personality Questionnaire (TPQ) is a self-report instrument which measures three higher-order personality dimensions of temperament [Cloninger, 1987a]. These dimensions (Fig. 1), which are thought to be independently heritable, are composed of Novelty Seeking (NS), Harm Avoidance (HA), and Reward Dependence (RD), each of which is composed of four lower-order dimensions [Cloninger et al., 1991]. The TPQ was individually administered to each subject at UCLA. Scores were obtained for each of the three higher order dimensions and their four lower order dimensions.

Molecular Genetic Analysis

Grandy et al. [1989a,b] described the cloning and chromosomal mapping of the human DRD2 gene. They also found, at this locus, a two-allele *Taq*I A RFLP in

NOVELTY SEEKING (NS)	HARM AVOIDANCE (HA)	REWARD DEPENDENCE (RD)
NS 1: Exploratory excitability vs. Stoic rigidity	HA 1: Anticipatory worry vs. Uninhibited optimism	RD 1: Sentimentality vs. Insensitiveness
NS 2: Impulsiveness vs. Reflective	HA 2: Fear of uncertainty vs. Confidence	RD 2: Persistence vs. Irresoluteness
NS 3: Extravagance vs. Reserve	HA 3: Shyness with strangers vs. Gregariousness	RD 3: Attachment vs. Detachment
NS 4: Disorderliness vs. Regimentation	HA 4: Fatigability and asthenia vs. Vigor	RD 4: Dependence vs. Independence

Fig. 1. Tridimensional Personality Questionnaire Scales and Subscales.

Caucasians, with a minor (A1) and a major (A2) allele. This RFLP was detected with the genomic phage clone λhD2G1, which is located in the 3' untranslated portion of the DRD2 gene. By using additional phage and cosmid clones in the vicinity of the DRD2, Hauge et al. [1991] found a new two-allele *Taq*I B RFLP, with a minor (B1) and a major (B2) allele, located 5' of the first coding exon of the DRD2 gene. Sarkar and colleagues [1991a,b] have reported another intronic variant in the DRD2 gene, a guanine (G) vs. thymine (T) substitution in Intron 6. These DRD2 intronic polymorphisms are shown in Figure 2.

Van Tol et al. [1991] cloned and Kennedy et al. [1992] localized the DRD4 on chromosome 11p15.5, a gene that has structural and pharmacological similarities to the DRD2. An interesting aspect of the structure of the DRD4 is the heterogeneity of the third cytoplasmic loop imparted by the 48 bp tandem repeat polymorphism. It has been suggested [Van Tol et al., 1992] that the receptor function covaries with the variation of the repeat sequence.

In order to determine DRD2 *Taq*I A, *Taq*I B, Intron 6 alleles and DRD4 repeat alleles, a 10 ml blood sample was drawn from each subject. DNA was extracted [Old, 1986] and subsequently used as a template for PCR [Saiki et al., 1988].

The primers and methods for determining the *Taq*I A DRD2 alleles have been previously described [Grandy et al., 1993; Noble et al., 1994b]. Two alleles were obtained: the A1 allele (the uncleaved 310 bp fragment) and the A2 allele (the cleaved 180 bp and 130 bp fragments).

The primers and methods for determining the *Taq*I B DRD2 alleles described by Castiglione et al. [1995] were utilized. Two alleles were obtained: the B1 allele (the uncleaved 459 bp fragment) and the B2 allele (the cleaved 267 bp and 192 bp fragments).

The primers and methods for determining Intron 6 DRD2 alleles were those described by Sarkar and collelagues [1991a] and modified by Comings et al. [1993]. Two alleles were obtained: the 1 allele (a T → G substitution) and the 2 allele (a G → T substitution).

The primers and methods for determining the DRD4 repeat alleles described by Lichter et al. [1993] were utilized. Several repeat (R) alleles were obtained. These included the 2R (379 bp), 3R (427 bp), 4R (475 bp), 5R (523 bp), 6R (571 bp), 7R (619 bp), and 8R (667 bp) alleles.

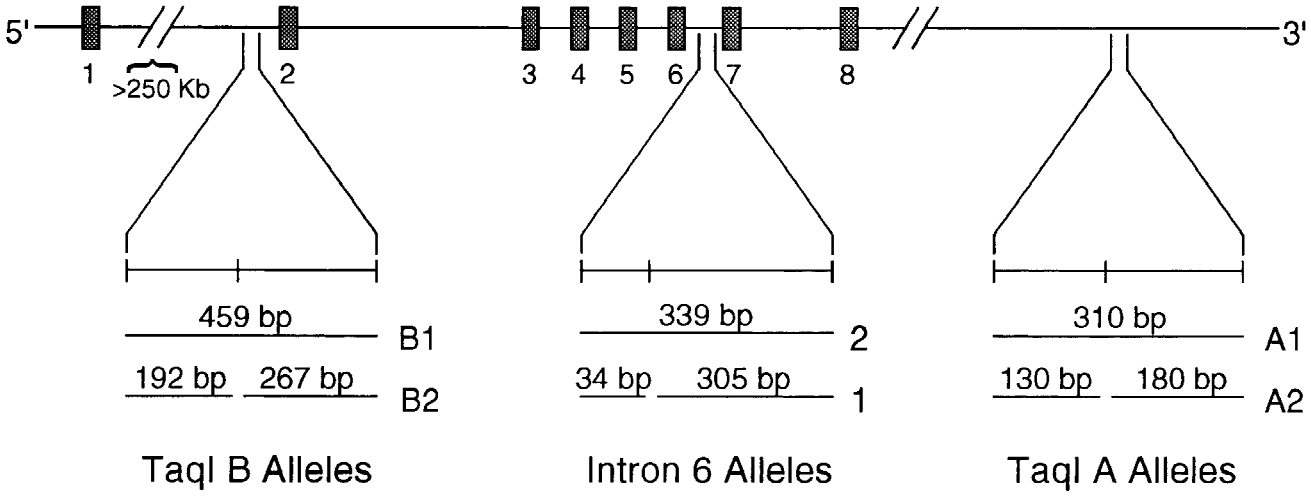

Fig. 2. D2 Dopamine Receptor Alleles.

