

Review Article

D2 Dopamine Receptor Gene in Psychiatric and Neurologic Disorders and Its Phenotypes

Ernest P. Noble*

Department of Psychiatry and Biobehavioral Sciences, and the Brain Research Institute University of California, Los Angeles, California

The D2 dopamine receptor (DRD2) has been one of the most extensively investigated gene in neuropsychiatric disorders. After the first association of the TaqI A DRD2 minor (A1) allele with severe alcoholism in 1990, a large number of international studies have followed. A meta-analysis of these studies of Caucasians showed a significantly higher DRD2 A1 allelic frequency and prevalence in alcoholics when compared to controls. Variants of the DRD2 gene have also been associated with other addictive disorders including cocaine, nicotine and opioid dependence and obesity. It is hypothesized that the DRD2 is a reinforcement or reward gene. The DRD2 gene has also been implicated in schizophrenia, posttraumatic stress disorder, movement disorders and migraine. Phenotypic differences have been associated with DRD2 variants. These include reduced D2 dopamine receptor numbers and diminished glucose metabolism in brains of subjects who carry the DRD2 A1 allele. In addition, pleiotropic effects of DRD2 variants have been observed in neurophysiologic, neuropsychologic, stress response, personality and treatment outcome characteristics. The involvement of the DRD2 gene in certain neuropsychiatric disorders opens up the potential of a targeted pharmacogenomic approach to the treatment of these disorders. © 2003 Wiley-Liss, Inc.

KEY WORDS: D2 dopamine receptor gene; DRD2 A1 allele; association; linkage; alcoholism; drug

dependence; nicotine dependence; obesity; schizophrenia; bipolar disorder; movement disorders; brain D2 dopamine receptors; P300; stress; personality; treatment outcome

INTRODUCTION

The advent of molecular genetic knowledge and techniques, in the past two decades, has revolutionized our understanding of inherited disorders. Although much success has been achieved in localizing genes in Mendelian disorders, great difficulty has been experienced in identifying genes in behavioral disorders.

In contrast to most monogenic Mendelian diseases, psychiatric disorders do not have simple Mendelian traits since a clear mode of transmission has not been demonstrated for them. Unlike Mendelian traits, genetic factors, in general, account for only 50% of the variance in behavior [Plomin, 1990], although in some conditions, the estimates are as high as 70–95%. In part, contributing variables to the expression of behavioral disorders are environmental factors that frequently are unknown or difficult to quantify. Compounding this problem is the difficulty of determining which, if any, of the clinical subtypes (let alone considering ascertainment bias) constitute an etiologically homogeneous phenotype. Moreover, behavioral disorders are polygenic in nature with each gene contributing a modest increase to liability. Put together, these complexities have made it difficult to identify genes in these disorders.

Despite the past difficulties encountered in identifying genes in complex behavioral disorders, recent rapid advances in methodology and techniques in identifying risk and protective gene variants in these disorders are becoming available [Owen et al., 2000]. Positive results of candidate genes from case-control studies are being verified by analysis of the transmission of alleles from heterozygous parents to affected and unaffected children [e.g., Bennett et al., 1995] or by other linkage

*Correspondence to: Prof. Ernest P. Noble, UCLA Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024-1759. E-mail: epnoble@ucla.edu

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techniques. Moreover, the availability of single nucleotide polymorphisms (SNPs), interspersed throughout the genome, is making possible the identification of genes in genome-wide association studies. These genetic associations to a disorder in question would have clinical relevance, however, if they identify significant polymorphism either within the coding sequence that alters structure of the gene product or in the promotor/intronic sequences that regulate gene expression, or if the polymorphism in question is in linkage disequilibrium (LD) with other variants that affect gene function. Moreover, the increasing availability of clear phenotypes of the disorder through clinical subtypes (e.g., age of onset, severity, symptom patterns) or trait markers (e.g., brain evoked potential, brain mapping, personality measures) is making it feasible to define genetically valid phenotypes. It is then not too optimistic to indicate that these and other developments in molecular genetics coupled with rigorous statistical approaches will, in the near future, lead to the identification of relevant genes in complex behavioral disorders.

This review presents the involvement of variants of the D2 dopamine receptor (DRD2) gene in various neuropsychiatric disorders and their phenotypes. Figure 1 shows the location of nine DRD2 variants that have been commonly studied with the TaqIA site being the most frequently studied.

PSYCHIATRIC DISORDERS

Alcoholism

It has been known since antiquity that alcoholism runs in families. Systematic studies of families of alcoholics were not initiated, however, until late in the 19th

century. With almost no exceptions to the rule, every family study of alcoholism, regardless of country of origin, has shown higher rates of alcoholism among relatives of alcoholics than occur in the general population. Still, familial is not synonymous with genetic. The main problem in assessing the relative importance of genes as distinct from environmental factors is that both are usually provided by an individual's progenitors. Family, adoption, and twin studies [Goodwin, 1979; Cloninger et al., 1981; Pickens et al., 1991; Prescott et al., 1999], however, are pointing to hereditary factors as significant contributors to alcoholism.

Population-based studies. If a diathesis toward alcoholism is, in part, determined by heredity, then it should have a molecular genetic representation. In 1990, a significant association of the TaqIA D2 dopamine receptor (DRD2) minor (A1) allele with severe alcoholism was first reported [Blum et al., 1990]. Since then, a large number of national and international studies have attempted to replicate this observation. Whereas many studies have affirmed this significant association, others have not. This has generated some controversy as to whether such an association actually exists. At least eight independent meta-analyses of alcoholics and controls [Cloninger, 1991; Pato et al., 1993; Uhl et al., 1993; Gorwood et al., 1994; Blum et al., 1995; Neiswanger et al., 1995; Noble, 1998a; Gurling and Cook, 1999] have demonstrated this association to be robust. An earlier meta-analysis [Gelernter et al., 1993] did not find a significant association; however a re-analysis of that data did show a significant association [Noble and Blum, 1993].

Table I presents a summary of the extant peer-reviewed and full-published articles of alcoholics where the TaqI A DRD2 genotypes were available and which

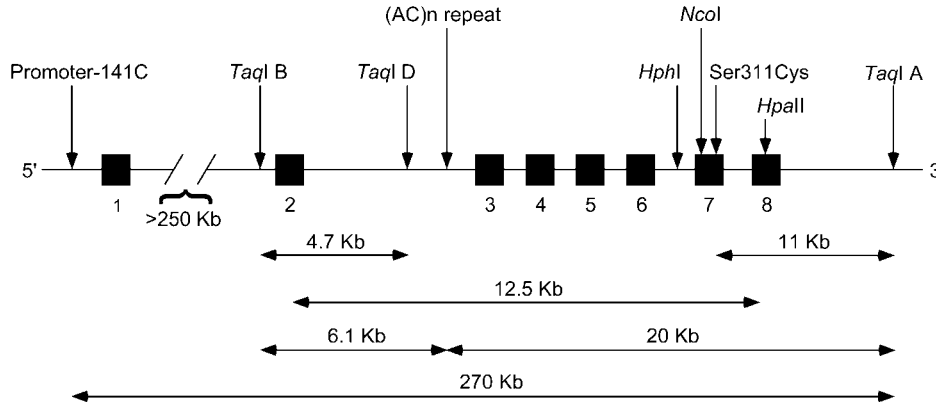


Fig. 1. The human D2 dopamine receptor gene and locations of the most commonly studied polymorphisms. Boxes represent exons and lines represent introns. Distances between various sites are represented by enclosed arrows. DRD2 polymorphisms: promoter -141C [Arinami et al., 1997], consists of the presence or absence of a cytosine at position -141, a functional variant [Jönsson et al., 1996b]. TaqIB [Hauge et al., 1991], G to A transversion, a functional variant [Jönsson et al., 1999b]. TaqID [Persian et al., 1991a], unclear functional significance. (AC)n repeat [Hauge et al., 1991], unclear functional significance. HphI [Sarkar et al., 1991], is C-G transversion, unclear functional significance. NcoI [Sarkar et al., 1991], transversion at amino acid 313 that encodes a silent polymorphism, unclear functional significance. Ser311Cys [Itokawa et al., 1993], is C-G transversion, nonfunctional variant [Pohjalainen et al., 1997]. HpaII

[Finckh et al., 1996], is A-G transversion, unclear functional significance. TaqIA [Grandy et al., 1993], a G-A transversion, a functional variant [Noble et al., 1991; Thompson et al., 1997; Pohjalainen et al., 1998; Jönsson et al., 1999b]. Linkage disequilibrium between some DRD2 polymorphisms in Caucasians: TaqIA is in LD with TaqIB [Hauge et al., 1991; Kidd et al., 1998; Noble et al., 2000]. TaqIA and TaqIB are in LD with intron 6 [Noble et al., 2000]. TaqIA and TaqIB are in LD with (AC)n repeat [Kidd et al., 1998]. TaqIA and TaqID are not in LD [Gelernter et al., 1998]. Promoter -141C is in LD with TaqIA [Gelernter et al., 1998; Noble et al., 2000] or with TaqIB or with intron 6 [Noble et al., 2000]. NcoI is not in LD with TaqIA, TaqIB or intron 6, but in weak LD with Promoter -141C [Noble et al., 2000]. HpaII is in LD with Promoter -141C [Samochowiec et al., 2000].

TABLE I. TaqI A DRD2 Genotypic Distribution in Studies of Caucasian Heterogeneous Alcoholics and Controls

	Alcoholics ^a										Controls ^b						
	Genotypes					Prevalence of					Genotypes				Frequency of		Prevalence of
	A1A1	A1A2	A2A2	A1 allele (%)	AI allele (%)	A1A1	A1A2	A2A2	A1 allele (%)	AI allele (%)	A1A1	A1A2	A2A2	A1 allele (%)	AI allele (%)	AI allele (%)	
Blum et al., 1990	1	13	8	34.1	63.6	0	4	20	8.3	16.7							
Bolos et al., 1990	2	13	25	21.3	37.5	8	30	89	18.1	29.9							
Parsian et al., 1991b	0	13	19	20.3	40.6	0	3	22	6.0	12.0							
Comings et al., 1991	3	41	60	22.6	42.3	0	24	84	11.1	22.2							
Gelernter et al., 1991	1	18	25	22.7	43.2	3	21	44	19.9	35.3							
Blum et al., 1991	3	39	47	25.3	47.2	0	6	25	9.7	19.4							
Cook et al., 1992	1	4	15	15.0	25.0	0	6	14	15.0	30.0							
Goldman et al., 1992	0	14	32	15.2	30.4	2	11	23	20.8	36.1							
Amadéo et al., 1993	3	18	28	24.5	42.9	0	7	36	8.1	16.3							
Suarez et al., 1994	1	29	52	18.9	36.6	2	23	63	15.3	28.4							
Noble et al., 1994a	1	20	23	25.0	47.7	3	14	41	17.2	29.3							
Gejjer et al., 1994	3	29	61	18.8	34.4	5	24	52	21.0	35.8							
Neiswanger et al., 1995	1	28	23	28.8	55.8	0	4	26	6.7	13.3							
Heinz et al., 1996	3	31	63	19.1	35.1	4	35	74	19.0	34.5							
Lawford et al., 1997	10	62	129	20.4	35.8	3	11	32	18.5	30.4							
Hietala et al., 1997	1	29	40	22.1	42.9	0	11	39	11.0	22.0							
Ovchinnikov et al., 1999	7	19	16	39.3	61.9	4	23	49	20.4	35.3							
Samochowiec et al., 2000	13	78	201	17.8	31.2	5	51	136	15.9	29.2							
Bau et al., 2000	5	52	58	27.0	49.6	6	36	72	21.1	36.8							
Pastorelli et al., 2001	2	15	43	15.8	28.3	2	13	49	13.3	23.4							
Anghelescu et al., 2001	13	75	155	20.8	36.2	3	32	63	19.4	35.7							
Total subjects ($n = 3,329$)	74	640	1,123 ^c	21.4 ^d	38.9 ^e	50	389	1,053 ^c	16.4 ^d	29.4 ^e							

^aIncludes both less severe and more severe alcoholics.

