Personality Traits and Dopamine Receptors (D2 and D4): Linkage Studies in Families of Alcoholics

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Activation of the mesolimbic dopamine pathway appears to promote drug- and alcohol-seeking behavior in laboratory animals. Results for association and linkage analysis between various alcohol dependence phenotypes and the dopamine receptors have been quite mixed. Similarly, both positive and negative results have been presented concerning dopamine receptor genes and temperament. Cloninger has postulated that the novelty seeking factor from the Tridimensional Personality Questionnaire (TPQ) may be related to the dopamine neurotransmitter system. As novelty seeking is a trait of some importance for substance-dependent individuals, our goal was to test this relationship within a sample of families of alcoholics. No evidence favoring linkage between D2, D4, or DAT1 was found for TPQ novelty seeking. However, the harm-avoidance trait from the TPQ showed evidence for linkage to both the D4 and one of the D2 loci (TaqI A). The Multidimensional Personality Questionnaire (MPQ) was used to provide converging evidence for these results. The TPQ harm-avoidance scale loads heavily on introversion (worry, pessimism, shyness), characteristics that may be especially salient in alcoholic families. Thus, planned comparisons were made between selected MPQ traits measuring the affective dimension (negative affectivity, stress reaction, alienation, and well-being). We find evidence favoring linkage between the D2 and D4 receptor loci and these MPQ traits, with stronger evidence being seen for the D2 polymorphisms. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 88:634–641, 1999.
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INTRODUCTION

The heritability of human personality traits has been estimated to be between 30 and 60% based on data from twin and adoption studies [Plomin et al., 1994]. Because adult personality is a blend of both inherited predispositions to certain temperaments and the interplay between experience with varying environments, personality traits provide a challenge to those interested in their genetic mediation. Few studies have addressed specific genes with respect to major personality types. Therefore, the reports from different laboratories [Ebstein et al., 1996; Benjamin et al., 1996; Noble et al., 1998; Ono et al., 1997] suggesting a causal relationship between D4 receptor genotypes and one personality trait, novelty seeking, are especially noteworthy. However, several studies have not found significant associations between the novelty seeking trait and variants of the D4 receptor polymorphism [Vandenbergh et al., 1997; Gelernter et al., 1997; Malhotra et al., 1996; Sander et al., 1997].

Ebstein et al. [1996] measured novelty seeking using the Tridimensional Personality Questionnaire (TPQ), an instrument developed by Cloninger [1987] as a three-factor model of personality designed to measure temperament domains including novelty seeking, harm avoidance, and reward dependence. Cloninger [1987] has proposed that individual variation in the novelty seeking trait is mediated by genetic variability in dopamine transmission. Individuals who score higher than average on the novelty seeking scale are impulsive, excitable, exploratory, and quick tempered compared to those who score lower than average and who are more likely to be loyal, stoic, reflective, and frugal. The study by Benjamin and colleagues used items from the Neo Personality Inventory-Revised (NEO-PI-R) that have a high correlation with the TPQ novelty seeking scale. Whereas novelty seeking and D4 have been reported to be genetically associated, previous attempts to find an association between either reward dependence or harm avoidance and D4 receptor loci have been negative [Ebstein et al., 1996; Benjamin et al., 1996; Noble et al., 1998].

The D4 receptor gene is of interest because it con-

tains an unusually polymorphic 16 amino acid repeat region. Moreover, the length of the D4 exon III-repeat sequences has been shown to affect the binding of ligands to the receptor [Van Tol et al., 1992; Asghari et al., 1994]. These physiological differences in binding have been observed between the most common short receptor containing four repeats and the most frequently occurring long receptor containing seven repeats [Van Tol et al., 1992; Asghari et al., 1994].