Statistical Analysis

Three polymorphic loci in the DRD2 gene were classified and individually assessed. These haplotypes included alleles at the following sites: *Taq*I A ($A1^+$ [A1/A1 and A1/A2 genotypes] vs. $A1^-$ [A2/A2 genotype]), *Taq*I B ($B1^+$ [B1/B1 and B1/B2 genotypes] vs. $B1^-$ [B2/B2 genotype]), and Intron 6 (1^+ [1/1 and 1/2 genotypes] vs. 1^- [2/2 genotype]). DRD4 alleles were classified and assessed on the basis of the presence or absence of the 7 repeat ($7R^+$ [7R/7R and 7R/Non7R genotypes] vs. $7R^-$ [Non7R/Non7R genotypes]) alleles.

Association between TPQ scores and genetic type from each of the DRD2 polymorphic sites was determined by separate one-way analysis of variance (ANOVA). Specifically, the independent variables in the separate ANOVAs were the DRD2 ($A1^+$ vs. $A1^-$, $B1^+$ vs. $B1^-$, 1^+ vs. 1^-) and the DRD4 ($7R^+$ vs. $7R^-$) alleles. The dependent variables in the ANOVAs were scores on the three primary TPQ scales (NS, RD, and HA) or one of the four subscale scores of the three primary TPQ scales (NS1, NS2, NS3, NS4; RD1, RD2, RD3, RD4; and HA1, HA2, HA3, HA4).

A second set of ANOVAs was conducted in order to determine whether the effect of combined DRD2 polymorphic sites strengthens or weakens the association of the TPQ scores and genetic types. Specifically, comparisons were made between subjects who had all three minor haplotypes of the DRD2 ($A1^+$, $B1^+$, and 1^+ alleles) and subjects who had none of these three haplotypes ($A1^-$, $B1^-$, and 1^-). The dependent variables were the three TPQ primary scale scores and their four subscale scores.

Finally, a third set of ANOVAs was carried out so as to determine whether the effect of DRD2 haplotypes in combination with DRD4 alleles further strengthens or weakens the association of the TPQ scores and genetic types. In this analysis, comparisons were made between subjects who had all three minor haplotypes of the DRD2 and the DRD4 7R alleles ($A1^+$, $B1^+$ and 1^+, and $7R^+$ alleles) and subjects who had none of these alleles ($A1^-$, $B1^-$, 1^-, and $7R^-$). Again the dependent variables were the three TPQ primary scale scores and their four subscale scores.

The hypothesis proposed herein is that subjects with polymorphisms in the DRD4 and DRD2 genes that result in lower dopaminergic activity will have the highest Novelty Seeking scores. That the dopaminergic system is a major modulator of Novelty Seeking has been previously suggested [Cloninger, 1987b], and low dopaminergic activity has been found to associate with high Novelty Seeking in healthy volunteers [Joyce et al., 1994]. Thus, with respect to DRD4 polymorphisms, our hypothesis, supported by empirical data [Ebstein et al., 1996; Benjamin et al., 1996], is that subjects with the 7R allele will have higher Novelty Seeking score than subjects without this allele. Furthermore, since subjects with the DRD2 A1 allele have reduced dopaminergic activity compared to subjects without this allele [Noble et al., 1991; Pohjalainen et al., 1996], we also hypothesize that carriers of the minor DRD2 alleles in the three intronic loci under study (which are in linkage disequilibrium) will each have a higher Novelty Seeking score than the respective major allele.

P values $\leq .05$ were considered statistically significant, and P values $<.10$ were considered approaching significant levels. No Bonferroni adjustments for multiple comparisons were applied, as such corrections may inappropriately increase Type II error rates [Rothman, 1990]. For other statistical considerations, see the Discussion.

RESULTS

Table I shows the genotypes and frequencies of DRD2 *Taq*I A, *Taq*I B, and Intron 6 alleles and DRD4 alleles in the 119 subjects studied. The frequencies of the DRD2 A1, B1, and Intron 6 1 alleles and the DRD4 7R allele ranged from .15 to .20.

Table II presents the association among DRD2 *Taq*I A, *Taq*I B and Intron 6, and DRD4 genotypes. Hardy-Weinberg frequencies to observed data in the total sample were calculated [Ott, 1985]. Six pair-wise comparisons were analyzed. These included *Taq*I A vs. Intron 6, *Taq*I A vs. *Taq*I B, *Taq*I B vs. Intron 6, *Taq*I A vs. DRD4, Intron 6 vs. DRD4, and *Taq*I B vs. DRD4 alleles. The results showed no evidence of significant deviation ($P > .05$) from Hardy-Weinberg equilibrium. Moreover, a strong association was found between *Taq*I A and *Taq*I B sites ($\chi^2 = 83.3$, $P < .0001$), *Taq*I A and Intron 6 sites ($\chi^2 = 104$, $P < .0001$), and *Taq*I B and Intron 6 sites ($\chi^2 = 122$, $P < .0001$), indicating linkage among these loci. Not unexpectedly, because of different localization of these two genes (DRD2 on the long arm and DRD4 on the short arm of chromosome 11), no significant association was found between *Taq*I A and DRD4 sites, *Taq*I B and DRD4 sites, and Intron 6 and DRD4 sites ($P > .05$).