^bIncludes both nonalcoholics and subjects drawn from the general population (alcoholics not excluded).

^cSignificant difference was found in genotypes between alcoholics and controls ($\chi^2 = 32.7, P = 7.93 \times 10^{-6}$).

^dThe frequency of the A1 allele was significantly higher in the alcoholic than in the control group ($\chi^2 = 26.9, 95\% \text{ CI } 1.23-1.58, \text{ odds ratio} = 1.39, P = 2.14 \times 10^{-5}$).

^eThe prevalence of the A1 allele (A1A1 and A1A2 genotypes) was significantly higher in the alcoholic than in the control group ($\chi^2 = 32.0, 95\% \text{ CI } 1.31-1.77, \text{ OR} = 1.53, P = 1.54 \times 10^{-6}$).

used their own controls. To avoid stratification, only studies of Caucasians were included. In this most recent meta-analysis, a total of 1,837 heterogeneous alcoholics (both more severe and less severe) were compared to 1,492 heterogeneous controls (both assessed and unassessed for alcoholism). Eighteen of these individual studies [Blum et al., 1990, 1991; Bolos et al., 1990; Comings et al., 1991; Gelernter et al., 1991; Parsian et al., 1991b; Amadéo et al., 1993; Suarez et al., 1994; Noble et al., 1994a; Neiswanger et al., 1995; Heinz et al., 1996; Hietala et al., 1997; Lawford et al., 1997; Ovchinnikov et al., 1999; Bau et al., 2000; Samochowiec et al., 2000; Angheliescu et al., 2001; Pastorelli et al., 2001] showed a higher frequency and prevalence of the A1 allele in alcoholics than controls, whereas three studies [Cook et al., 1992; Goldman et al., 1992; Geijer et al., 1994] showed a lower frequency and prevalence of this allele in alcoholics when compared to controls. When the combined data (Table I) were analyzed, a significantly higher frequency ($P = 2.14 \times 10^{-7}$) and prevalence ($P = 1.54 \times 10^{-8}$) of the A1 allele were found in alcoholics when compared to controls. Moreover, a significant genotypic difference ($P = 7.93 \times 10^{-8}$) was found between these two groups.

Despite the combined studies showing a strong association of the DRD2 A1 allele with alcoholism, the question remains why some individual studies have found this association to be significant, whereas others have not. Besides sample size consideration, three key issues may be contributing factors to this difference: 1) the type of alcoholics selected; 2) the nature of the comparative controls; and 3) the modest contribution of a single gene in a polygenic disorder.

Alcoholism is generally acknowledged to be a heterogeneous disorder that is influenced by genetic and

environmental factors. At least two different alcoholism typologies have been described [Cloninger, 1987; Babor et al., 1992]. First, a more severe, more genetic and early onset type of alcoholism, and second, a less severe, more environmental and late onset type of alcoholism. If individual DRD2 A1 allelic association studies obtain alcoholics of predominately one type over the other type, then it may be likely that such an association could be either strong or weak. To ascertain this possibility, the prevalence of the A1 allele was assessed in all available Caucasian alcoholism studies wherein the severity of this disorder was determined using a variety of means. Table II shows that in twelve studies where alcoholism severity was ascertained, the prevalence of the A1 allele was 49.3% in 361 more severe alcoholics and 32.3% in 387 less severe alcoholics, a difference that was significant ($P = 3.28 \times 10^{-6}$). This suggests that the severity of alcoholism is an important determinant in A1 allelic association studies.

Whereas in these studies (Table II), one index of alcoholism severity was generally ascertained, a very recent study [Connor et al., 2002] determined the relationship of a range of alcoholism severity indices in the same group of alcoholics who carried the A1+ allele (A1A1 and A1A2 genotype) or A1- allele (A2A2 genotype) of the DRD2 gene. The results show that alcoholics with the A1+ allele compared to those with the A1- allele had significantly: 1) consumed larger quantities of alcohol per drinking occasion; 2) higher weekly alcohol consumption; 3) higher Alcohol Dependence score; 4) an earlier age of onset of alcohol problems; 5) developed problem drinking sooner after initial exposure to alcohol; and 6) higher treatment utilization. These findings support the view that alcoholics with the A1 allele experience a range of more

TABLE II. TaqI A DRD2 Allelic Distribution in Studies of Caucasian More Severe and Less Severe Alcoholics*

	More severe alcoholics			Less severe alcoholics			Odds ratio
	Al ⁺	Al ⁻	%Al ⁺	A1 ⁺	Al ⁻	%A1 ⁺	
Bolos et al., 1990 ^a	9	11	45.0	6	14	30.0	1.91
Parsian et al., 1991b ^b	6	4	60.0	7	15	31.8	3.21
Blum et al., 1991 ^b	33	19	63.5	15	29	34.0	3.36
Gelernter et al., 1991 ^c	12	11	52.2	7	13	35.0	2.03
Cook et al., 1992 ^d	4	11	26.7	1	4	20.0	1.45
Turner et al., 1992 ^b	4	18	18.2	5	20	20.0	0.89
Noble et al., 1994a ^d	19	15	55.9	15	15	50.0	1.27
Geijer et al., 1994 ^e	20	36	35.7	3	15	16.7	2.78
Geijer et al., 1994 ^f	6	4	60.0	3	6	33.3	3.00
Lawford et al., 1997 ^b	23	20	53.9	49	109	31.0	2.56
Hietala et al., 1997 ^d	23	29	44.2	7	11	38.9	1.25
Ovchinnikov et al., 1999 ^g	19	5	79.1	7	11	38.9	5.97
Total subjects ($n = 748$)	178	183	49.3 ^h	125	262	32.3 ^h	2.04

*Al⁺ allele subjects include A1A1 and A1A2 genotypes; Al⁻ allele subjects include A2A2 genotype only. More severe ($n = 361$) and less severe ($n = 387$) alcoholics were differentiated by a variety of means as follows.

^aThe Michigan Alcoholism Screening Test (MAST).

^bThe presence or absence of medical complications of alcoholism.

^cAlcohol consumption.

^dSeverity of Alcohol Dependence Questionnaire (SADQ).

^eDSM-III-R criteria (P2 group vs. P1 minus P2 group).

^fAutopsy determination (P6 group vs. P5 minus P6 group).

^gPresence of early age of onset and family history of alcoholism or late age of onset and negative family history of alcoholism.

^hThe prevalence of the A1 allele was significantly higher in the more severe than in the less severe alcoholic group ($\chi^2 = 21.7$, 95% CI 1.55–2.77, $P = 3.28 \times 10^{-6}$).

severe alcohol-related problems than alcoholics without this allele.

As indicated above, another important issue in DRD2 alcoholism association studies is the nature of the controls used. Because alcohol abuse/dependence is a major problem in Western societies (e.g., lifetime U.S. prevalence 14% [Regier et al., 1990] to 23% [Robins et al., 1988]) and because other drug problems, *vide infra*, have also been associated with the DRD2 A1 allele, it is important that controls be carefully assessed to exclude individuals with substance use disorders; if not, A1 allelic association with alcoholism may be weakened. To determine whether indeed there is A1 allelic difference between unassessed (alcoholics or drug abusers not excluded) and assessed (alcoholics or drug abusers excluded) controls, the prevalence of the A1 allele was compared between these two groups. Table III shows the prevalence of the A1 allele was 31.2% in the 845 unassessed controls and 15.7% in the 236 assessed controls, a difference that was significant ($P = 3.44 \times 10^{-6}$). This supports the view that the nature of controls is an important factor in A1 allelic prevalence.

Figure 2 recapitulates the data in more severe and less severe alcoholics and in unassessed and assessed controls. The prevalence of the A1 allele was significantly higher in the more severe than in the less severe alcoholics, with the prevalence of this allele being also significantly higher in the unassessed than in the assessed controls. Moreover, the more severe alcoholics had a three-fold higher prevalence of the A1 allele than the assessed controls ($OR = 5.23, P < 10^{-10}$). The prevalence of the A1 allele in the less severe alcoholics was virtually identical to that of the unassessed controls.

Family-based studies. In one study of two small nuclear families [Bolos et al., 1990], no linkage was found between alcoholism and the DRD2 gene using parametric linkage analysis. A second study using 17 nuclear families and a nonparametric method [Parsian et al., 1991b] failed to find linkage, although there was a trend for those with more severe alcoholism to more often share the DRD2 A1 allele than the less severe alcoholics. Moreover, in that study, a significant association was found between the DRD2 A1 allele with alcoholism using a population-based analysis. Another study of 20 high density alcoholic families [Neiswanger et al., 1995] failed to link the DRD2 locus with alcoholism using parametric linkage techniques, although it too found a significant association of the DRD2 A1 allele with alcoholism using a population-based analysis. A more recent study by these authors [Hill, 1998; Hill et al., 1999] employed an expanded sample (54 families) of high density alcoholic families and tested linkage by a nonparametric technique (SIBPAL). Whereas no linkage of the DRD2 alleles was found in sib-pairs when the total alcoholic sample was compared to the controls, a significant linkage was observed between the DRD2 A1 allele and alcoholism when the more severe alcoholics were compared to the nonalcoholic controls.

A nonparametric linkage analysis of sib-pairs, utilizing the Extended Sib-Pair Analysis (ESPA) method, was conducted in the United Kingdom on a second sample of seven Caucasian alcoholic families [Cook et al., 1996]. These families were chosen in an attempt to replicate evidence for DRD2 gene linkage obtained in a first sample of 11 families [Cook et al., 1993]. In the first sample, standard identity by descent (IBD) analysis

TABLE III. TaqI A DRD2 Allelic Distribution in Studies of Caucasian Controls That Did or Did Not Exclude Alcoholics or Drug Abusers*

Study	Alcoholics/or drug abusers not excluded			Study	Alcoholics/or drug abusers excluded		
	A1 ⁺	A1 ⁻	%A1 ⁺		A1 ⁺	A1 ⁻	%A1 ⁺
Grandy et al., 1989 ^a	16	27	37.2	Blum et al., 1990 ^e	4	20	16.7
Bolos et al., 1990 ^{a,i}	21	41	33.9	Parsian et al., 1991b ^e	3	22	12.0
Gelernter et al., 1991 ^{a,i}	24	44	35.3	Comings et al., 1991 ^e	3	17	15.0
Comings et al., 1991 ^a	21	67	23.9	Blum et al., 1991 ^e	6	25	19.4
Smith et al., 1992 ^b	6	14	30.0	Smith et al., 1992 ^f	8	28	22.2
Amadéo et al., 1993 ^a	5	18	21.7	Amadéo et al., 1993 ^e	2	18	10.0
Noble et al., 1994a ^c	17	32	34.7	Noble et al., 1994a ^g	4	16	20.0
Lawford et al., 1997 ^d	14	32	30.4	Neiswanger et al., 1995 ^h	4	26	13.3
Ovchinnikov et al., 1999 ^c	27	49	35.5	Lawford et al., 1997 ^h	3	27	10.0
Samochowiec et al., 2000 ^c	56	136	29.2				
Bau et al., 2000 ^a	42	72	36.8				
Pastorelli et al., 2001 ^c	15	49	23.4				
Total subjects (n = 1,081)	264	581	31.2		37	199	15.7

*A1⁺ allele subjects include A1A1 or A1A2 genotypes; A1⁻ allele subjects include A2A2 genotype only. The prevalence of the A1⁺ allele was significantly higher in the "not excluded" group than in the "excluded" ($\chi^2 = 21.5, 95\% \text{ CI } 1.65-3.64, OR = 2.44, P = 3.44 \times 10^{-6}$).