Variations in D2 alleles have been shown to alter pharmacokinetic properties and receptor number in brain. Noble and Blum [1991], in a study involving both alcoholics and nonalcoholics, found that individuals who were homozygous for the A1 allele had lower densities of the dopamine D2 receptors in striatum than did individuals who were homozygous for the A2 allele. Recently these results have been strengthened by the findings of Thompson et al. [1997]. Using [^{3}H]raclopride to detect D2 ligand binding, autoradiography of the caudate, putamen, and nucleus accumbens was performed in tissue from normal middle-aged and elderly individuals without histories of substance abuse, neurological disorders, or psychopathology. Analysis of the data revealed that the presence of one or both A1 alleles was associated with reduced receptor binding throughout the striatum with statistically significant decreases being found in the ventral caudate and putamen. Further support for a relationship between variants of the TaqI A polymorphisms and pharmacokinetic properties of D2 receptors comes from a recent in vivo study of 54 healthy Finnish volunteers [Pohjalainen et al., 1998]. These investigators used positron emission tomography (PET) to study D2 receptor density in the striatum. Pohjalainen and colleagues determined D2 receptor binding density (Bmax), affinity (Kd), and availability (Bmax/Kd) in the volunteers using [^{11}C]raclopride to perform the PET studies. A statistically significant reduction in D2 receptor availability reflecting an alteration in receptor density was observed in the A1/A2 genotype group compared to the A2/A2 group. These results suggest that the A1 allele of the TaqI A polymorphism may be in linkage disequilibrium with a mutation in the promoter/regulatory gene element that affects dopamine D2 receptor expression.

The D2 gene, which was first described by Grandy et al [1989a], has been localized on 11q22-23. A two-allele TaqI Restriction Fragment Length Polymorphism (RFLP) was initially detected at this locus [Grandy et al., 1989b]. Additional polymorphisms within or close to the D2 gene have been found including the microsatellite C locus [Hauge et al., 1991], which has been localized to the intron separating exons 2 and 3. The D2 receptor is of some interest with respect to personality variation because the mesolimbic dopaminergic system is believed to be involved in regulation of emotions [Joyce, 1993; Amalric and Koob, 1993].

The D2 TaqI A receptor has been explored with respect to the TPQ personality dimensions and with the Eysenck Personality Inventory [Noble et al., 1998; Compton et al., 1996]. Both studies found the A1 allele associated with the TPQ novelty seeking scale, with no differences being seen for reward dependence or harm avoidance.

The dopamine transporter, which plays an important role in regulation of dopaminergic neurotransmission, mediates the active reuptake of synaptic dopamine. This gene has not been investigated with respect to personality variables. However, several lines of evidence suggest that dopamine may play a role in both substance abuse and bipolar disorders, especially in mania. Amphetamines and other psychostimulants including cocaine increase synaptic dopamine [Kuczenski and Segal, 1994; Leshner, 1996]. Because mania resembles the euphoria seen in intoxication due to the use of these substances, it has been suggested that similar dopaminergic involvement may explain the manic phase of bipolar disorder. Evidence for a bipolar disorder susceptibility locus near the DAT locus on chromosome 5 [Kelsoe et al., 1996] has been identified using linkage analysis of affected sib pairs. Dopamine transporter gene polymorphisms have also been investigated with respect to substance abuse with both positive [Sander et al., 1997] and negative [Persico et al., 1993] outcomes. The prevalence of the nine-repeat allele of the variable number tandem repeat (VNTR) polymorphism of the DAT1 polymorphism has been found to be increased in alcoholics displaying withdrawal seizures or delirium, compared to ethnically matched controls [Sander et al., 1997].

The purpose of the present study was, first, to determine if the D4 VNTR previously found to be associated with novelty seeking would be confirmed in a linkage study of alcoholic families, and second, to determine if the novelty seeking trait from the TPQ showed evidence for genetic linkage to two D2 polymorphisms in these same alcoholic families. One of these polymorphisms (TaqI A) had previously been investigated with respect to personality typology [Compton et al., 1996; Noble et al., 1998]. The third purpose was to investigate the dopamine transporter gene which has not been studied with respect to personality traits; and fourth, to test for possible relationships between harm avoidance or reward dependence and the D2 and D4 dopamine receptor polymorphisms. These traits had not been found to be associated with the D2 [Compton et al., 1996; Noble et al., 1998] or D4 receptor polymorphisms [Ebstein et al., 1996; Benjamin et al., 1996] in previous studies.

Although the relationship between the D2 and D4 dopamine receptor genotypes and temperament has been investigated in samples of normal individuals, this relationship has been explored less frequently in samples of alcoholics [Malhotra et al., 1996; Gelernter et al., 1997; Sander et al., 1997]. The current investigation used a sample of alcoholic probands and their nonalcoholic and alcoholic family members to investigate genetic linkage. A commonly observed difference in temperament between alcoholics and controls is the tendency for alcoholics to score higher on scales measuring novelty seeking [Cloninger, 1987; S.Y. Hill et al., unpublished observations]. Also, Cloninger et al. [1988] reported that childhood personality characteristics (high novelty seeking and low harm avoidance) were predictive of early-onset alcohol abuse. All of the

studies reported to date were conducted as association studies. Therefore, linkage between the D4 genotypes and personality traits have not previously been undertaken. Therefore, finding a relationship between this trait and dopaminergic receptors would be of considerable interest.