TABLE I. Genotypes and Frequencies of DRD2 *Taq*I A, *Taq*I B, Intron 6 Allelles, and DRD4 Repeat (R) Alleles

DRD2 and DRD4 alleles	Genotypes			Frequencies	
DRD2 *Taq*I A alleles	A1/A1	A1/A2	A2/A2	A1	A2
	7	33	79	.20	.80
DRD2 *Taq*I B alleles	B1/B1	B1/B2	B2/B2	B1	B2
	5	28	86	.16	.84
DRD2 Intron 6 alleles	1/1	1/2	2/2	1	2
	2	32	85	.15	.85
DRD4 R alleles	7R/7R	7R/Non7R	Non7R/Non7R	7R	Non7R
	2	43[a]	74[b]	.20	.80

[a]Consists of 3 2R/7R and 40 4R/7R genotypes.
[b]Consists of 2 2R/2R, 13 2R/4R, 7 3R/4R, 46 4R/4R, 3 4R/5R, 1 4R/6R, and 2 4R/8R genotypes.

TABLE II. Association Among DRD2 *Taq*I A (A1,A2), *Taq*I B (B1,B2) and Intron 6 (1,2), and DRD4 (7R,Non 7R) Genotypes

	B1/B1	B1/B2	B2/B2	7R/7R	7R/Non 7R	Non 7R/Non 7R
A1/A1	2	4	1	0	3	4
A1/A2	2	23	8	1	18	14
A2/A2	1	1	77	1	22	56
	1/1	1/2	2/2	7R/7R	7R/Non 7R	Non 7R/Non 7R
B1/B1	1	4	0	0	2	3
B1/B2	0	27	1	1	13	14
B2/B2	1	1	84	1	28	57
	A1/A1	A1/A2	A2/A2	7R/7R	7R/Non 7R	Non 7R/Non 7R
1/1	2	0	0	0	2	0
1/2	5	26	7	1	15	16
2/2	0	1	78	1	26	58

Table III compares NS scores in subjects with the DRD2 $A1^+$ and $A1^-$, $B1^+$ and $B1^-$, Intron 6 1^+ and 1^- alleles, and the DRD4 $7R^+$ and $7R^-$ alleles. Total NS score was significantly higher in $A1^+$ compared to $A1^-$ allelic subjects ($P = .032$, $r^2 = .040$) and in $B1^+$ compared to $B1^-$ allelic subjects ($P = .035$, $r^2 = .039$). Significant differences in NS 4 subscale scores were found between $A1^+$ and $A1^-$ ($P = .027$, $r^2 = .043$), $B1^+$ and $B1^-$ ($P = .004$, $r^2 = .075$), and 1^+ and 1^- ($P = .017$, $r^2 = .051$) allelic subjects. In subjects with the $7R^+$ allele, total NS score was significantly higher ($P = .049$, $r^2 = .034$) than in subjects without this allele. Furthermore, a significant difference ($P = .015$, $r^2 = .052$) in NS 3 subscale score was also found between subjects with 7 R^+ and 7 R^- alleles. It should be noted that the NS 3 subscale is dependent on answers to only a few questions and the results should therefore be interpreted cautiously.

Table IV compares HA scores in subjects with the DRD2 $A1^+$ and $A1^-$, $B1^+$ and $B1^-$, Intron 6 1^+ and 1^- alleles, and the DRD4 $7R^+$ and $7R^-$ alleles. There were no significant differences in total HA scores in any of these comparative allelic groups. However, significant differences were found in the HA 3 subscale scores between 1^+ and 1^- ($P = .049$, $r^2 = .034$) and $7R^+$ and $7R^-$ ($P = .030$, $r^2 = .041$) allelic subjects.

In Table V, RD scores are compared between subjects with the DRD2 $A1^+$ and $A1^-$, $B1^+$ and $B1^-$ and Intron 6 1^+ and 1^- alleles and DRD4 $7R^+$ and $7R^-$ alleles. $B1^+$ allelic subjects had significantly higher scores in total RD ($P = .036$, $r^2 = .039$) and RD 2 subscale ($P = .015$, $r^2 = .052$) when compared to $B1^-$ allelic subjects. Significant differences were also found between 1^+ and 1^- allelic subjects in total RD scores ($P = .037$, $r^2 = .038$), RD 2 subscale scores ($P = .043$, $r^2 = .037$), and RD 3 subscale scores ($P = .026$, $r^2 = .044$).