^aAlcoholics and drug abusers not excluded.

^bAlcohol and other drug abusers not excluded.

^cAlcoholics excluded but not drug abusers or cigarette smokers.

^dAlcohol abusers not excluded.

^eAlcoholics excluded.

^fAlcoholics and drug abusers excluded.

^gAlcoholics, drug abusers and smokers excluded.

^hAlcoholics and subjects with family history of alcoholism excluded.

ⁱExcludes CEPH subjects included in Comings et al., 1991.

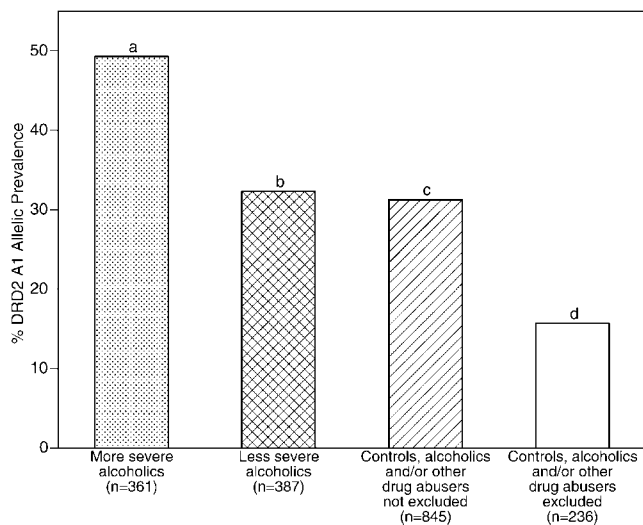


Fig. 2. The prevalence of the DRD2 A1 allele in Caucasian more severe and less severe alcoholics and in Caucasian controls that did or did not exclude alcoholic or other drug abusers.

showed a highly significant effect at the TaqI A and C microsatellite sites on the liability to develop both heavy drinking and Research Diagnostic Criteria (RDC) alcoholism phenotype. Whereas the excess sharing allele was explained by segregation in a single large sibship in the first sample of families studied, it was not observed in the second sample of families. The combined 18 families, however, still showed significant linkage for both the TaqI A and C microsatellite polymorphisms for the RDC model of affection.

A family-based analysis for the involvement of the DRD2 gene in alcoholism was published [Edenberg et al., 1998] by the Collaborative Study on the Genetics of Alcoholism (COGA). In 105 families, neither the transmission disequilibrium test (TDT) nor the affected family-based controls test showed evidence of linkage or association between the DRD2 locus and alcoholism. More recently, the same COGA dataset was analyzed by a British group [Curtis et al., 1999]. They compared two model-free methods of linkage analysis, the GENEHUNTER [Kruglyak and Lander, 1998] and the MFLINK [Curtis and Sham, 1995]. The former method implements nonparametric methods that measure allele-sharing between affected subjects, whereas the latter uses parametric methods that make use of likelihoods calculated under a variety of different transmission models. The MFLINK significantly linked the DRD2 gene with alcoholism, whereas the GENEHUNTER did not. The COGA dataset was also analyzed by yet another group [Waldman et al., 1999]. Using a logistic regression extension of the TDT for continuous traits, this group found evidence indicating significant LD between the DRD2 gene and quantitative indices of alcoholism. In another family-based TDT study [Blomqvist et al., 2000], a higher but nonsignificant excess transmission of the A1 allele (58%) vs. the A2 allele (42%) was found in 26 small Caucasian nuclear families with alcohol dependence. The authors suggest

that a larger sample size or LD in subsets of probands with more refined phenotypes may have rendered the findings significant.

Illicit Drug Use Disorders

Because alcohol increases brain dopamine levels and exerts its reinforcing effects through the dopaminergic system of the mesocorticolimbic pathways of the brain [Wise and Rompre, 1989] and because many other abused substances also increase brain dopamine levels, the question was raised as to whether the DRD2 gene is also implicated in drug use disorders other than alcoholism.

Polysubstance abuse/dependence. In Caucasian polysubstance dependent subjects [Comings et al., 1991], a significantly higher prevalence of the DRD2 A1 allele was found when compared to controls ($P = 0.009$). Another study of polysubstance (nicotine, alcohol, heroin, cocaine, marijuana and other drugs) abusers [Smith et al., 1992] found a non-significantly higher prevalence of the A1 allele in heavy users than in sparse users. In yet another study of Caucasian polysubstance users [O'Hara et al., 1993], a significantly higher prevalence of the A1 allele ($P < 0.025$) and the B1 allele ($P < 0.006$) was found when compared to nonusers [O'Hara et al., 1993]. These associations remained significant, even after alcohol abusers were removed from the polysubstance abusing group. No such differences in the A1 and B1 alleles were found between African-American polysubstance abusers and nonusers. Another study [Comings et al., 1994] has similarly ascertained DRD2 polymorphisms in Caucasian polysubstance abuse/dependent subjects. It found the A1 allele to be significantly associated with these subjects ($P = 0.006$). Multiple regression analyses showed a highly significant association between the A1 allele and multiple substances abused ($P = 0.0003$) and early age of onset of abuse ($P < 0.0001$). Moreover, A1+ allelic carriers exceeded A1- allelic carriers for a history of being expelled from school for fighting ($P = 0.001$) and of their being ever jailed for violent crimes ($P = 0.011$). The authors of this study conclude that the possession of the DRD2 A1 allele is associated with drug abuse/dependence and some aggressive behaviors.

Psychostimulant abuse/dependence. The A1 and B1 alleles have been examined in Caucasian cocaine-dependent (CD) subjects [Noble et al., 1993]. The prevalence of the A1 allele was significantly higher in these subjects than in the nondrug-abusing controls ($P < 10^{-4}$), as was the B1 allele ($P < 10^{-2}$). These associations remained significant even after comorbid alcohol dependent subjects were removed from the sample of CD subjects. Logistic regression analysis of CD subjects identified potent routes of cocaine use (intravenous, free base and 'crack' cocaine) ($P = 0.007$) and the interaction of early deviant behaviors and parental alcoholism ($P = 0.016$) as significant risk factors associated with the A1 allele. The cumulative number of these three risk factors in CD subjects was significantly and positively related to A1 allelic prevalence ($P < 10^{-3}$). Another study [Gelernter et al., 1999a] found a non-significant 20% higher frequency of the A1 allele in

Caucasian CD subjects when compared to controls. No significant differences, however, were found in TaqI B and TaqI D alleles or in haplotypes at the TaqI A, TaqI B, and TaqI D sites. None of these DRD2 sites nor their haplotypes were associated with African-American CD subjects. The DRD2 gene was also studied in Caucasian psychostimulant (cocaine, amphetamine)-preferring abusers [Persico et al., 1996]. A significantly higher prevalence of the A1 allele ($P = 0.024$) and the B1 allele ($P = 0.048$) was found in psychostimulant-preferring subjects when compared to controls. Another study [Serý et al., 2001], however, found no association of the A1 allele with methamphetamine dependence.

Opioid dependence. A recent study followed opioid-dependent subjects treated with methadone in an outpatient setting [Lawford et al., 2000]. The frequency of the DRD2 A1 allele was significantly higher ($P = 0.02$) in these patients than in controls free of current and past alcohol/other drug abuse. Mean daily heroin consumption was twice as great in A1+ (A1A1 and A1A2 genotypes) than A1- (A2A2 genotype) allelic patients ($P = 0.003$) during the year before entry into the treatment program. Moreover, the frequency of the A1 allele was more than four times greater in patients who were treatment failures when compared to those who were treatment successes ($P = 0.00002$) over the 1-year course of methadone administration. These findings show DRD2 genotypic differences between opioid-dependent subjects and controls and in pretreatment heroin use and post-treatment outcome of opioid-dependent subjects. They suggest that patients with the A1+ allele have a greater risk at failing in standard methadone treatment programs than patients with the A1- allele.

Another study determined association of variants of the DRD2, DRD3, 5-HT_{2A} and GABA_Aγ2 receptors and serotonin transporter genes with heroin abuse in Chinese subjects [Li et al., 2002]. The only variant of these genes that was associated with heroin abuse was the DRD2 promoter -141C polymorphism (genotype-wise and allele-wise, $P = 0.05$). When heroin abusers were divided into nasal inhalers and IM or IV injectors, a significant difference was found between inhalers and controls (genotype-wise, $P = 0.006$, allele-wise, $P = 0.016$) but not between injectors of heroin and controls.

Table IV presents all published and peer-reviewed studies of the TaqI A DRD2 alleles in subjects with illicit drug use disorders. One study [Gelernter et al., 1999a] was not included because it could not be compared to the rest of the studies as no DRD2 genotypes nor A1 allelic prevalence data were provided. The table includes only studies of Caucasians because no studies, thus far, have implicated the DRD2 gene in African American illicit drug abusers [O'Hara et al., 1993; Berrettini and Persico, 1996; Gelernter et al., 1999a].

Analysis of the data in Table IV showed a significantly higher prevalence of the A1+ allele in the 717 illicit drug abusers/dependents when compared to the 649 controls ($P = 2.99 \times 10^{-7}$, OR = 1.83).

Nicotine dependence. Smoking (nicotine-dependent) subjects have also been examined for their as-

TABLE IV. TaqI A DRD2 Allelic Distribution in Studies of Caucasian Illicit Drug Abusing/Dependent Subjects and Controls*

	Drug abusers/dependents			Non-drug abusers			OR
	A1+	A1-	%A1+	A1+	A1-	%A1+	
Comings et al., 1994	19	33	36.5	10	59	14.5	3.39
Smith et al., 1992	45	80	36.0	8	28	22.2	1.97
O'Hara et al., 1993	96	141	40.5	45	115	28.1	1.74
Noble et al., 1993	27	26	50.9	16	84	16.0	5.45
Persico et al., 1996	27	35	43.6	33	86	27.7	2.01
Lawford et al., 2000	35	60	36.8	3	30	9.1	5.83
Serý et al., 2001	36	57	39.1	57	75	43.2	0.88
Total subjects ($n = 1,366$)	285	432	39.7	172	477	26.5	1.83

*In the total sample of drug users/abusers/dependents, the prevalence of the A1+ allele was significantly higher than in the total sample of 649 controls ($\chi^2 = 39.8$, 95% CI 1.44-2.32, $P = 2.99 \times 10^{-7}$).

sociation with DRD2 polymorphism. In one study of Caucasians drawn from the general population [Noble et al., 1994b], the prevalence of the A1 allele progressively increased in the order of nonsmokers, past smokers and active smokers ($P = 0.006$). Moreover, A1 allelic prevalence was found to be significantly higher in active smokers ($P = 0.024$) and past smokers ($P = 0.044$) when each was compared to the nonsmokers. Another study [Comings et al., 1996a], examined Caucasian smokers attending a smoking cessation clinic. A1 allelic prevalence was found to be significantly higher ($P < 10^{-8}$) in the active smokers than in nonalcoholic, nondrug-abusing controls. Moreover, there was a significant ($P = 0.02$) inverse relationship between the prevalence of the A1 allele and the age of onset of smoking and the maximum duration of time the smokers had been able to quit smoking on their own ($P = 0.02$). Another study [Singleton et al., 1998], however, could not associate the DRD2 A1 allele with cigarette smokers in a United Kingdom population.