MATERIALS AND METHODS
Samples

DNA samples for 81 male and 46 female alcoholics along with 38 male and 77 female nonalcoholics, sibs, or parents from 52 families were genotyped for the D4 48-bp region, the D2 polymorphisms TaqI A and C, and the DAT1 transporter gene (see Table I). All of the individuals were members of one of two alcoholism family studies currently in progress in which sib pairs were available for study. One of the studies selected families through the presence of two alcoholic sisters (AA 08082 - Biological Risk Factors in Relatives of Alcoholic Women) while the other included families where there were two alcoholic brothers (AA 05909 - Cognitive and Personality Factors in Relatives of Alcoholics). Members of both studies had been administered the Diagnostic Interview Schedule (DIS) to determine the presence or absence of alcohol dependence and other major axis I psychopathology by DSM-III criteria. (DSM-III was the nomenclature in use when the initial study was begun.) All subjects were administered a structured set of questions to determine the presence or absence of alcohol dependence by Feighner criteria [Feighner et al., 1972]. These criteria require that an individual diagnosed as alcoholic have at least one symptom in three out of four symptom areas. Those judged to be nonalcoholic could not meet even probable criteria for alcohol dependence (two symptom categories).

All subjects were administered clinical interviews to determine the appropriate diagnosis and asked to fill out two personality inventories: the TPQ and the Multidimensional Personality Questionnaire (MPQ).

Personality Scales

The TPQ was originally developed as a three-factor personality inventory to include major dimensions of the normal human personality traits of novelty seeking, harm avoidance, and reward dependence [Cloninger, 1987]. The MPQ was originally developed by Tellegen [1982] at the University of Minnesota and applied to the large-scale twin studies located there. The instrument includes 11 primary scales: well being, so-

cial potency, achievement, social closeness, stress reaction, alienation, aggression, harm avoidance, traditionalism, absorption and control, and three higher scales termed negative affectivity, positive affectivity, and constraint.

The structural validity of the TPQ has been examined [Waller et al., 1991] by comparing results of administration of the TPQ and the MPQ to adult members of twin pairs and twin family members who participated in the Minnesota Twin Registry. Administration of both the TPQ and MPQ to individuals in the present sample provided opportunities for comparison of results across instruments either establishing convergence or providing evidence for lack of it. Thus, greater information about gene/temperament relationships was possible than could be obtained by administration of either instrument alone. Few of the factors in the two instruments purport to measure exactly the same constructs. However, the TPQ and MPQ each assess personality factors termed "harm avoidance." There is reason to believe they may tap somewhat different factors. Waller and colleagues [1991] performed a factor analysis of both the TPQ and MPQ, finding that the TPQ harm avoidance dimension appears to tap primarily a negative affectivity or neuroticism factor rather than a disposition toward behavioral inhibition. Thus, though similar in name, the two harm avoidance scales show minimal overlap conceptually. This is of some importance to the present investigation because significant results were found for TPQ harm avoidance with the D2 TaqI A polymorphism and with the D4 receptor polymorphism.

Dopamine Receptor Polymorphisms

Two D2 polymorphisms located on chromosome 11 (11q23) were tested, the TaqI A locus and the C allele system. The D4 receptor VNTR polymorphism located on 11p15.5 was also tested. This receptor contains an unusually polymorphic 16 amino acid repeat region. The exon III region contains a 48-bp region of two to eight repeats, with the most commonly observed alleles being the four and seven repeats. These alleles have received particular attention because differences in ligand binding have been reported for the short (four repeat) and long receptor (seven repeat) alleles [Van Tol et al., 1992; Asghari et al., 1994].

The dopamine transporter gene located at 5p15.3 was genotyped. This gene has a key role in dopaminergic neurotransmission by actively mediating the reuptake of synaptic dopamine. This gene contains a polymorphic VNTR. The 3′ untranslated sequence contains a 40-bp region consisting of three to 11 repeats. Over 90% of the population have either the 440- or 480-bp bands.