In Cloninger's original model, RD 2 (Persistence) was thought to be a component of RD. However, subsequent studies [Nixon and Parsons, 1989; Cloninger et al.,

TABLE III. Novelty Seeking Scores in Subjects With DRD2 and DRD4 Alleles*

	$A1^+/A1^-$		$B1^+/B1^-$		$1^+/1^-$		$7R^+/7R^-$	
NS 1	$A1^+$	5.72 ± 1.53	$B1^+$	5.63 ± 1.55	1^+	5.70 ± 1.52	$7R^+$	5.66 ± 1.34
	$A1^-$	5.39 ± 1.47	$B1^-$	5.45 ± 1.47	1^-	5.42 ± 1.48	$7R^-$	5.40 ± 1.57
		F (1.33)		F (.35)		F (.86)		F (.87)
		$P = .252$		$P = .555$		$P = .355$		$P = .354$
NS 2	$A1^+$	3.40 ± 2.00	$B1^+$	3.21 ± 1.90	1^+	3.12 ± 1.92	$7R^+$	3.31 ± 1.92
	$A1^-$	3.13 ± 1.66	$B1^-$	3.22 ± 1.74	1^-	3.26 ± 1.73	$7R^-$	3.16 ± 1.00
		F (.62)		F (.00)		F (.16)		F (.20)
		$P = .434$		$P = .977$		$P = .694$		$P = .653$
NS 3	$A1^+$	3.72 ± 1.76	$B1^+$	3.90 ± 1.68	1^+	3.79 ± 1.75	$7R^+$	3.91 ± 2.04
	$A1^-$	3.18 ± 1.20	$B1^-$	3.15 ± 1.98	1^-	3.19 ± 1.97	$7R^-$	3.03 ± 1.78
		F (2.14)		F (3.74)		F (2.40)		F (6.12)
		$P = .146$		$r^2 = .032$		$P = .124$		$r^2 = .052$
				$P = .056$				$P = .015$
NS 4	$A1^+$	5.65 ± 1.76	$B1^+$	5.91 ± 1.72	1^+	5.76 ± 1.79	$7R^+$	5.40 ± 1.68
	$A1^-$	4.86 ± 1.84	$B1^-$	4.83 ± 1.82	1^-	4.87 ± 1.82	$7R^-$	4.96 ± 1.93
		F (5.01)		F (8.73)		F (5.92)		F (1.60)
		$r^2 = .043$		$r^2 = .075$		$r^2 = .051$		$P = .209$
		$P = .027$		$P = .004$		$P = .017$		
NS Total	$A1^+$	18.49 ± 4.29 (n = 40)	$B1^+$	18.65 ± 3.98 (n = 33)	1^+	18.37 ± 4.21 (n = 34)	$7R^+$	18.28 ± 4.62 (n = 45)
	$A1^-$	16.56 ± 4.75 (n = 79)	$B1^-$	16.65 ± 4.82 (n = 86)	1^-	16.74 ± 4.77 (n = 85)	$7R^-$	16.55 ± 4.61 (n = 74)
		F (4.71)		F (4.53)		F (3.02)		F (3.96)
		$r^2 = .040$		$r^2 = .039$		$r^2 = .026$		$r^2 = .034$
		$P = .032$		$P = .035$		$P = .085$		$P = .049$

*$A1^+$ = A1/A1 and A1/A2 genotypes and $A1^-$ = A2/A2 genotype; $B1^+$ = B1/B1 and B1/B2 genotypes and $B1^-$ = B2/B2 genotype; 1^+ = Intron 6 1/1 and 1/2 genotypes and 1^- = Intron 6 2/2 genotype of the DRD2. $7R^+$ = 7R/7R and 7R/Non 7R genotypes and $7R^-$ = Non 7R/Non 7R genotypes of the DRD4. Values represent mean ± S.D. Comparisons that are significant ($P \leq .05$) or approaching significant ($P < .10$) levels are bold, r^2 = variance.

TABLE IV. Harm Avoidance Scores in Subjects With DRD2 and DRD4 Alleles*

	$A1^+/A1^-$		$B1^+/B1^-$		$1^+/1^-$		$7R^+/7R^-$	
HA 1	$A1^+$ 3.57 ± 1.84		$B1^+$ 3.80 ± 1.98		1^+ 3.95 ± 1.92		$7R^+$ 3.77 ± 1.83	
	$A1^-$ 3.51 ± 2.35		$B1^-$ 3.43 ± 2.26		1^- 3.36 ± 2.27		$7R^-$ 3.39 ± 2.38	
	F (= .04)		F (.68)		F (1.78)		F (.80)	
	P = .852		P = .410		P = .185		P = .368	
HA 2	$A1^+$ 3.33 ± 2.02		$B1^+$ 3.09 ± 2.04		1^+ 3.12 ± 2.03		$7R^+$ 3.13 ± 1.89	
	$A1^-$ 3.30 ± 1.82		$B1^-$ 3.40 ± 1.82		1^- 3.39 ± 1.83		$7R^-$ 3.42 ± 1.88	
	F (.00)		F (.62)		F (.50)		F (.64)	
	P = .954		P = .432		P = .481		P = .424	
HA 3	$A1^+$ 2.83 ± 1.63		$B1^+$ 2.94 ± 1.75		1^+ 2.76 ± 1.74		$7R^+$ 2.82 ± 1.66	
	$A1^-$ 3.49 ± 1.80		$B1^-$ 3.39 ± 1.77		1^- 3.47 ± 1.75		$7R^-$ 3.54 ± 1.78	
	F (3.87)		F (1.58)		F (3.95)		F (4.82)	
	r^2 = .033		P = .211		r^2 = .034		r^2 = .041	
	P = .058				P = .049		P = .030	
HA 4	$A1^+$ 2.38 ± 2.01		$B1^+$ 2.42 ± 1.98		1^+ 2.32 ± 2.01		$7R^+$ 2.73 ± 2.09	
	$A1^-$ 2.91 ± 2.17		$B1^-$ 2.85 ± 2.18		1^- 2.89 ± 2.16		$7R^-$ 2.73 ± 2.16	
	F (1.70)		F (.95)		F (1.76)		F (.00)	
	P = .195		P = .331		P = .187		P = .993	
HA Total	$A1^+$ 12.11 ± 4.61	(n = 40)	$B1^+$ 12.26 ± 4.95	(n = 33)	1^+ 12.16 ± 4.89	(n = 34)	$7R^+$ 12.45 ± 4.70	(n = 45)
	$A1^-$ 13.21 ± 5.75	(n = 79)	$B1^-$ 13.07 ± 5.58	(n = 86)	1^- 13.12 ± 5.60	(n = 85)	$7R^-$ 13.08 ± 5.81	(n = 74)
	F (1.11)		F (.54)		F (.76)		F (.38)	
	P = .295		P = .465		P = .386		P = .539	

*For symbol designations, see Table III.