A case-control study ascertained DRD2 polymorphisms and smoking status in Caucasian lung cancer patients [Spitz et al., 1998]. The prevalences of the A1 and B1 alleles were higher in the smokers than in the non-smokers. Moreover, the age of onset of smoking occurred significantly earlier ($P = 0.02$) in subjects who carried either the A1 or the B1 allele. In addition, subjects with the A1 allele made fewer attempts to quit smoking than those without this allele ($P = 0.02$), indicating a greater difficulty in abstaining by the former subjects. Another lung cancer case-control study of DRD2 gene polymorphisms among Mexican-Americans and African-Americans [Wu et al., 2000], showed the cigarette pack-years in the control subjects for the two ethnic groups combined were 30.8, 21.9, and 18.6 for the A1A1, A1A2, A2A2 genotypes and 36.5, 20.8, and 18.5 for the B1B1, B1B2, B2B2 genotypes respectively. There was a 3.6 times greater frequency of smoking-related cancers among the first-degree relatives of case subjects with an A1 allele than among those without this allele. Moreover, there was a 1.8 times greater frequency of smoking-related cancers among first-degree relatives of case subjects with a B1 allele compared to patients without a B1 allele.

Polymorphisms of the DRD2 gene were also examined in German smokers [Batra et al., 2000]. Whereas no association of smoking was found with DRD2 TaqI A alleles, a significant association was found between the DRD2-Fok1-1 allele and the onset and intensity of smoking. Another study [Lerman et al., 1999] considered the role of two dopaminergic genes, the dopamine transporter (SLC6A3) and the DRD2, in smoking behavior. The results showed that the association with smoking was modified by DRD2 genotype, resulting in 50% reduction in smoking risk for individuals who carry the SLC6A3-9 (9 non9) and the DRD2 A1- (A2A2) genotypes.

A family-based study for the involvement of the DRD2 gene in smoking was published by COGA [Bierut et al., 2000]. Using the TDT, the study found increased transmission of the A1 allele (55% transmitted vs. 45% not transmitted) in smokers, but this did not reach statistical significance. The same group [Anokhin et al., 1999] however using the same data set found that when the moderating influence of the P300 (an event-related potential) on the association of DRD2 alleles and smoking was tested, a significant association was found between the A1 allele and smoking in the lower, but not in the higher P300 amplitude group. No such association was observed in subjects who did not carry the A1 allele. Moreover, a significant excess transmission of the A2 allele was found in individuals who had never smoked, suggesting a protective effect of the A2A2 genotype. Another group of investigators [Waldman et al., 1999] also examined the COGA data set on the DRD2 gene and smoking. They found evidence for significant LD between the DRD2 gene and whether or not subjects currently smoked.

Two additional studies on the DRD2 gene and smoking have been published, one showing a decreased prevalence of the A1 allele [Costa-Mallen et al., 2000] and the other showing an increased prevalence of this allele [Pastorelli et al., 2001] in smokers compared to nonsmokers.

Table V presents all published and peer-reviewed studies of Caucasian smokers and nonsmokers where the prevalence of TaqIA DRD2 alleles was available [Noble et al., 1994b; Comings et al., 1996a; Singleton

TABLE V. TaqI A DRD2 Allelic Distribution in Studies of Caucasian Smokers and Nonsmokers*

	Smokers			Nonsmokers			OR
	A1 ⁺	A1 ⁻	%A1 ⁺	A1 ⁺	A1 ⁻	%A1 ⁺	
Noble et al., 1994b	72	100	41.9	51	131	28.0	1.85
Comings et al., 1996a	152	160	48.7	185	529	25.9	2.72
Singleton et al., 1998	32	72	30.8	50	67	42.7	0.60
Spitz et al., 1998	98	154	38.9	9	19	32.1	1.34
Lerman et al., 1999	88	149	37.1	68	139	32.9	1.21
Bierut et al., 2000	153	235	39.4	196	370	34.6	1.22
Batra et al., 2000	31	79	28.2	22	38	36.7	0.68
Costa-Mallen et al., 2000	41	84	32.8	67	135	33.2	0.98
Pastorelli et al., 2001 ^a	7	14	33.3	8	35	18.6	2.19
Total subjects ($n = 3,840$)	674	1,047	39.2	656	1,463	31.0	1.44

*DRD2 genotype data were not provided in some of these studies. All studies provided data on the prevalence of the A1⁺ allele (A1A1 and A1A2 genotypes combined) and A1⁻ allele (A2A2 genotype). In the total sample of 1,721 smokers, the prevalence of the A1⁺ allele was significantly higher than in the total sample of 2,119 nonsmokers ($\chi^2 = 27.9$, 95% CI 1.25–1.64, $P = 1.29 \times 10^{-7}$).

^aPrevalence of the TaqI A alleles in smokers and nonsmokers was provided by Pastorelli (personal communication).

et al., 1998; Spitz et al., 1998; Lerman et al., 1999; Batra et al., 2000; Bierut et al., 2000; Costa-Mallen et al., 2000; Pastorelli et al., 2001]. Data analysis showed a significantly higher prevalence of the A1+ allele in the 1,721 smokers when compared to the 2,119 nonsmokers ($P = 1.29 \times 10^{-7}$, OR = 1.44).

Obesity and Associated Disorders

The reinforcing properties of food have also led to an examination of the involvement of DRD2 polymorphisms in obesity. Haplotype 4 (GT) of intron 6 and exon 7 of the DRD2 gene was found to be associated with increasing risk for obesity [Comings et al., 1993]. In another study, the DRD2 A1 allele was present in 45.2% of obese subjects [Noble et al., 1994c], a prevalence similar to that found in alcoholics and nicotine- and other drug-dependent subjects. Moreover, the A1 allele was significantly associated with carbohydrate craving. Variants of the human obesity (OB) and the DRD2 genes have been examined in relationship to obesity [Comings et al., 1996b]. Polymorphisms of the OB gene and the DRD2 A1 allele each associated significantly with obesity. These two polymorphisms together accounted for about 20% of the variance in body mass index (BMI), particularly in younger women. Another study has ascertained the relationship of the DRD2 A1 allele in obese subjects with and without comorbid substance use disorders [Blum et al., 1996a]. In obese subjects, A1 allelic prevalence was significantly higher than in controls ($P < 10^{-4}$). Moreover, the progressive increase in comorbid substance use disorders in these obese subjects was positively related to increased A1 allelic prevalence ($P < 10^{-6}$). Finally, another case control study [Spitz et al., 2000] compared variants of the DRD2 gene in obese (BMI ≥ 30) and non-obese control subjects. The DRD2 A1 allele was significantly higher in obese subjects compared to controls ($P = 2 \times 10^{-3}$) as was the DRD2 B1 allele ($P = 3 \times 10^{-3}$). The risk of obesity associated with the DRD2 A1 genotype was 3.48 compared to 4.55 for the DRD2 B1 genotype.

There is strong evidence from epidemiological studies of a positive relationship between increased body weight and hypertension [Tyroler et al., 1975; Haffner et al., 1992; Thomas et al., 1999]. Moreover, hypertension in combination with obesity exhibits a high degree of heritability [Carmelli et al., 1994], suggesting a common genetic diathesis in these disorders. To ascertain whether a common gene is involved, the role the DRD2 gene TaqI A polymorphism plays in modulating blood pressure (BP) and obesity was determined in 209 nondiabetic hypertensive and 174 age-matched normotensive Chinese subjects [Thomas et al., 2000]. The frequency of the A1 allele was decreased in the hypertensives (42%) compared to the control subjects (52%, $P = 0.006$). In the combined population ($n = 383$), systolic, diastolic and mean arterial BP were lower in subjects with the A1A1 genotype relative to the A2A2 genotype (all $P < 0.05$), whereas, skinfold thickness was increased at the iliac ($P = 0.001$) and triceps ($P < 0.03$) sites. In a more recent study, the same group [Thomas et al., 2001] assessed TaqI A DRD2 alleles in 484 obese and 506

non-obese Chinese subjects. Obese subjects, using either BMI or waist-to-hip ratio criteria, had a significantly higher prevalence of the A1 allele ($P = 0.02$) and A1 allelic frequency ($P = 0.03$) than non-obese subjects. Moreover in 471 of these subjects who were normoglycemic, a significant increase in mean arterial pressure ($P = 0.04$) was found with increasing proportions of the A2 allele (A1A1, A1A2 and A2A2 genotypes in that order).

Two recent studies [Jenkinson et al., 2000; Tataranni et al., 2001], assessed the role of other DRD2 mutations on weight and energy expenditure in Pima Indians. Individuals with a Cys-encoding allele had a higher BMI than those homozygous for the Ser311-encoding allele [Jenkinson et al., 2000]. Further, total energy expenditure and 24-hr resting energy expenditure were lower in homozygotes for the Cys311-encoding allele when compared to heterozygotes and homozygotes for the Ser-311-encoding allele [Tataranni et al., 2001]. Finally, another study [Rosmond et al., 2001] determined the association of a NcoI polymorphism (C to T transition) in exon 6 of the DRD2 gene with hypertension. Subjects with the TT genotype had significantly higher systolic blood pressure than subjects with the CT genotype ($P = 0.049$). Moreover, subjects with TT genotype had significantly higher diastolic blood pressure than either subjects with the CT or CC genotype ($P = 0.011$).

Gambling

Besides alcoholism and other substance use disorders, the DRD2 gene has been assessed in another addictive behavior; pathological gambling. Pathological gamblers were found to have a significantly higher prevalence of the DRD2 A1 allele than controls [Comings et al., 1996c]. Moreover, when subjects were divided into halves based on the severity of their pathological gambling (PG), there was a progressive and significant increase in the prevalence of the DRD2 A1 allele from controls to gamblers in the lower half, to gamblers in the upper half of the PG score. Another study [Ibanez et al., 2001] assessed DRD2 TG microsatellite polymorphism in intron 2 in pathological gamblers with and without comorbid psychiatric disorders. A significantly different allelic distribution in this polymorphism was found between these two types of gamblers with the C4 allele being significantly higher in gamblers with than gamblers without comorbid disorders.