Genotyping Methods

D2 TaqI A1/A2 alleles. DNA was extracted from both immortalized cell lines and peripheral blood using minor modifications of the salting out method [Miller et al., 1988]. Genomic DNA (10 μg) was restricted overnight using a threefold excess of TaqI restriction endonuclease, according to the manufacturer's specifications (New England Labs, Inc.). Samples were size fractionated by electrophoresis on 1.0% agarose gels

TABLE I. Individuals Genotyped for DRD4, TAQI A, and C Polymorphisms of DRD2 and DAT-1: A Total of 250 Sib Pairs Were Analyzed Using SIBPAL

Gender	Alcoholic sibs (N = 107)[a]	Nonalcoholic sibs (N = 67)	Parents (N = 68)
Male	66	27	26
Female	41	40	42

[a]Number of individuals genotyped for whom phenotypic data were available are displayed in parentheses.

and transferred overnight by capillary action [Southern, 1975] to MSI nylon transfer membranes (Magna NT; Micron Separations, Inc.). Filters were prehybridized 2–4 hr at 42°C in 50% formamide, 5× Denhardt's solution, and 450 µg/ml sheared salmon sperm DNA. The TaqI A probe used in these analyses was the 1.7-kb BamHI fragment of HD2G1 provided by Dr. David Grandy (Vollum Institute, Oregon Health Sciences University). The probe was radiolabeled by random priming [Feinberg and Vogelstein, 1983] to a specific activity of $>10^9$ cpm/µg with [α-^{32}P]dCTP. Hybridization reactions were carried out at 42°C for 24–72 hr in 50% formamide, 6× SSC, 1× Denhardt's solution, 10% dextran sulfate, 0.5% SDS, and 800 µg/ml sheared salmon sperm DNA. Filters were washed extensively at a final stringency of 0.1× SSC at 65°C and exposed to Kodak XAR-5 film at –70°C for 3–7 days.

Microsatellite polymorphism C locus. Using the sequence described by Hauge et al. [1991] primers 509 (CAGGAGCACGTTTCTCATAC) and 419 (CGAGGGCGGTGCGGTCAT) were used to amplify the microsatellite. We performed polymerase chain reaction (PCR) in a total volume of 12.5 µl containing 50 ng of genomic DNA, 1 pmol of one primer 5′-end-labeled with ^{32}P, 5 pmol of the unlabeled primer, 50 mM KCl, 10 mM Tris-Cl-, pH 8.3, 1.5 mM MgCl$_2$, 200 µM dATP, dTTP, dGTP, and dCTP, and 0.5 unit of *Taq* polymerase (Promega). After an initial denaturation at 94°C for 3 min, amplification in a Perkin-Elmer thermocycler was for 30 cycles of 30-sec denaturation at 94°C, 30-sec annealing at 58°C, and 30-sec extension at 72°C. PCR products were resolved by electrophoresis on 6% denaturing polyacrylamide DNA sequencing gels and were detected by overnight autoradiography. Fragment sizes were measured relative to a size standard, a DNA sequence ladder derived from bacteriophage M13mp18.

VNTR polymorphism for D4. Using the sequence described by Lichter et al. [1993], primers D4-3 (GCG ACT ACG TGG TCT ACT CG) and D4-42 (AGG ACC CTC ATG GCC TTG) were used to amplify the VNTR. PCR was performed in a total volume of 25 µl containing 100 ng of genomic DNA, 10% DMSO, 200 µM dATP, dTTP, and dCTP, 100 µM dGTP and 100 µM deaza-dGTP, 1 µM each primer, 1× *Taq* polymerase buffer (10 mM Tris-8.3, 50 mM KCl, 1 mM MgCl$_2$, 5 µM EDTA, 0.01% gelatin), and 3 units of DNA *Taq* polymerase (Promega). DNA was denatured at 99°C for 1 min prior to the addition of the other components. Using the Perkin-Elmer 9600 thermocycler, 40 cycles of 95°C (20 sec), 54°C (20 sec), and 72°C (40 sec) were performed followed by a 4-min chase at 72°C. After amplification, loading dye was added and the total volume (25 µl) was loaded onto a 3.5% agarose gel. The gel was run for 2½ hr and then stained with ethidium bromide. Two size standards were used in order to determine number of repeats: Phi X174 HmfI and Msp I digest of pBR322.