1991] showed that RD 2 was uncorrelated with other aspects of RD [Sentimentality (RD 1), Social Attachment (RD 3), and Dependence on Approval (RD 4)]. Thus, the total scores of RD 1, RD 3, and RD 4 (RD 134) were compared between the different allelic groups. In these comparisons, there were no significant differences between the DRD2 $A1^+$ and $A1^-$ allelic groups (12.8±3.3 vs. 12.3±3.5, P = .482), the $B1^+$ and $B1^-$ allelic groups (13.1±3.2 vs. 12.2±3.5, P = .196), the intron 6 1^+ and 1^- allelic groups (13.2±3.1 vs. 12.2±3.5, P = .135), or between the DRD4 $7R^+$ and $7R^-$ allelic groups (13.0±2.8 vs. 12.1±3.7, P = .152).

Table VI compares NS scores in subjects with the three DRD2 haplotypes alone and in combination with DRD4 alleles. Of the 119 subjects studied, 31 had all three minor DRD2 haplotypes, whereas 77 had none of these haplotypes. Total NS score was significantly higher in the former compared to the latter group (P = .029, r^2 = .046). Similarly, in the NS 4 subscale, subjects with all three minor DRD2 haplotypes had a significantly higher score than those without them (P = .008, r^2 = .069). When subjects having all three minor DRD2 haplotypes and the DRD4 7R allele were assessed, 16 subjects had all these alleles, whereas 54 had none of them. Total NS score was significantly higher in the former compared to the later group (P = .010, r^2 = .104). Similarly, significantly higher NS 3 subscale score (P = .002, r^2 = .146) and NS 4 sub-

TABLE V. Reward Dependence Scores in Subjects With DRD2 and DRD4 Alleles*

	$A1^+/A1^-$		$B1^+/B1^-$		$1^+/1^-$		$7R^+/7R^-$	
RD 1	$A1^+$ 3.50 ± 1.20		$B1^+$ 3.61 ± 1.12		1^+ 3.53 ± 1.19		$7R^+$ 3.47 ± 1.31	
	$A1^-$ 3.29 ± 1.23		$B1^-$ 3.27 ± 1.25		1^- 3.30 ± 1.23		$7R^-$ 3.30 ± 1.17	
	F (.78)		F (1.85)		F (.90)		F (.54)	
	P = .380		P = .176		P = .344		P = .465	
RD 2	$A1^+$ 5.68 ± 1.65		$B1^+$ 6.00 ± 1.68		1^+ 5.88 ± 1.70		$7R^+$ 5.62 ± 1.60	
	$A1^-$ 5.20 ± 1.84		$B1^-$ 5.12 ± 1.77		1^- 5.15 ± 1.78		$7R^-$ 5.20 ± 1.88	
	F (1.88)		F (6.11)		F (4.17)		F (1.56)	
	P = .173		r^2 = .052		r^2 = .037		P = .215	
			P = .015		P = .043			
RD 3	$A1^+$ 7.01 ± 2.30		$B1^+$ 7.28 ± 2.08		1^+ 7.42 ± 2.07		$7R^+$ 7.00 ± 2.00	
	$A1^-$ 6.52 ± 2.29		$B1^-$ 6.45 ± 2.34		1^- 6.39 ± 2.32		$7R^-$ 6.49 ± 2.45	
	F (1.21)		F (3.17)		F (5.10)		F (1.39)	
	P = .274		r^2 = .027		r^2 = .044		P = .241	
			P = .077		P = .026			
RD 4	$A1^+$ 2.25 ± 1.21		$B1^+$ 2.21 ± 1.32		1^+ 2.24 ± 1.28		$7R^+$ 2.56 ± 1.25	
	$A1^-$ 2.48 ± 1.30		$B1^-$ 2.48 ± 1.25		1^- 2.47 ± 1.27		$7R^-$ 2.31 ± 1.28	
	F (.88)		F (1.03)		F (.83)		F (1.04)	
	P = .351		P = .311		P = .364		P = .310	
RD Total	$A1^+$ 18.43 ± 4.29	(n = 40)	$B1^+$ 19.10 ± 3.90	(n = 33)	1^+ 19.07 ± 3.92	(n = 34)	$7R^+$ 18.64 ± 3.91	(n = 45)
	$A1^-$ 17.49 ± 4.10	(n = 79)	$B1^-$ 17.31 ± 4.18	(n = 86)	1^- 17.31 ± 4.18	(n = 85)	$7R^-$ 17.30 ± 4.27	(n = 74)
	F (1.35)		F (4.50)		F (4.46)		F (2.95)	
	P = .248		r^2 = .039		r^2 = .038		r^2 = .025	
			P = .036		P = .037		P = .089	

*For symbol designations, see Table III.