Other Psychiatric Disorders

Mood disorders. Alterations in the dopaminergic system have been observed in mood disorders and variants of the DRD2 gene have been studied in these disorders. An association between Japanese patients with mood-incongruent psychotic affective disorders and Ser311Cys polymorphism has been found [Arinami et al., 1996]. A study of Chinese with bipolar affective disorder (BPAD) reported an association with promoter -141C polymorphism [Li et al., 1999]. The same study also found a significant increase of the TaqI A allele and haplotype promoter -141C and TaqI A. This study,

however, observed no association between either promoter $-141C$ or TaqI A polymorphism in Caucasians with BPAD. A very recent European multicenter study [Massat et al., 2002] reported an association of the (AC)-repeat polymorphism and BPAD but not in patients with unipolar affective disorder (UPAD). Many studies using association and linkage approaches could not, however, implicate the DRD2 gene in mood disorders [Holmes et al., 1991; Byerely et al., 1992; Nothen et al., 1992; Craddock et al., 1995; Manki et al., 1996; Oruc et al., 1996; Souery et al., 1996; Furlong et al., 1998; Savoye et al., 1998; Stober et al., 1998; Bocchetta et al., 1999; Kirov et al., 1999; Heiden et al., 2000; Serretti et al., 2000].

Schizophrenia. The psychotomimetic effects of dopamine agonists and the antipsychotic effects of D2 dopamine receptor antagonists suggest that a defect in the DRD2 gene may be a contributing factor to the genetic susceptibility in schizophrenia [Seeman, 1987]. A Ser³¹¹/Cys³¹¹ polymorphism was found to be associated with schizophrenia [Arinami et al., 1994], particularly in schizophrenics with the absence of negative symptoms [Arinami et al., 1996]. This association was confirmed in another study of schizophrenics [Shaikh et al., 1994] and in schizophrenics exhibiting disorganized symptoms [Serretti et al., 1998]. Another study [Serretti et al., 2000] found an association of DRD2 Ser/Cys311 variant with delusional and disorganizational symptomatologies in major psychoses. Two other polymorphisms in the DRD2 gene were also found to associate with schizophrenia, a functional ($-141 C$ Ins/Del) polymorphism in the promoter region of the DRD2 gene [Arinami et al., 1997; Breen et al., 1999; Inada et al., 1999; Jönsson et al., 1999a] and the TaqI A DRD2 polymorphism [Golimbet et al., 1998]. Further, a positive association and excess transmission of DRD2 haplotypes (TaqI A2 and TaqI B2 alleles) was recently reported in French schizophrenics [Dubertret et al., 2001]. A study of Russian schizophrenic patients found the TaqI A A2A2 genotype to be more frequently observed in patients with more pronounced negative symptoms and high hereditary burden of the disorder [Golimbet et al., 2001]. Finally, significant differences in microsatellite (GT) n allele frequencies in intron 2 were found between schizophrenic and control groups for the DRD2 gene in the whole sample and for the DRD2 and neurotrophin-3 genes only in women [Virgos et al., 2001]. Several other studies, however, could not implicate the DRD2 gene in schizophrenia [Sobell et al., 1994; Crawford et al., 1996; Tanaka et al., 1996; Verga et al., 1997; Arranz et al., 1998; Stober et al., 1998; Tallerico et al., 1999; Suzuki et al., 2000; Hori et al., 2001].

Posttraumatic stress disorder. Because there is a large body of evidence that suggests the involvement of the dopaminergic system in stress, the role of the DRD2 gene was examined in subjects with posttraumatic stress disorder (PTSD). Two studies [Comings et al., 1991, 1996d] have implicated the DRD2 A1 allele in PTSD, whereas one [Gelernter et al., 1999b] has not. The findings of one study [Comings et al., 1996d] are particularly striking because it studied Vietnam veterans who had been exposed to severe combat condi-

tions and examined the prevalence of the DRD2 TaqI A1 allele in those who developed PTSD versus those who did not. The prevalence of the A1 allele was 60% in those with PTSD compared to 5% in those without PTSD ($P = 0.001$). In these previous studies, however, the combat veterans' substance use patterns were not presented and the control groups employed were not screened for substance use. In a very recent study [Young et al., in press], the frequency of A1 allele was significantly higher ($P = 0.006$) in PTSD combat veterans than controls free of substance abuse problems. In a subgroup of PTSD harmful drinkers (≥ 60 g alcohol/day), A1 allelic frequency was significantly higher ($P = 0.04$) than in the subgroup of PTSD nonharmful drinkers (< 60 g alcohol/day), the former being also significantly higher ($P = 0.0004$) than in the controls. There was no difference, however, between PTSD nonharmful drinkers and controls. Further, the PTSD patients with the A1+ (A1A1, A1A2) allele consumed twice the amount of daily alcohol ($P = 0.002$) at twice the hourly rate ($P < 10^{-7}$) when compared to the respective A1- (A2A2 genotype) allelic patients.

NEUROLOGICAL DISORDERS

Movement Disorders

In a study of French and British Parkinson disease (PD) patients and controls [Planté-Bordeneuve et al., 1997], four dopaminergic genes were investigated: the DRD2, the dopamine transporter (DAT), and monoamine oxidase A (MAOA) and B (MAOB) genes. Variants of the DAT, MAOA and MAOB were not associated with this disorder. Dinucleotide repeat alleles within intron 2 of the DRD2 gene were significantly associated with both sporadic and familial PD. In another study [Oliveri et al., 1999], variants of both the D1 dopamine receptor (DRD1) and the DRD2 genes were assessed in an Italian case-control study of PD patients and in PD patients with and without L-dopa-induced dyskinesias. No variants of the DRD1 gene associated with PD or with patients with L-dopa-induced dyskinesias. Dinucleotide repeat alleles within intron 2 of the DRD2 gene, however, were significantly associated with PD. Perhaps more importantly, the frequency of these alleles was significantly different in patients who developed than in those who did not develop L-dopa-induced dyskinesias. The above group of researchers has recently published a study on Italian PD patients examining several other variants of the DRD2 gene [Oliveri et al., 2000]. They observed no significant differences between these patients and controls in the promoter ($-141 C$ Ins/Del) and in the Ser³¹¹/Cys³¹¹ variants. Patients carrying the TaqIA A1 and TaqIB B1 alleles, however, had a significantly increased risk of developing PD. Another group [Makoff et al., 2000] studying patients with PD found that late-onset hallucinations induced by treatment with L-dopa and dopamine agonists were associated with the DRD2 TaqI A1 allele. Finally, two recent studies of Norwegian [Grevle et al., 2000] and Chinese [Wang et al., 2001] PD patients have also implicated the DRD2 gene in this disorder. In the first study [Grevle

et al., 2000], the frequency of the TaqI A1 allele was significantly associated with the overall PD patients when compared to controls. This association was even more significant when only patients with definite PD were considered. In the second study [Wang et al., 2001], the association between DRD2 and DRD3 gene polymorphisms and the risk of developing motor fluctuations in PD was investigated. The study found the DRD2 TaqI A1 allele to be significantly associated with the motor fluctuators when compared to the motor nonfluctuators but no significant difference was found between these two groups when polymorphisms in the DRD3 gene were considered. Despite these positive association studies of DRD2 variants with PD, a few studies could not implicate the DRD2 gene in PD [Nanko et al., 1994; Pastor et al., 1999; Maude et al., 2001].

TaqI A DRD2 alleles have been ascertained in tardive dyskinesia (TD), an iatrogenic involuntary hyperkinetic disorder associated with long-term neuroleptic treatment [Chen et al., 1997]. Whereas a significant genotypic difference and excess homozygosity of the A2A2 was detected in female TD patients compared to female non-TD patients, this difference was not significant in male patients. A trend toward a higher frequency of the promoter -141C Del allele was reported [Inada et al., 1999] in schizophrenic patients susceptible to neuroleptic-induced extrapyramidal symptoms. Another study [Mihara et al., 2000b], however, found no relationship between TaqI A polymorphism of the DRD2 gene and extrapyramidal effects of D2 dopamine antagonists.

The role of the DRD2 gene has also been examined in myoclonus dystonia, another movement disorder characterized by involuntary lightning jerks and dystonic movements. Linkage analysis identified a region in chromosome 11 that harbors the DRD2 gene [Klein et al., 1999]. Moreover, sequencing of the coding region of the DRD2 indicated that all affected and obligate carriers were heterozygous for a Val¹⁵⁴Ile change in exon 3 of the protein. This change was found neither in unaffected members of the pedigree nor in 250 control chromosomes.

Migraine

A growing body of data suggests that dopaminergic activation is a primary pathophysiologic component in certain subtypes of migraine [Peroutka, 1997]. This has led to an examination of DRD2 variants in this disorder. In one study [Peroutka et al., 1997], the NcoI DRD2 C to T polymorphism located in exon 6 was assessed in individuals having migraine with aura (MWA) and without aura (MO). Individuals having MWA had a significantly higher frequency of the DRD2 C allele than did controls or MO individuals. No DRD2 C allele frequency difference was found, however, between the latter two groups. The same laboratory [Peroutka et al., 1998] also studied the association of NcoI DRD2 variants in comorbid migraine with aura, anxiety and depression. The DRD2 C allele frequency was significantly higher in individuals with MWA, anxiety disorders or major depression than in individuals who had none of these disorders.

Another group [Del Zompo et al., 1998] utilized the Transmission Disequilibrium Test and the dinucleotide repeat alleles within intron 2 of the DRD2 gene to test for association with patients affected by migraine without aura. Although no difference was observed in DRD2 repeat allelic distribution in the overall sample, allelic distribution differed significantly in a subgroup of dopaminergic migraineurs. Another DRD2 gene polymorphism (promoter -141C Ins/Del), however, was not found to be associated with migraine [Maude et al., 2001]. Finally, in a large study of subjects with typical migraine and controls, a significant and independent association was found of SNPs in the insulin receptor and the DRD2 SNP93 (NcoI polymorphism) with migraine subjects [McCarthy et al., 2001].

PHENOTYPES

Pharmacology and Metabolism

Receptor binding. There is emerging evidence that subjects with the TaqI A1+ allele (A1A1 and A1A2 genotypes) have reduced brain dopaminergic function compared to carriers of the A1- allele (A2A2 genotype). In the first study of its kind, postmortem caudate nucleus samples obtained from alcoholics and non-alcoholics were ascertained for D2 dopamine receptor binding [Noble et al., 1991]. Using [³H]spiperone as the binding ligand, two important D2 dopamine receptor binding characteristics were obtained: B_{max} (number of binding receptors) and K_d (binding affinity). In the brain samples with the A1+ allele, the B_{max} was found to be significantly reduced (by almost 30%) when compared to the B_{max} of the samples with the A1- allele ($P < 0.008$ unadjusted and $P < 0.01$ covariate adjusted for log K_d and age). This reduction in the A1+ allelic subjects was found in both the alcoholic and nonalcoholic samples, with no significant differences observed either between the A1+ allelic alcoholic and nonalcoholic samples, or between the A1- allelic alcoholic and nonalcoholic samples. Moreover, a significant progressively reduced B_{max} was observed in the A2A2, A1A2, and A1A1 genotypes, respectively, ($P = 0.01$). No significant difference, however, was observed in the K_d between A1+ and A1- allelic samples (either unadjusted or covariate adjusted for B_{max}).

A confirmation of the above study in the United Kingdom has been obtained on brain autopsy samples [Thompson et al., 1997]. D2 dopamine receptor binding was measured by autoradiography in the caudate, putamen and nucleus accumbens using the specific D2 dopamine receptor ligand [³H]raclopride. The presence of the A1 allele was associated with reduced density of D2 dopamine receptors in all areas of the striatum, reaching statistical significance in the ventral caudate and putamen ($P = 0.01$ and $P = 0.04$, respectively). Specifically, there was a 30–40% reduction in D2 dopamine receptor density in the striatum of individuals with the DRD2 A1 allele compared to those homozygous for the A2 allele.