DAT1 40-bp VNTR. Using the sequence described by Vandenbergh et al. [1992], primers T3-5Long (5′-TGTGGTGTAGGGAACGGCCTGAG-3′) and T7-3aLong (5′-CTTCCTGGAGGTCACGGCTCAAGG-3′) were used to amplify the VNTR. PCR was performed in a total volume of 12.5 µl containing 50 ng of genomic DNA, 1 pmol of one primer 5′-end-labeled with ^{32}P, 5 pmol of the unlabeled primer, 50 mM KCl, 10 mM Tris-Cl-, pH 8.3, 1.5 mM MgCl$_2$, 200 µM dATP, dTTP, dGTP, and dCTP, and 1.25 units of *Taq* polymerase (Promega). After an initial denaturation at 94°C for 3 min, amplification in a Perkin- Elmer 9600 was as follows: denaturing for 1 min at 93°C and annealing/extension for 1 min at 72°C for 35 cycles. PCR products were resolved by electrophoresis on 6% polyacrylamide DNA sequencing gels and were detected by overnight autoradiography.

Linkage Analysis

A total of 52 multigenerational families were used. At least one parent was genotyped in 93% of cases (in 39% of cases both were typed). A total of 250 sib pairs were available for analysis. A robust nonparametric sib-pair method was used to test for linkage [Haseman and Elston, 1972] in full sibs using SIBPAL (version 3.1) from the Statistical Analysis for Genetic Epidemiology (SAGE) package. No half-sibs were included. The SIBPAL routine for testing for linkage between a quantitative trait and a marker locus was used. In this method, the sib-pair marker data, together with parental marker data, where available, are used to estimate the proportion of alleles identical by descent (IBD) for each sib pair at each polymorphic marker locus. In the present analysis evidence for linkage in all possible pairs, irrespective of alcoholism status, was simultaneously determined [Haseman and Elston, 1972] using the squared sib-pair differences for each personality trait. These squared differences were regressed on the estimated proportion of alleles (IBD) for each sib pair for each marker locus in order to detect possible linkage, with all sib pairs being assumed to be independent [Blackwelder and Elston, 1985]. The partial regression coefficient of the dependent variable on the independent variable was tested with a *t*-statistic.

First, analyses were performed for the TPQ scales of novelty seeking, harm avoidance, and reward dependence. Based on results of the TPQ analysis, further analyses were performed for MPQ scales selected for their conceptual relationship to negative affect and as a means of providing converging evidence concerning the significant relationship found between the TPQ harm avoidance scale and the markers tested. Thus, the following scales from the MPQ were selected: harm avoidance, negative affectivity (a higher order factor), the lower order scales comprising this higher order trait (alienation, stress reaction, and aggression), and well-being, a lower order factor tapping absence of dysthymia.

RESULTS

There was no evidence for linkage between novelty seeking and the D4 polymorphism or either of the D2 polymorphisms tested (see Table II). However, the D2 and D4 polymorphisms tested showed evidence favoring linkage to an MPQ trait, stress reaction, associated with the negative affect construct and the TPQ trait of harm avoidance which also appears to measure negative affect. The higher order factor of negative affectiv-

TABLE II. Linkage Results for Three Primary TPQ Scales and Selected Scales From the MPQ

	TAQI A		C		DRD4		DAT-1	
	t	P	t	P	t	P	t	P
TPQ								
Novelty seeking	0.61	ns	0.64	ns	0.16	ns	0.49	ns
Harm avoidance	3.68	0.0003	1.46	ns	1.80	0.04	0.35	ns
Reward dependence	0.03	ns	0.65	ns	0.22	ns	0.58	ns
MPQ								
Harm avoidance	0.28	ns	0.86	ns	1.37	ns	0.18	ns
Negative affectivity	2.83	0.003	1.89	0.03	0.72	ns	0.45	ns
Stress reaction	1.84	0.03	1.08	ns	1.62	0.05	0.57	ns
Alienation	3.30	0.0007	2.23	0.01	0.28	ns	0.17	ns
Aggression	1.50	ns	1.88	0.04	1.35	ns	0.30	ns
Well-being	2.37	0.01	2.01	0.02	1.79	0.04	1.22	ns
Degrees of freedom	102		97		113		109	

ity showed evidence for linkage to both the TaqI A and C polymorphisms. This MPQ higher order factor is largely comprised of three lower order scales: stress reaction, alienation, and aggression. Thus, it is consistent with findings for negative affectivity that these lower order traits also displayed some evidence of linkage to all three markers. Furthermore, consistency of results is seen with evidence for linkage between well being and both D2 and D4 polymorphisms. No evidence for linkage between the DAT1 gene and any of the personality traits was seen.

