

Addiction and its reward process through polymorphisms of the D₂ dopamine receptor gene: a review

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Summary – Since 1990, association studies have amassed strong evidence implicating the D₂ dopamine receptor (DRD2) gene in alcoholism. Specifically, the *TaqI* A minor (A1) allele of the DRD2 gene has been associated with alcoholism. The DRD2 gene has also been found to be involved in other substance use disorders including cocaine, nicotine and opioid dependence, and obesity. Beyond association studies, pharmacologic studies have shown reduced brain D₂ dopamine receptor numbers in A1⁺ allele carriers (A1A1 and A1A2 genotypes) compared to A1⁻ allele carriers (A2A2 genotype). Through a number of other approaches, different phenotypes have also been identified in subjects with the A1⁺ and A1⁻ alleles. These include metabolic, neurophysiological, neuropsychological, personality, stress and treatment studies. It is hypothesized that in an effort to compensate for deficiencies in the dopaminergic system, substance abusers may seek to stimulate the mesocorticolimbic circuits of the brain, long thought to be important in behavioral reward and reinforcement. In effect, one form of the DRD2 gene, the A1 allele, renders the dopaminergic system inefficient and rewards substance abuse that increases brain dopamine levels. © 2000 Éditions scientifiques et médicales Elsevier SAS

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THE DRD2 GENE IN ALCOHOLISM

Twin and adoption studies support a strong hereditary component in alcoholism. If indeed such a hereditary component exists, it must have a molecular genetic representation. However, the question this raises is, which of the approximately 100,000 genes in the human genome are implicated in this disorder? Given that substantial evidence prevails for the involvement of the dopaminergic system in alcoholism (for review see [42]), genes in this system may be strong candidates for investigation.

In 1990, an association of the *TaqI* A D₂ dopamine receptor (DRD2) minor (A1) allele with alcoholism was first reported [9]. Since then, a large number of

international studies have attempted to replicate this observation. Whereas many studies have affirmed this finding, others have not. This has generated some controversy as to whether such an association actually exists. However, at least eight independent meta-analyses of Caucasian alcoholics and controls have demonstrated this association to be robust [10, 13, 20, 28, 41, 43, 58, 70]. An earlier meta-analysis [25] did not find a significant association; however, see [46].

Table I presents a summary of the extant peer-reviewed and full-published articles of Caucasian alcoholics where DRD2 genotypes were available and which used their own controls. In this analysis, a total of 1,085 heterogeneous alcoholics (both more severe and less severe) was compared to 948 heterogeneous

Table I. *TaqI* A DRD2 genotypic distribution in studies of Caucasian heterogeneous alcoholics and controls

	<i>Alcoholics^a</i>					<i>Controls^b</i>				
	Genotypes			Prevalence of A1 Allele (%)	Frequency of A1 Allele (%)	Genotypes			Prevalence of A1 Allele (%)	Frequency of A1 Allele (%)
	A1A1	A1A2	A2A2			A1A1	A1A2	A2A2		
Blum et al. [9]	1	13	8	63.6	34.1	0	4	20	16.7	8.3
Bolos et al. [11]	2	13	25	37.5	21.3	8	30	89	29.9	18.1
Parsian et al. [57]	0	13	19	40.6	20.3	0	3	22	12.0	6.0
Comings et al. [14]	3	41	60	42.3	22.6	0	24	84	22.2	11.1
Gelernter et al. [26]	1	18	25	43.2	22.7	3	21	44	35.3	19.9
Blum et al. [8]	3	39	47	47.2	25.3	0	6	25	19.4	9.7
Cook et al. [19]	1	4	15	25.0	15.0	0	6	14	30.0	15.0
Goldman et al. [27]	0	14	32	30.4	15.2	2	11	23	36.1	20.8
Amadéo et al. [2]	3	18	28	42.9	24.5	0	7	36	16.3	8.1
Suarez et al. [66]	1	29	52	36.6	18.9	2	23	63	28.4	15.3
Noble et al. [55]	1	20	23	47.7	25.0	3	14	41	29.3	17.2
Geijer et al. [24]	3	29	61	34.4	18.8	5	24	52	35.8	21.0
Neiswanger et al. [41]	1	28	23	55.8	28.8	0	4	26	13.3	6.7
Heinz et al. [30]	3	31	63	35.1	19.1	4	35	74	34.5	19.0
Lawford et al. [37]	10	62	129	35.8	20.4	3	11	32	30.4	18.5
Hietala et al. [31]	1	29	40	42.9	22.1	0	11	39	22.0	11.0
Total subjects (n = 2033)	34	401	650 ^c	40.1 ^d	21.6 ^e	30	234	684 ^c	27.9 ^d	15.5 ^e

a: Includes both less severe and more severe alcoholics. b: Includes both nonalcoholics and subjects drawn from the general population (alcoholics not excluded). c: Significant difference was found in genotypes between alcoholics and controls ($\chi^2 = 36.0$, $P = 1.55 \times 10^{-8}$). d: The prevalence of the A1 allele (A1A1 and A1A2 genotypes) was significantly higher in the alcoholic than in the control group ($\chi^2 = 33.1$, 95% confidence limits: 1.43 and 2.10, odds ratio = 1.73, $P = 8.80 \times 10^{-9}$). e: The frequency of the A1 allele was significantly higher in the alcoholic than in the control group ($\chi^2 = 24.4$, 95% confidence limits: 1.27 and 1.77, odds ratio = 1.50, $P = 7.83 \times 10^{-7}$).