A more recent study [Pohjalainen et al., 1998] determined D2 dopamine receptor binding density (B_{max}),

affinity (K_d) and availability (B_{max}/K_d) in healthy Finnish volunteers using positron emission tomography (PET) and [^{11}C]raclopride to ascertain whether the A1 allele was associated with an in vivo difference in D2 dopamine receptor characteristics. A statistically significant decrease in D2 dopamine receptor availability, reflecting a reduction in receptor density, was observed in the striatum of the A1A2 group compared to the A2A2 group. There was, however, no difference in K_d between the two groups. The authors conclude that their study provides an in vivo neurobiological correlate to the A1 allele in healthy volunteers.

Another study [Laruelle et al., 1998] determined in living subjects (healthy controls and schizophrenics) striatal D2 dopamine receptor binding potential using the D2 dopamine receptor radiotracer [^{123}I]IBZM. In the total population studied, there was no significant difference in D2 dopamine receptor binding potential between A1+ and A1- allelic subjects. When the controls and schizophrenics were separately examined, however, a trend for a lower binding potential was found in A1+ allelic controls, whereas a trend for a higher binding potential was noted in A1+ allelic schizophrenics when compared to the respective A1- allelic subjects. Because the above two studies [Laruelle et al., 1998; Pohjalainen et al., 1998] appeared simultaneously in the same journal issue, an editorial [Hitzemann, 1998] reviewed the merits of these studies. It suggests that the study using [^{123}I]IBZM [Laruelle et al., 1998] had insufficient power to detect a significant difference between A1+ and A1- allelic controls. Moreover, because schizophrenics showed a trend in the opposite direction, compared to the controls, the results on D2 dopamine receptor binding potential and allelic association may have been confounded in the schizophrenic subjects by prior neuroleptic treatment. Indeed, a recent study [Silvestri et al., 2000] did find increased D2 dopamine receptor binding in schizophrenics after treatment with antipsychotics.

A subsequent PET study [Jönsson et al., 1999b], again using [^{11}C]raclopride, examined DRD2 polymorphisms and striatal D2 dopamine receptor density in healthy Swedish volunteers. The results further confirmed the above studies in showing a significant association of the DRD2 TaqI A1 ($P = 0.01$) and TaqI B1 ($P = 0.01$) alleles with measures of low D2 dopamine receptor density and a significant association with the promoter DRD2 -141C Del allele ($P = 0.02$) with high receptor density.

Table VI summarizes the various studies on the relationship between DRD2 TaqI A and TaqI B polymorphism and D2 dopamine receptor binding.

It may be of interest to note that using PET in non-molecular genetic studies, low levels of D2 dopamine receptors have been reported in the brains of subjects with substance use disorders. These include subjects with alcohol [Hietala et al., 1994], cocaine [Volkow et al., 1993], and opioid [Wang et al., 1997] dependence and obesity [Wang et al., 2001]. As the above pharmacological studies of DRD2 variants indicate, however, it is only subjects with the A1 or B1 allele who have the reduced expression of the DRD2 gene. This would suggest that a substantial fraction of the total substance abusing

TABLE VI. Taq I A and Taq I B D2 Dopamine Receptor Polymorphisms and D2 Dopamine Receptor Binding in the Brain

Reference	Subjects	Type of study	Radioligand	Brain area	Polymorphisms investigated	Results
In vitro studies Noble et al., 1991	Controls ($n = 33$; Caucasians = 24, African Americans = 9); Alcoholics ($n = 33$; Caucasians = 21, African Americans = 12) from the USA	Homogenates	[3H] spiperone	Caudate	Taq IA	A1 ⁺ genotypes associated with reduced binding in Caucasians and in the total sample
Thompson et al., 1997	Healthy Caucasians ($n = 44$) from England	Autoradiography	[3H]raclopride	Ventral caudate, putamen, nucleus accumbens	Taq IA	A1 ⁺ genotypes associated with reduced binding
In vivo studies Laruelle et al., 1998	Healthy controls and schizophrenics ($n = 70$; controls/schizophrenics = 47/23, Caucasians = 50, African Americans = 16, Hispanics = 3, Asian = 1) from the USA	SPECT	[^{123}I]IBZM	Striatum	Taq IA, Taq IB	A1 ⁺ and B1 ⁺ genotypes associated with reduced binding trend in controls and with increased binding trend in schizophrenics. No association was found in the total sample
Pohjalainen et al., 1998	Healthy Caucasians ($n = 54$) from Finland	PET	[^{11}C]raclopride	Striatum	Taq IA	A1 ⁺ genotypes associated with reduced D2 dopamine receptor availability
Jönsson et al., 1999b	Healthy Caucasians ($n = 56$) from Sweden	PET	[^{11}C]raclopride	Striatum	Taq IA, Taq IB	A1 ⁺ and B1 ⁺ genotypes associated with reduced binding

population have reduced D2 dopamine receptor levels (i.e., those with the A1 or B1 allele), placing them at highest risk for developing severe substance use disorders.

Glucose metabolism. PET studies have identified brain metabolic deficits in alcoholics and other drug abusers. In abstinent alcoholics compared to non-alcoholic controls, hypometabolism was found in various brain areas using as tracers [^{11}C]glucose [Wik et al., 1988] and 2-deoxy-2- [^{18}F]fluoro-D-glucose (FDG) [Adams et al., 1993]. FDG studies of cocaine abusers [Volkow et al., 1992, 1993] have also shown hypometabolism in a number of brain areas that remained even after several months post detoxification. It has not been determined, however, whether some of these deficits were a consequence of prolonged substance abuse or due to a preexisting condition. These studies raise the question as to whether the observed decreases in glucose metabolism in the substance-abusing subjects are due, in part, to their association with the TaqIA DRD2 A1 allele. To establish inherent differences in brain glucose metabolism between A1+ and A1- allelic subjects, however, it is necessary to exclude the toxic effects of the alcohol/drug abuse state on this measure. To initiate such a study, brain FDG metabolism was compared in healthy non-alcohol/non drug-abusing subjects who had either the A1+ or the A1- allele [Noble et al., 1997]. The results showed that brains of the A1+ allelic group had significantly lower mean relative glucose metabolic rates (GMRs) than those of the A1- allelic group in a large number of brain regions. These include: the left (L)-Broca's area, and L-middle frontal, L-middle temporal, right (R)-inferior temporal, and R-lateral orbital inferior frontal gyri, as well as striatal regions, including the L-caudate, L-putamen, and L-nucleus accumbens. Furthermore, the A1+ allelic group also had significantly lower relative mean GMRs in the R-orbital, L-medial prefrontal, and L- and R-lateral occipito-temporal cortices than the A1- allelic group. Similarly, significant reductions were found in the L-anterior insula, L- and R-temporal poles, R-hippocampus, and the midbrain in the cerebral peduncle and the substantia nigra. These findings support phenotypic differences, based on brain glucose metabolism between A1+ and A1- allelic subjects.

Hormonal effects. The phenotypic expression of DRD2 variants has been examined in the heritability of stature. The rationale for conducting such studies is based partly on the known role of the dopaminergic system in the regulation of growth hormone (GH)-releasing hormone. Japanese children with idiopathic short stature (ISS) were compared for their TaqIA DRD2 alleles to normal children [Miyake et al., 1999]. The frequency of the A1 allele was significantly higher ($P < 0.01$) in the former than the latter group. Children with ISS were then divided into two groups, those with the A1+ and the A1- alleles, and their various characteristics were studied. The ratio of bone age to chronological age and levels of insulin-like growth factor-1 were significantly reduced ($P < 0.01$) in the A1+ compared to the A1- allelic ISS subjects. The ISS children were then subjected to an L-dopa test to stimulate the

release of GH. Children with the A1+ allele released significantly less GH ($P < 0.05$) than those without this allele. The authors suggest that individuals with the A1 allele may have a mild dysfunction of GH secretion associated with deficits in the dopaminergic system leading to short stature. In another Japanese study [Arimami et al., 1999], sib-pair children and adults were examined for the relationship of DRD2 polymorphism and stature. IBD-shared sib-pair analysis showed a significant linkage ($P = 0.004$) between dinucleotide repeat alleles within intron 2 of the DRD2 gene and stature. Further, to examine within pedigree association of promoter (-141C Ins/Del) polymorphism, sibs with the Del/Ins genotype were found to be significantly taller ($P = 0.009$) than co-sibs with the Ins/Ins genotype. Finally in male adults, the -141C Ins/Del polymorphism significantly associated ($P = 0.006$) with stature.

Neurophysiology and Neuropsychology

Another approach to study the differential expression of the DRD2 A1+ and A1- alleles is to investigate the relationship of these alleles to relevant features of neurophysiologic functioning. The rationale for undertaking such a study is based, in part, on evidence suggesting a hereditary component in the generation of the P300 (an event-related potential) and a growing number of studies implicating the dopaminergic system in the generation of the P300. Moreover, in certain clinical populations (e.g., Parkinson disease), prolonged P300 latency or decreased P300 amplitude have been associated with decreased CNS dopaminergic activity. To determine whether a relationship exists between P300 characteristics and TaqIA DRD2 alleles, a sample of young Caucasian boys was studied [Noble et al., 1994d]. This sample consisted of three groups of children: 1) sons of active (nonabstinent) alcoholic (SAA) fathers; 2) sons of recovering (abstinent) alcoholic (SRA) fathers; and 3) sons of social drinker (SSD) fathers. None of these boys had yet begun to consume alcohol, tobacco, or other psychoactive drugs, obviating the effects of these drugs on brain function. In these three groups of boys, the relationship of target P300 amplitude and latency at Pz to DRD2 alleles was ascertained. Analysis of covariance (ANCOVA) of P300 amplitude showed no significant main effect of allele (A1+, A1-) or group (SAA, SRA, SSD) and no interaction between allele and group. In contrast, allele/group ANCOVA of P300 latency showed a main effect of allele (A1+ = 455 ± 12 msec, A1- = 412 ± 8 msec, $P = 0.004$), but no significant group effect or interaction between allele and group.

Further studies have followed on the relationship of DRD2 alleles to P300 characteristics. In a psychiatric population, P300 latency was found to be significantly prolonged in A1 homozygotes compared to A2 homozygotes ($P = 0.01$) [Blum et al., 1994]. No significant difference, however, was found in P300 amplitude between DRD2 genotypes. In a study of healthy adult subjects, a significantly reduced P300 amplitude was observed in A1+ compared to A1- allelic individuals [Gabbay et al., 1996]. Another study of children at high

risk for developing alcoholism found small but non-significant prolongation of the P300 latency but a significant reduction ($P = 0.001$) in P300 amplitude in A1+ compared to A1- allelic subjects [Hill et al., 1998]. A study of adult children of alcoholics [Ratsma et al., 2001] found reduced P300 amplitude and the presence of the A1 allele to be independently associated with alcoholism risk, but only in males. Finally, in a study of normal young females [Lin et al., 2001] the A1 allele was not found to be associated with P300 components.