TABLE VI. Novelty Seeking Scores in Subjects With DRD2 Haplotypes Alone and in Combination With DRD4 Alleles*

	$A1^+,B1^+,1^+/A1^-,B1^-,1^-$			$A1^+,B1^+,1^+,7R^+/A1^-,B1^-,1^-,7R^-$		
NS 1	$A1^+,B1^+,1^+$	5.67 ± 1.57		$A1^+,B1^+,1^+,7R^+$	5.61 ± 1.44	
	$A1^-,B1^-,1^-$	5.40 ± 1.47		$A1^-,B1^-,1^-,7R^-$	5.29 ± 1.53	
		F (.73)			F (.56)	
		$P = .395$			$P = .456$	
NS 2	$A1^+,B1^+,1^+$	3.23 ± 1.96		$A1^+,B1^+,1^+,7R^+$	3.19 ± 1.98	
	$A1^-,B1^-,1^-$	3.13 ± 1.69		$A1^-,B1^-,1^-,7R^-$	3.07 ± 1.65	
		F (.06)			F (.05)	
		$P = .803$			$P = .818$	
NS 3	$A1^+,B1^+,1^+$	3.90 ± 1.71		$A1^+,B1^+,1^+,7R^+$	4.55 ± 1.54	
	$A1^-,B1^-,1^-$	3.16 ± 2.00		$A1^-,B1^-,1^-,7R^-$	2.94 ± 1.86	
		F (3.29)			F (9.94)	
		$r^2 = .031$			$r^2 = .146$	
		$P = .073$			$P = .002$	
NS 4	$A1^+,B1^+,1^+$	5.87 ± 1.77		$A1^+,B1^+,1^+,7R^+$	5.81 ± 1.91	
	$A1^-,B1^-,1^-$	4.82 ± 1.85		$A1^-,B1^-,1^-,7R^-$	4.63 ± 1.92	
		F (7.36)			F (4.72)	
		$r^2 = .069$			$r^2 = .069$	
		$P = .008$			$P = .033$	
NS	$A1^+,B1^+,1^+$	18.68 ± 4.06	(n = 31)	$A1^+,B1^+,1^+,7R^+$	19.16 ± 3.46	(n = 16)
Total	$A1^-,B1^-,1^-$	16.50 ± 4.78	(n = 77)	$A1^-,B1^-,1^-,7R^-$	15.94 ± 4.47	(n = 54)
		F (4.91)			F (7.06)	
		$r^2 = .046$			$r^2 = .104$	
		$P = .029$			$P = .010$	

*$A1^+$ = A1/A1 and A1/A2 genotypes and $A1^-$ = A2/A2 genotype; $B1^+$ = B1/B1 and B1/B2 genotypes and $B1^-$ = B2/B2 genotype; 1^+ = Intron 6 1/1 and 1/2 genotypes and 1^- = Intron 6 2/2 genotype of the DRD2. $7R^+$ = 7R/7R and 7R/Non7R genotypes and $7R^-$ = Non7R/Non7R genotypes of the DRD4. Values represent mean ± S.D. Comparisons that are significant ($P \leq .05$) or approaching significant ($P < .10$) levels are bold; r^2 = variance.

scale score ($P = .033$, $r^2 = .069$) were found in subjects with all three minor DRD2 haplotypes and the DRD4 $7R^+$ allele when compared to those without any of these alleles.

Tables VII and VIII present, respectively, HA and RD scores in subjects with the three DRD2 haplotypes alone and in combination with DRD4 alleles. HA 3 subscale score was significantly lower ($P = .037$,$r^2 = .067$) in subjects with all three minor DRD2 haplotypes in combination with the DRD4 $7R^+$ allele than in subjects without any of these alleles. With respect to RD, the only significant difference found was in the RD 2 subscale score, with subjects carrying the DRD2 minor haplotypes having a significant higher score ($P = .050$, $r^2 = .037$) than subjects without any of these haplotypes.

DISCUSSION

Neurochemical, electrophysiological, and behavioral studies in animals and humans have shown the in-

TABLE VII. Harm Avoidance Scores in Subjects With DRD2 Haplotypes Alone and in Combination With DRD4 Alleles*

	$A1^+,B1^+,1^+/A1^-,B1^-,1^-$			$A1^+,B1^+,1^+,7R^+/A1^-,B1^-,1^-,7R^-$		
HA 1	$A1^+,B1^+,1^+$	3.76 ± 1.83		$A1^+,B1^+,1^+,7R^+$	4.40 ± 1.54	
	$A1^-,B1^-,1^-$	3.48 ± 2.31		$A1^-,B1^-,1^-,7R^-$	3.50 ± 2.46	
		F (.35)			F (1.93)	
		$P = .554$			$P = .170$	
HA 2	$A1^+,B1^+,1^+$	3.13 ± 2.06		$A1^+,B1^+,1^+,7R^+$	3.00 ± 2.00	
	$A1^-,B1^-,1^-$	3.33 ± 1.82		$A1^-,B1^-,1^-,7R^-$	3.48 ± 1.82	
		F (.24)			F (.83)	
		$P = .628$			$P = .367$	
HA 3	$A1^+,B1^+,1^+$	2.74 ± 1.59		$A1^+,B1^+,1^+,7R^+$	2.63 ± 1.63	
	$A1^-,B1^-,1^-$	3.43 ± 1.77		$A1^-,B1^-,1^-,7R^-$	3.69 ± 1.78	
		F (3.50)			F (4.55)	
		$r^2 = .033$			$r^2 = .067$	
		$P = .064$			$P = .037$	
HA 4	$A1^+,B1^+,1^+$	2.42 ± 2.05		$A1^+,B1^+,1^+,7R^+$	3.19 ± 2.34	
	$A1^-,B1^-,1^-$	2.92 ± 2.20		$A1^-,B1^-,1^-,7R^-$	3.02 ± 2.27	
		F (1.20)			F (.07)	
		$P = .276$			$P = .796$	
HA	$A1^+,B1^+,1^+$	12.05 ± 4.96	(n = 31)	$A1^+,B1^+,1^+,7R^+$	13.22 ± 4.63	(n = 16)
Total	$A1^-,B1^-,1^-$	13.15 ± 5.79	(n = 77)	$A1^-,B1^-,1^-,7R^-$	13.69 ± 5.99	(n = 54)
		F (.87)			F (.08)	
		$P = .352$			$P = .774$	

*For symbol designations, see Table VI.