The families of the 52 proband pairs included in this analysis were typical of proband pairs in our entire sample with one exception. All of the families included in this analysis were Caucasian. Because normative personality data for nonwhite samples are quite meager, the decision was made to exclude nonwhites from the present analysis. By study design, comorbidity was uncommon. Specifically, families with evidence of recurrent depression, schizophrenia, or primary drug dependence were excluded. However, certain disorders were allowed to freely vary within the sample (e.g., antisocial personality disorder). For the alcoholic probands, the lifetime prevalence for other disorders were: secondary drug dependence (42.5%), depression (18.8%), antisocial personality disorders (32.5%), and anxiety disorders (2.5%).

The alcoholic families for whom personality variants and polymorphic markers were investigated had multiple indicators of greater alcoholism severity: 1) moderately high recurrence risks and 2) early onset of alcohol dependence.

The familial distribution of the lifetime prevalence of alcohol dependence was determined by interviewing the sibs of the proband pair and determining their diagnostic status (alcohol dependent or not alcohol dependent) and comparing these to a randomly ascertained control sample in which DSM-III criteria were obtained [Helzer et al., 1991]. The risk ratio obtained for all sibs of the proband pairs was 3.90, with a ratio of 2.85 for males and 6.37 for females. Thus, the relative risks for alcohol dependence in the families included in this sample are sufficiently large to allow for detection of alcoholism susceptibility genes of moderate size [Risch, 1990].

The median age of onset for the alcoholics included in the present analysis, determined as the age at which

the first DSM-III symptom and/or Feighner symptom category was achieved, was 18 years in males and 17 years for females. The age of onset for this highly selected sample is earlier than that seen in other family studies in which consecutive series are studied from the same birth cohort [Reich et al., 1988]. Reich and colleagues found that individuals born later have earlier ages of onset. Therefore, the modal age of onset for a consecutive series of female alcoholics born in 1953 was found to be 24 years compared to 32 years for women born in 1938. For the present series, the women alcoholics tended to be younger at interview and most similar to the published data of Reich and colleagues available for women born in 1953. With an average onset of 17 years for the present sample, these women alcoholics have an earlier age of onset than a comparable age cohort selected at random. This earlier onset would be expected, however, based on the ascertainment strategy used to identify families through a proband pair of sisters.

Although the purpose of the study was not to seek genes linked to alcoholism susceptibility but rather to uncover a possible linkage between dopamine receptor polymorphisms and personality, the power to detect alcoholism susceptibility genes might appear unrelated to the goal of the study. However, if significant associations exist between personality and alcohol dependence, then having a sample enriched for alcoholism susceptiblity genes might be useful.

DISCUSSION

The present study sought to identify a possible genetic linkage between D4 genotypes and novelty seeking in a sample of families of alcoholic individuals. The rationale for undertaking this study was the two reports of genetic association between novelty seeking scores and variations in the dopamine D4 receptor variance [Ebstein et al., 1996; Benjamin et al., 1996]. Moreover, alcoholic individuals more often have higher scores for the novelty seeking traits than do nonalcoholics making the possibility of linkage between novelty seeking and D4 even more intriguing. However, the present study did not support a linkage between the D4 receptor alleles and novelty seeking. There may be many reasons why this study failed to observe a relationship. First, the study by Ebstein and collabora-

tors was based on a normal population of Ben-Gurion University students while the participants in the Benjamin et al. study were normal controls who had participated in a variety of National Institutes of Health studies. In the present study alcohol dependence was either present in the individual tested or his relatives. The present results may differ from those based on largely nonalcoholic "control" samples because variation in personality traits that may underlie alcohol dependence could alter the relationship between the dopaminergic receptors and the personality traits in question. Also, the possibility exists that D4 is unrelated to novelty seeking as recently reported by others [Jonsson et al., 1997; Gelernter et al., 1997].