Alcoholics are characterized by specific impairments in their visuospatial ability (i.e., how objects in space are perceived). These impairments extend to young children of alcoholics, suggesting that their presence in alcoholics may be, in part, antecedent to their drinking problems. Moreover, because visuospatial performance, like the P300, has a dopaminergic component, the question is raised as to whether this CNS measure is differentiated by the DRD2 allelic status. In an attempt to answer this question, a sample of alcohol- and other drug-naive young sons of active alcoholic, recovered alcoholic, and nonalcoholic fathers was studied [Berman and Noble, 1995]. These children were administered a visuospatial task (Benton's Judgement of Line Orientation Test), which makes minimal motor/verbal demands. Boys with the A1+ allele had a significantly poorer visuospatial score than boys with the A1- allele ($P = 0.005$), with the poorest score being found in the sons of the active alcoholic group who carried the A1+ allele, and the best score being found in the sons of the social drinker group who carried the A1- allele. This study suggests that the DRD2 alleles contribute differentially to the expression of visuospatial performance, and supports the view that visuospatial defects previously observed in children of alcoholics may be, in part, genetically determined.

Stress

There is growing evidence for the involvement of the dopaminergic system in response to stress [Kreek and Koob, 1998; Pani et al., 2000]. More recently and specifically, studies are showing an important gene (DRD2); environment (stress) interaction in human cognitive functioning and alcohol problem outcome. Stress, in pre-adolescent children, differentially affected cognitive markers, including visuospatial ability (Benton's Line Orientation) and event-related potential (P300 amplitude), in subjects with the DRD2 A1+ and A1- alleles [Berman and Noble, 1997]. Specifically, increasing stress was negatively correlated with cognitive functioning in DRD2 A1+ allelic children, but no such correlation was found in children with the DRD2 A1- allele. These findings have been supported and extended in subsequent investigations. In a sample of alcoholic patients, stress-related variables were significantly associated with severity of physiological dependence in patients with the DRD2 A1+ allele but not in patients without this allele [Bau et al., 2000]. Another study [Madrid et al., 2001], ascertained the relationship between stress, severity of alcohol problems and the DRD2 alleles. It found that alcohol problems increased

significantly with increasing stress in DRD2 A1+ allelic subjects, but not in A1- allelic subjects.

Personality

It has been hypothesized that Novelty Seeking (NS) behavior, as determined by the Tridimensional Personality Questionnaire (TPQ), has a dopaminergic component [Cloninger, 1987]. In support of this hypothesis, is a study that found extrastriatal D2 dopamine receptors, using PET, to be significantly and negatively associated with NS in healthy subjects [Suhara et al., 2001]. Another study of healthy subjects [Sugiura et al., 2000] reported a positive correlation between regional cerebral blood flow (rCBF) and NS, consistent with the inhibitory influence of the dopaminergic system on rCBF. Additional studies have examined whether polymorphisms of dopaminergic genes are associated with NS and other personality traits. A positive association was reported [Ebstein et al., 1996] between the 7-repeat (7R) allele of the D4 dopamine receptor (DRD4) gene and the personality trait of NS of the TPQ. In a back-to-back publication in the same journal issue, another group [Benjamin et al., 1996] reported a study, using another questionnaire, and found a similar association.

In a subsequent study [Noble et al., 1998], the relationship of NS of the TPQ to polymorphisms of both the DRD2 and DRD4 genes was determined in young sons of Caucasian alcoholics and non-alcoholics, none of whom had yet begun to consume alcohol and other drugs of abuse. NS score was significantly higher ($P = 0.029$) in boys having, in common, all three minor DRD2 alleles (A1, B1, and Intron 6 1) compared to boys lacking any of these alleles. Boys with the DRD4 7R allele also had a higher NS score that achieved a statistically significant level ($P = 0.049$), than boys without this allele. The greatest difference in NS score, however, was found when boys having all three minor DRD2 alleles and the DRD4 7 allele were contrasted to those without any of these alleles ($P = 0.01$). In sum, DRD2 and DRD4 polymorphisms individually associate with NS behavior. The combined DRD2 and DRD4 polymorphisms, however, contribute more markedly to this behavior than when these two gene polymorphisms are individually considered.

Another study [Hill et al., 1999a] assessed the relationship of polymorphism of the DRD2 and DRD4 genes to three primary TPQ scales and scales from the Minnesota Personality Questionnaire (MPQ) in alcoholic sibs, nonalcoholic sibs and their parents. Harm Avoidance score of the TPQ was most strongly linked with TaqIA DRD2 alleles ($P = 0.0003$) followed by linkage with VNTR polymorphism of the DRD4 gene ($P = 0.04$). With respect to the MPQ scales, Negative Affectivity score was linked with the TaqIA alleles ($P = 0.003$) and with dinucleotide repeat alleles within intron 2 of the DRD2 gene ($P = 0.03$). Stress Reaction score was linked with TaqIA DRD2 alleles ($P = 0.03$) and with DRD4 alleles ($P = 0.05$). Alienation score was linked to TaqIA DRD2 alleles ($P = 0.0007$) and to the dinucleotide repeat alleles of the DRD2 ($P = 0.02$) and with the DRD4 alleles ($P = 0.04$).

A recent study [Ratsma et al., 2001] found the presence of the DRD2 A1 allele to be positively and significantly associated with sensation seeking, a personality characteristic similar to NS. Several studies, however, could not associate polymorphisms in either the DRD2 nor the DRD4 genes with NS or other personality traits [Malhotra et al., 1996; Jönsson et al., 1997; Sander et al., 1997; Vandenbergh et al., 1997; Katsuragi et al., 2001].

Other Neurotransmitter Systems

Because there is growing evidence that the dopaminergic and opioidergic systems are anatomically and functionally interconnected, the binding of the opioid antagonist naloxone was studied in brains of deceased Caucasian subjects [Ritchie and Noble, 1996]. Reduced [³H]naloxone binding was found in all five brain regions examined (frontal cortex, caudate nucleus, amygdala, hippocampus, and cerebellum) of DRD2 A1+ compared to A1- allelic subjects. The reduced binding was greatest (by almost 30%) and most significant ($P=0.008$) in the caudate nucleus of the A1+ allelic subjects compared to the caudate nucleus of A1- allelic subjects.

Because low platelet monoamine oxidase B (MAO-B) activity and the presence of TaqI A1 allele of the DRD2 gene have independently been proposed as "biological/genetic" markers for alcoholism, the relationship between these markers was investigated in Caucasian alcoholics with mean daily ethanol consumption of 85 g [Eriksson et al., 2000]. Platelet MAO-B activity was significantly lower in individuals with the DRD2 A1 allele compared to those without it. This relationship remained unchanged when subjects who fulfilled DSM-IV criteria for alcohol dependence were included. The finding suggests that alcoholics who are carriers of the DRD2 A1 allele have lower platelet MAO-B activity.

Striatal dopamine transporter (DAT) densities were studied, using single-photon emission tomography, in alcoholics with TaqI A genotypes of the DRD2 gene [Laine et al., 2001]. Alcoholics with the A1/A2 genotype had significantly higher DAT densities than subjects with the A2/A2 genotype.

Treatment

If A1+ allelic subjects have reduced numbers of brain D2 dopamine receptors [Noble et al., 1991; Thompson et al., 1997; Pohjalainen et al., 1998; Jönsson et al., 1999b] and diminished CNS dopaminergic tone [Noble et al., 1994d; Berman and Noble, 1995], could a D2 dopamine receptor agonist, such as bromocriptine, have a more salutary effect on alcoholics with the A1+ than those with the A1- allele? To answer this question, a double-blind bromocriptine (BRO)-placebo (PLA) trial was conducted on hospitalized alcoholics over a 6-week period [Lawford et al., 1995]. Besides ascertaining TaqIA DRD2 alleles, three behavioral measures were assessed (craving, anxiety, and depression). Moreover, the patients' retention rate during the trial was obtained. In the four groups studied (BRO A1+, BRO

A1-, PLA A1+, and PLA A1-), the greatest and most significant decreases in craving and anxiety occurred in the A1+ allelic patients receiving bromocriptine (BRO A1+). Additionally, the retention rate of the A1+ allelic alcoholics receiving bromocriptine during the 6-week trial was greater than each of the other three groups and significantly more when compared to A1+ allelic alcoholics receiving placebo (PLA A1+). These findings indicate that alcoholics who carry the A1+ allele are more amenable to treatment by a dopaminergic agent than alcoholics who lack this allele.

As indicated earlier, the DRD2 A1 allele was found to be associated with opioid dependence [Lawford et al., 2000]. Relevant to methadone treatment outcome, however, opioid dependent patients who failed, compared to those who succeeded in treatment had more than four times the frequency of the A1 allele (42.1% vs. 9.3%). The results suggest that DRD2 variants are not only predictors of heroin use but also of methadone treatment outcome.

DRD2 genotypes have also been differentially associated in patients treated with antipsychotic agents. Schizophrenic patients with the A1 allele showed greater prolactin response [Mihara et al., 2000a] and better therapeutic response [Suzuki et al., 2000] to nemonapride, a selective antagonist of D2 dopamine-like receptors, than patients without this allele. Similarly, bromperidol, a close structural analogue of haloperidol, showed a greater prolactin response in female schizophrenics with the DRD2 A1 allele than in those without this allele [Mihara et al., 2001]. A further study [Suzuki et al., 2001] found the frequency of the A1 allele to be significantly higher in psychiatric patients who had developed neuroleptic malignant syndrome than in patients who had not. Another study [Schäfer et al., 2001] investigated the association of response to short-term haloperidol treatment in psychotic patients with TaqI A polymorphism of the DRD2 gene. It found DRD2 A1 allelic patients showed a greater improvement in positive, but not in negative, symptoms on all treatment days than patients without this allele.

Variants of the DRD2 gene have also been studied on depression and anxiety in various behavioral disorders. The DRD2 promoter -141C Ins/Del polymorphism has been found to associate with anxiolytic and antidepressive effects of neuroleptic treatment [Suzuki et al., 2001]. Another study [Lucht et al., 2001] found an association between the DRD2 Exon 8 homozygous A/A genotype and increased dose of the D2 dopamine receptor antagonist tiapride for treating alcohol withdrawal symptomatology. This study replicated an earlier one by the same group [Finckh et al., 1997] that showed increased depression and anxiety in DRD2 A/A genotype in alcoholics after detoxification. Further support concerning the influence of DRD2 Exon 8 upon withdrawal severity has been reported [Koehnke et al., 2000] where an association was found between DRD2 Exon 8 A/A genotype and history of delirium in patients with alcohol dependence. Another study [Serretti et al., 2001] found no association between Ser311Cys variant of the DRD2 gene and antidepressant activity of selective serotonin reuptake inhibitors (fluvoxamine and

paroxetine) in patients affected by a major depressive episode. Finally, the administration of another selective serotonin reuptake inhibitor (citalopram) was found to reduce alcohol consumption in heavy alcohol drinkers having the DRD2 A2/A2 genotype [Eriksson et al., 2001].

COMMENTS

The DRD2 has been one of the most extensively and intensively studied gene in neuropsychiatric disorders. What are some of the lessons learned from these studies?