TABLE VIII. Reward Dependence Scores in Subjects With DRD2 Haplotypes Alone and in Combination With DRD4 Alleles*

	$A1^+,B1^+,1^+/A1^-,B1^-,1^-$		$A1^+,B1^+,1^+,7R^+/A1^-,B1^-,1^-,7R^-$	
RD 1	$A1^+,B1^+,1^+$	3.68 ± 1.11	$A1^+,B1^+,1^+,7R^+$	3.56 ± 1.09
	$A1^-,B1^-,1^-$	3.31 ± 1.24	$A1^-,B1^-,1^-,7R^-$	3.19 ± 1.18
		F (2.04)		F (1.30)
		$P = .156$		$P = .259$
RD 2	$A1^+,B1^+,1^+$	5.87 ± 1.65	$A1^+,B1^+,1^+,7R^+$	5.56 ± 1.97
	$A1^-,B1^-,1^-$	5.13 ± 1.80	$A1^-,B1^-,1^-,7R^-$	4.85 ± 1.92
		F (3.92)		F (1.68)
		$r^2 = .037$		$P = .200$
		$P = .050$		
RD 3	$A1^+,B1^+,1^+$	7.37 ± 2.12	$A1^+,B1^+,1^+,7R^+$	7.31 ± 1.85
	$A1^-,B1^-,1^-$	6.53 ± 2.32	$A1^-,B1^-,1^-,7R^-$	6.37 ± 2.41
		F (2.99)		F (2.07)
		$r^2 = .028$		$P = .155$
		$P = .087$		
RD 4	$A1^+,B1^+,1^+$	2.23 ± 1.33	$A1^+,B1^+,1^+,7R^+$	2.31 ± 1.30
	$A1^-,B1^-,1^-$	2.49 ± 1.30	$A1^-,B1^-,1^-,7R^-$	2.35 ± 1.28
		F (.92)		F (.01)
		$P = .340$		$P = .914$
RD	$A1^+,B1^+,1^+$	19.14 ± 4.02 (n = 31)	$A1^+,B1^+,1^+,7R^+$	18.75 ± 3.99 (n = 16)
Total	$A1^-,B1^-,1^-$	17.47 ± 4.15 (n = 77)	$A1^-,B1^-,1^-,7R^-$	16.76 ± 4.17 (n = 54)
		F (3.65)		F (2.87)
		$r^2 = .034$		$r^2 = .042$
		$P = .059$		$P = .095$

*For symbol designations, see Table VI.

volvement of the mesocorticolimbic dopaminergic reward pathways of the brain in complex cognitive functions [Brozoski et al., 1979; Simon et al., 1980; Sawaguchi et al., 1990; Luciana et al., 1992]. Moreover, individual variations in these functions have been ascribed, in part, to genetic differences in the dopaminergic system [Fink and Reis, 1981; Sved et al., 1984; Oades et al., 1985; Noble et al., 1994a; Berman and Noble, 1995, 1997]. Dopaminergic activity has also been implicated in certain personality traits. D_2 dopamine receptor agonist-induced reactivity has been specifically associated with trait levels of Extraversion or Positive Emotionality but not with other personality traits [Depue et al., 1994]. A recent positron emission tomography (PET) study has shown an inverse relationship between the personality trait of Detachment and D_2 dopamine receptor numbers [Farde et al., 1997]. That variation, among humans, in some personality traits may be, in part, also genetically determined is suggested by studies showing a positive association between the 7R allele of the DRD4 gene and the personality trait of NS [Benjamin et al., 1996; Ebstein et al., 1996].

Many complex human behaviors, including personality traits, are quantitative and thus continuous in nature. In these behaviors, where no clear patterns of inheritance are known, multiple genes and environmental factors contribute to their expression [Bouchard, 1994; Mann, 1994; Plomin et al., 1994]. Thus, in ascertaining hereditary factors, no single gene may be either necessary or sufficient in explaining the likelihood of the development of these behaviors; rather, it is the combination of genes. An example of this is a recent study where three dopaminergic genes were found to associate with the severity of attention deficit hyperactivity disorder [Comings et al., 1996b]. Since the contribution of a single gene may account for only part of the variance in the behavior under study, the principle of examining more than one putative gene in any single study should also apply to personality traits.

To minimize differences in individual characteristics, all the subjects in the present study were males of European (non-Hispanic) descent and of narrow IQ and age range. Moreover, since alcohol and other drug use behaviors may influence personality trait scores, none of the subjects had yet begun to use any drugs of abuse. Another unique feature of this study is that it examined the relationship of haplotypes of one gene (DRD2), singly and in combination, to various aspects of personality. Moreover, it assessed the contribution of these haplotypes in combination with polymorphism in another gene (DRD4) to personality characteristics.