The new findings that emerged from this study were the demonstration of evidence for linkage between the TaqI A polymorphism of the D2 receptor and the TPQ harm avoidance construct along with a significant finding for TPQ harm avoidance and the D4 receptor polymorphism. We speculated that the harm avoidance trait of the TPQ Personality Inventory might be measuring dimensions other than avoidance of bodily harm, as it was first described by Murray [1938]. Thus, we attempted to confirm the harm avoidance finding using the MPQ. We reasoned that if a linkage was not found between harm avoidance from the MPQ and either the D2 or D4 loci, we would have reason to believe the TPQ harm avoidance finding might be due to other underlying traits associated with the TPQ harm avoidance measure. Our suspicion that the harm avoidance scale of the TPQ might be showing linkage because of a high loading for particular subscales, such as scale 1, "Worry and Pessimism," was confirmed by the fact that a significant relationship was uncovered between the MPQ negative affectivity measure and the TaqI A locus. Both the TaqI A and C loci of the D2 receptor were found to be significantly linked to the MPQ trait of negative affectivity. This higher order factor loads heavily on three lower order scales: stress reaction, alienation, and aggression. Again, significant findings were found for both D2 and D4 for stress reaction and for both the TaqI A and C polymorphisms with the MPQ alienation trait. Relatively greater evidence for linkage between the MPQ measures of negative affectivity and alienation was seen for the two D2 polymorphisms than was seen for the D4. If Bonferroni corrections are applied to the 36 tests conducted, the TPQ harm avoidance and the MPQ alienation findings would remain significant, suggesting that the D2 polymorphism may provide greater explained variance than does the D4 in the personality traits tested.

It is notable that no linkages were found between any of the personality dimensions studied and the dopamine transporter gene. This gene has been investigated with respect to a number of psychiatric disorders with both positive and negative results [Persico et al., 1993; Sander et al., 1997; Volkow et al., 1996; Gelernter et al., 1994]. However, a relationship between the dopamine transporter gene and personality variation has not previously been investigated.

The present findings showing a positive relationship between the TPQ harm avoidance trait, which we suspect is actually measuring negative affect, and the D4

are in agreement with other studies of negative affect [Lerman et al., 1998]. That study evaluated whether there are genetic subgroups of depressed individuals who are predisposed to engage in self-medication smoking practices. A significant interaction between the D4 genotype and depression was found for stimulation smoking and negative affect reduction smoking. Specifically, these smoking practices were significantly elevated in depressed smokers homozygous for the short alleles of D4 but not in those heterozygous or homozygous for long alleles of D4.

Further, the relationship between alcohol dependence and negative affect has a long history. Although many alcoholics do not meet criteria for major affective disorder, many alcoholics report having experienced life-long dysthymia. Previously we have reported that alcoholics differed significantly from controls as well as their nonalcoholic siblings on the MPQ traits of negative affectivity, stress reaction, alienation, and aggression [Hill et al., 1990]. Possbily there exists a subtype of alcoholism characterized by greater negative affect. Thus, the present results suggest that variation in negative affectivity may be a latent trait that might explain previously reported associations between dopamine receptors and alcoholism.

Studies relating alcohol dependence and the dopamine receptors (D2 and D4) continue to remain controversial. Population-based associations that are quite positive have been reported for D2 [Neiswanger et al., 1995; Cook et al., 1996; Turner et al., 1997], though clearly there have been numerous negative reports [Bolos et al., 1990; Goldman et al., 1993; Suarez et al., l994]. Also, a recent linkage study [Cook et al., 1996] has demonstrated linkage between research diagnostic criteria (RDC)-defined alcoholism and the C locus using SIBPAL analyses ($P = 0.0006$). However, results were significant only for specific alcoholism families and not all British pedigrees examined. Additionally, both positive [Chang et al., 1997; Muramatsu et al., 1996; George et al., 1993] and negative findings [Parsian et al., 1997; Adamson et al., 1995] for potential associations between alcohol dependence and D4 continue to be reported. While the findings for clinical studies remain controversial, there is little doubt that release of dopamine at the site of D2 receptors is associated with alcohol reward, based on animal studies [Hodge et al., 1992, 1994].

Finally, while the literature concerning the D2 and D4 receptors is clearly controversial, some of the variation may have to do with the subtype of alcohol dependence that has been studied. Possibly, more significant results are obtained when alcohol-dependent individuals with dysthymic personalities are investigated. The present results suggest the need for further study of personality types as mediating variables in the expression of alcohol dependence.

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