Association and Linkage Studies

There are some who attribute the results of positive association of the Taq I A DRD2 A1 allele with alcoholism in population-based studies as possibly due to false positive errors based on sample stratification. The DRD2 A1 allele, however, has shown significant association with alcoholism in several relatively homogeneous populations. These include the French [Amadéo et al., 1993], the Japanese [Arinami et al., 1993], the Finns [Hietala et al., 1997], the Slavs [Ovchinnikov et al., 1999], the Brazilians [Bau et al., 2000] and the Chinese [Lu et al., 2001]. Further, although large frequency variations in this allele are known to exist among certain racial/ethnic groups [Kidd et al., 1998], no significant variations in DRD2 A1 allelic frequency have been detected among Caucasians of different European nationalities [Goldman, 1993]. Moreover, examination of studies of controls with European background obtained from various geographic regions in the US, Europe and Australia showed no significant variations in DRD2 A1 allelic frequency among them [Noble, 1998a (Table III)]. Indeed few examples of stratification bias have been offered in the literature as an explanation for spurious or nonreplicable genetic association [Risch and Teng, 1998]. Furthermore, a recent study [Wacholder et al., 2000] found only a small bias from population stratification in a well-designed case-control study of genetic factors that ignores ethnicity among non-Hispanic U.S. Caucasians of European origin. Moreover, the study casts doubt that stratification bias is an explanation for the original study [Blum et al., 1990] implicating the DRD2 gene in alcoholism. Finally, it is highly unlikely that in the large number of Caucasian alcoholics and controls analyzed herein, the significantly different TaqI A DRD2 genotypes between these two groups ($P < 10^{-7}$) and the significantly higher prevalence ($P < 10^{-7}$) and frequency ($P < 10^{-6}$) of the DRD2 A1 allele in alcoholics compared to controls are due to false-positive errors based on stratification bias or are due to chance.

Another aspect that is revealed in this review is the heterogeneous nature of alcoholism based on DRD2 polymorphisms. The evidence shows that the more severe type of alcoholism is more strongly associated with the DRD2 A1 allele than the less severe type. Moreover, the heterogeneous nature of controls, based on DRD2 polymorphisms, is also found in this review. Specifically, controls that did not exclude alcoholics or other drug abusers had a two-fold greater and signifi-

cantly higher prevalence of the A1 allele than controls that did exclude these subjects ($P < 10^{-5}$). These findings are instructive in suggesting that in future DRD2 association studies, assuming an adequate number of subjects is employed, a significantly higher prevalence of the A1 allele would be expected when more severe alcoholics are compared to carefully assessed controls that exclude alcohol and other drug (including nicotine) abusers. No such allelic difference would be expected, however, if less severe alcoholics are compared to controls that do not exclude alcohol and other drug abusers.

Besides population-based, or case-control association studies, a few investigations have utilized family-based analyses to determine the involvement of the DRD2 gene in alcoholism. Although the objective of these studies is based, in part, on avoiding stratification bias, the results, like in population-based studies, have produced mixed findings. This problem is not unique to DRD2 alcoholism linkage studies; it has also afflicted replication of linkage studies in other complex behavioral disorders. It should be noted, however, that the interpretation of linkage results depends on the genetic model assumed, the set of parameters chosen for analysis, including phenotypes, and its statistical power to detect linkage (that is a function of the genetic model, parameters, and sample size).

When in the current review, the above factors are taken into consideration, the following observations emerge. With the exception of significant linkage of the DRD2 to alcoholism in one small sample of alcoholic families [Cook et al., 1996 ($n = 18$)], other studies with small samples [Bolos et al., 1990 ($n = 2$); Parsian et al., 1991b ($n = 17$); Neiswanger et al., 1995 ($n = 20$); Blomqvist et al., 2000 ($n = 26$)] have failed to detect linkage. One subsequent study [Hill, 1998; Hill et al., 1999] by the same group of investigators [Neiswanger et al., 1995], now using a larger number of high density alcoholic families ($n = 54$), did find linkage of the DRD2 A1 allele to the more severe but not to the less severe alcoholic phenotype.

The mode of genetic analysis also has an important bearing on the outcome of DRD2-alcoholism linkage studies. This is exemplified in the COGA study where the same data set, from a large number of alcoholic families ($n = 105$) was independently analyzed by three groups of investigators. The first group [Edenberg et al., 1998] found neither the TDT nor the affected family-based tests showed linkage or association between the DRD2 locus and alcoholism. The second group [Curtis et al., 1999] however, found linkage with the MFLINK but not with the GENEHUNTER method of genetic analysis. The third group [Waldman et al., 1999], using a logistic regression of the TDT for continuous traits, did find significant LD between the DRD2 gene and quantitative indices of alcoholism.

From the empirical evidence derived thus far, the following are some of the suggestions offered for future DRD2-alcoholism linkage studies. Like in association studies, family-based studies should carefully ascertain "unaffecteds" to include only subjects who are not only free of alcoholism but also of other drug (including

nicotine) use disorders [Noble, 1998c]. A minimum of 50 high density alcoholic families should be assessed. Genetic analyses should employ those methods that examine alcoholism not as a unitary disorder, but rather as one that has a number of different related variables (e.g., age of onset, symptom counts and quantitative indices of drinking).

The issue remains as to which approach then yields to a better identification of genes in complex disorders, like alcoholism: association or linkage studies? Whereas linkage analysis has been used successfully to identify major genes, a recent study [Risch and Merikangas, 1996] has shown that linkage studies, including Sib-Pair analyses, compared to association studies, have dramatically less power to detect the role of genes with a small effect size. For λ of approximately 2, which is in the range of the DRD2-alcoholism relationship, it is estimated [Risch and Merikangas, 1996] that 3,000 to 4,000 sib-pairs would be required, over a narrow range of allele frequencies for linkage analysis, compared to 300–400 case-control sets, over a wide range of allele frequencies for association analysis. Still, the number of sib-pairs and case-controls would be greatly reduced to obtain linkage or association in DRD2-alcoholism studies if, as indicated above, certain characteristics of the population studied are taken into consideration.

It is a well known clinical observation, backed by scientific data, that alcoholics have the co-existence of a number of other addictive problems. The question this raises is whether a common molecular genetic diathesis prevails in alcoholism and in other addictions. Meta-analysis of a substantial number of subjects with illicit drug abuse or with nicotine dependence show a significant association of the DRD2 A1 allele with these disorders. Similarly, the A1 allele and other DRD2 variants are also found to associate with obesity and gambling. These observations suggesting a common genetic basis for these disorders have led to the hypothesis that the DRD2 is a reinforcement or reward gene [Noble, 1996; Blum et al., 1996b].

Whereas this review deals with human studies, evidence that the DRD2 gene is also implicated in alcohol and other drug-related behaviors comes from animal models. Several quantitative trait locus (QTL) studies, using recombinant inbred mouse strain, localized QTLs for alcohol drinking preference in the region of the DRD2 gene [Phillips et al., 1994, 1995; Gehle and Erwin, 1998; Tarantino et al., 1998]. Studies of rats selectively inbred for alcohol preference show alcohol-preferring strains have lower brain D2 dopamine receptor levels than alcohol-nonpreferring strains [Kanes et al., 1993; McBride et al., 1993]. Finally, in a very recent study [Thanos et al., 2001], DRD2 gene vector injection into the nucleus accumbens significantly reduced alcohol self-administration in both P and NP rats. This suggests that high brain levels of D2 dopamine receptors protect against alcohol abuse, whereas low levels of this receptor facilitate alcohol abuse.

The role of the DRD2 gene in other psychiatric disorders has also been investigated, although not as intensively as in addictive disorders. Variants of this gene

have been implicated in mood disorders, schizophrenia and posttraumatic stress disorder although mixed findings are found here as well.

Because the DRD2 gene is highly expressed in brain areas involved in the control of bodily movement, variants of this gene have been examined in movement disorders. Among these disorders where the DRD2 gene has been implicated are, Parkinson disease, tardive dyskinesia and myoclonus dystonia. It has also been implicated in another neurological disorder, migraine. A few studies, however, have come up with negative findings.

Phenotypes

An important question that the DRD2 studies raise is, do variants of this gene, besides their involvement in addictive and other neuropsychiatric disorders, have biological meaning? This is a fundamental question because delineating the functional significance of these variants may help in understanding not only some of the mechanisms that underlie these disorders, but also how these variants affect certain relevant aspects of brain functioning.

The available evidence suggests that certain variants of the DRD2 are expressed as different phenotypes. Specifically, subjects carrying the DRD2 A1 allele have reduced brain D2 dopamine receptors compared to subjects lacking this allele. The reduced brain dopaminergic activity that characterizes A1 allelic subjects is reflected in other aspects of brain function and behavior. In subjects with the A1 allele, and who express lower levels of D2 dopamine receptors, reduced glucose metabolism, as measured by PET, was found in brain regions closely associated with the prefrontal system and interconnected cortical and subcortical structures. These structures are normally rich in dopamine receptors and are known to participate in a variety of complex cognitive and motivational states. That cognitive functioning is diminished in A1 allelic subjects comes from assessment of neurophysiologic (increased latency or decreased amplitude of the P300) and neuropsychologic (decreased visuospatial functioning) markers. With respect to stress, a differential response was found on these neurocognitive markers between subjects with and without the A1 allele. Specifically, an inverse relationship was observed between stress and P300 amplitude and visuospatial performance in subjects with the A1 allele. Stress, however, had no discernible effect on these neurocognitive markers in subjects without this allele. Further, when the role of stress was assessed in alcoholics, increasing stress was associated with increasing severity of alcohol problems in subjects with the A1 allele (presumably due to their decreased neurocognitive functioning) but not in subjects without this allele.

Implications for Clinical Practice and Public Health

Currently, alcoholics and other-drug dependent patients are treated as if they are a single group. Treatment outcome, however, is variable, with some patients

receiving lasting benefit, while others entering the “revolving-door” of treatment. The present review shows that alcohol/drug dependent subjects who inherit the A1 allele or other variants of the DRD2 gene, the so-called “genetic” type, develop the most severe form of the disorder. They are also the most difficult to treat. Identifying the “genetic” and “environmental” type of dependents could provide an individualized approach to the treatment of their disorder. Those with the A1 allele may be provided with a pharmacogenomic treatment (e.g., with a D2 dopamine receptor agonist), whereas those without this allele may be given an opportunity for a psychosocial approach to the treatment of their disorder. This targeted approach to these two types of dependents could lead to a more successful treatment outcome than the current conventional approach that treats dependent subjects as if they are a unitary group. A commentary in *Lancet* [Clark, 1998] and an editorial in the *Journal of the National Cancer Institute* [Noble, 1998b] discuss the potential benefit of knowledge of DRD2 variants in the development of more effective individualized therapy.

Treatment of psychiatric patients with neuroleptic agents and neurologic patients (e.g. with Parkinson disease) with dopaminergic agonists, is associated with serious debilitating side effects in some patients. These adverse effects include neuroleptic-induced malignant syndrome and hyperprolactinemia in psychiatric patients and L-dopa-induced dyskinesia in Parkinson disease patients. It is currently unknown who these patients are. The emerging evidence, however, suggests that variants of the DRD2 gene can help identify those patients who are the most susceptible to these drug-induced problems. Such knowledge can have a practical outcome. It can help clinicians provide such patients with lower doses of the preferred drug or treat them with other pharmacological agents.

Another area where knowledge of DRD2 gene variants can potentially have therapeutic benefits are children with idiopathic short stature. Treating such children with the DRD2 A1 alleles who have deficits in their central dopaminergic system, with dopamine receptor agonists, could lead to a more normalized growth.

Finally, with respect to public health, it is known currently that alcoholism, nicotine and illicit drug dependence and obesity are major problems in the U.S. Together, they afflict more than a third of the adult population. Their medical, psychological and economic costs are a major burden on our society. As this review shows, the DRD2 is a common gene involved in these disorders, with one of its variants (the A1 allele) being associated with about 40% of those who are harmed. This knowledge together with other information gathered on this gene during the past decade has led not only to a better understanding of brain function and behavior but has the potential of contributing to the prevention and treatment of these serious public health problems.

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