The results show that of the four temperaments studied (NS, HA, RD 134, and RD 2), NS was most strongly and positively associated with mutations in the DRD2 and the DRD4 genes alone (Table III) or in combination (Table VI). This was particularly true of the NS 3 (Extravagance) and NS 4 (Disorderliness) subscales. These findings comport with the hypothesized role of the dopaminergic system in this characteristic of temperament [Cloninger, 1987b]. With respect to Reward Dependence (RD 134), a trait in which another neurotransmitter system (norepinephrine) has been implicated [Cloninger, 1987b], no associations were found with mutations in the present two genes alone (Table V) or in combination (Table VIII). However, mutations in the DRD2 gene (Tables V and VIII) were positively associated with RD 2 (Persistence) characteristic of temperament. Interestingly, a previous study [Ebstein et al., 1996] found the NS scale was not correlated with either HA or RD 134 but was significantly correlated with RD 2. Concerning HA, a trait in which yet another neurotransmitter system (seroto-

nin) has been implicated [Cloninger, 1987b], mutations in the DRD2 and DRD4 genes alone (Table IV) or in combination (Table VII) were negatively associated with the HA 3 subscale (Shyness with Strangers) of this trait.

The finding that the DRD4 $7R^+$ allele was positively associated with NS is supported by some studies (see Introduction) but not by others. However, the positive association in the present study barely achieved a statistically significant level and accounted for only 3.4% of the variance (Table III). Similarly, the DRD2 minor haplotypes together also positively associated with NS and contributed 4.6% of the variance in this personality trait (Table VI). On the other hand, when the DRD2 minor haplotypes and the DRD4 $7R^+$ allele are combined, variance in NS increased to 10.4% (Table VI). This suggests that at least these two dopamine genes contribute to NS.

Put together, the composite profile of temperament that emerges from the present study is that subjects who carry the DRD2 minor haplotypes and the DRD4 $7R^+$ allele are more likely to display the characteristics of Extravagance (NS 3 positive), Disorderliness (NS 4 positive), Gregariousness (HA 3 negative), and Persistence (RD 2 positive), while subjects who do not carry these genetic variations are more likely to show the characteristics of Reserve (NS 3 negative), Regimentation (NS 4 negative), Shyness with Strangers (HA 3 positive), and Irresoluteness (RD2 negative).

In considering the impact of multiple significance tests, there were 90 tests of significance; 72 on subscales and 18 on total scale scores (Tables III–VIII). Across all 90 tests, 31 were significant at the $P = .10$ level and 21 were significant at the $P = .05$ level. If the null hypothesis held in each case, 9 results would be expected at the .10 level and 4.5 results at the .05 level due to chance alone. The discrepancy found between actual observations and theoretical expectations suggests that it is highly unlikely that all of the significant results found were due to chance alone. This interpretation is complicated by the fact that not all of the tests are independent, since subscale scores contribute to total score tests. Thus, when the 72 subscale tests were considered separately, 20 of the results were found at the $P = .10$ level compared to an expected number of 7.2, and 14 of the results were found at the $P = .05$ level compared to an expected number of 3.6, if the null hypothesis is held in all cases. Both of these discrepancies are significant at the $P = .0001$ level using a test of whether the sample proportion of significant results differ from the null values of .10 and .05, respectively. These results suggest that although some of the significant results found may be consequences of chance variation, it is highly unlikely that the full complement of the results found can be explained by chance alone.

Despite the finding that polymorphisms in dopaminergic genes associate with certain characteristics of temperament, the present study illustrates the complexities and difficulties entailed in identifying molecular genetic factors in personality. Even under the best of circumstances, where the dopaminergic system has been hypothesized to affect NS, and empirical evidence supports this link, polymorphisms in the DRD2 and DRD4 genes account for only 10% of the variance in this characteristic of temperament (Table VI). Taking the estimate that about 50% of the variance in behavioral traits is due to genetic determinants [Plomin et al., 1994] and assuming no epistatic interaction, the involvement of eight additional dopamine-related genes is suggested in this characteristic of temperament. Among such putative genes may be the other three dopamine receptors (D1, D3, and D5), dopamine β-hydroxylase, tyrosine hydroxylase, dopamine transporter, monoamine oxidase (MAO), and catechol-O-methyltransferase (COMT). However, assessing the incremental contributions of these and other genes to NS may not be an easy matter, since the possible small effects of these other genes may not only require a large number of subjects but also a clear control of nongenetic factors (still yet to be determined) that may influence this personality trait. Compounding these problems is the difficulty of estimating the likelihood of epistatic interactions (both positive and negative) among the various putative genes that associate with NS.

Another important issue in studying the relationship of genetic mutations to personality characteristics is that such mutations should have functional significance. Whereas there is some evidence that intronic mutations in the DRD2 gene affect brain D_2 dopamine receptor numbers [Noble et al., 1991; Pohjalainen et al., 1996] and physiological differences in ligand binding have been observed between the DRD4 7R and shorter repeats [Van Tol et al., 1992; Asghari et al., 1994], knowledge of the functional significance of mutations in other neurotransmitter genes, let alone the approximately 30,000 genes expressed in the brain, is exceedingly rare. It will be a daunting task to determine how such relevant mutations influence the variety of personality traits.

In conclusion, the present study shows that variations in the DRD2 and the DRD4 genes are most strongly and positively associated with NS. However, whereas a positive association was also found with RD2 and a negative association with HA 3, no association of these genes was observed with RD134. Given the relatively small variance found, the study suggests that a number of other genes will be implicated in various personality characteristics. The identification of these genes will be a great challenge for neuroscientists.

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