controls (both assessed and unassessed for alcoholism). Nine of these individual studies [2, 8, 9, 14, 31, 37, 41, 55, 57] showed a significant association of the A1 allele with alcoholism, whereas seven did not [11, 19, 24, 26, 27, 30, 66]. However, when the combined data (*table I*) were analyzed, a significant genotypic difference was found between alcoholics and controls ($P < 10^{-7}$). Moreover, the prevalence of the A1 allele was significantly higher in alcoholics than in controls ($P < 10^{-8}$), as was its frequency ($P < 10^{-6}$).

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 other studies have not. Besides sample size, two key issues may be contributing factors to this difference: a) the type of alcoholics selected, and b) the nature of the comparative controls employed.

It is generally acknowledged that alcoholism is a heterogeneous disorder, and it is likely that types of alcoholism vary according to the extent to which they are influenced by genetic and environmental factors. At

least two different alcoholism typologies have been described [3, 12]: a) a more severe, more genetic and early-onset type of alcoholism, and b) 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 11 studies where alcoholism severity was ascertained, the prevalence of the A1 allele was 47.2% in 337 more severe alcoholics and 32.0% in 369 less severe alcoholics, a difference that was significant ($P = 5.0 \times 10^{-5}$). This suggests that the severity of alcoholism is an important determinant of A1 allelic prevalence.

As indicated above, another important issue in DRD2 alcoholism association studies is the nature of the controls used. Since alcohol abuse/dependence is a common problem in society and because other drug

Table II. *TaqI* A DRD2 allelic distribution in studies of more severe and less severe Caucasian alcoholics

	<i>More severe alcoholics</i>			<i>Less severe alcoholics</i>			<i>Odds ratio</i>
	A1 ⁺	A1 ⁻	% A1 ⁺	A1 ⁺	A1 ⁻	% A1 ⁺	
Bolos et al. [11] a	9	11	45.0	6	14	30.0	1.91
Parsian et al. [57] b	6	4	60.0	7	15	31.8	3.21
Blum et al. [8] b	33	19	63.5	15	29	34.0	3.36
Gelernter et al. [26] c	12	11	52.2	7	13	35.0	2.03
Cook et al. [19]d	4	11	26.7	1	4	20.0	1.45
Turner et al. [69] d	4	18	18.2	5	20	20.0	0.89
Noble et al. [55] d	19	15	55.9	15	15	50.0	1.27
Geijer et al. [24] e	20	36	35.7	3	15	16.7	2.78
Geijer et al. [24] f	6	4	60.0	3	6	33.3	3.00
Lawford et al. [37] b	23	20	53.9	49	109	31.0	2.56
Hietala et al. [31] d	23	29	44.2	7	11	38.9	1.25
Total subjects (n = 706)	159	178	47.2*	118	251	32.0*	1.90

Note: A1⁺ allele subjects include A1A1 or A1A2 genotypes; A1⁻ allele subjects include A2A2 genotype only. More severe (n = 337) and less severe (n = 369) alcoholics were differentiated by a variety of means: a: The Michigan Alcoholism Screening Test (MAST); b: The presence or absence of medical complications of alcoholism; c: Alcohol consumption; d: Severity of Alcohol Dependence Questionnaire (SADQ); e: DSM-III-R criteria (P2 group vs. P1 minus P2 group); f: Autopsy determination (P6 group vs. P5 minus P6 group); * The prevalence of the A1 allele was significantly higher in the more severe than in the less severe alcoholic group ($\chi^2 = 16.4$, 95% confidence limits: 1.38 and 2.61, $P = 5.00 \times 10^{-5}$).

problems, as shown below, 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 are A1 allelic differences between unassessed (alcoholics and/or drug abusers not excluded) and assessed (alcoholics and/or drug abusers excluded) controls, the prevalence of the A1 allele was compared

between these groups. As *table III* shows, the prevalence of the A1 allele was 31.1% in the 399 unassessed controls and 15.7% in the 236 assessed controls, a difference that was significant ($P = 2.5 \times 10^{-5}$). This supports the view that the nature of controls is an important factor in A1 allelic prevalence.

To recapitulate the data in *tables II* and *III*, the prevalence of the A1 allele was significantly higher in the more severe than the less severe alcoholics, with the

Table III. *TaqI* A DRD2 allelic distribution in studies of Caucasian controls which did or did not exclude alcoholics and/or drug abusers

	<i>A: Controls</i> (<i>Alcoholics and/or drug abusers not excluded</i>)			<i>B: Controls</i> (<i>Alcoholics and/or drug abusers excluded</i>)			
	A1 ⁺	A1 ⁻	% A1 ⁺	A1 ⁺	A1 ⁻	% A1 ⁺	
Grandy et al. [29] a	16	27	37.2	Blum et al. [9] e	4	20	16.7
Bolos et al. [11] a †	21	41	33.9	Parsian et al. [57] e	3	22	12.0
Gelernter et al. [26] a †	24	44	35.3	Comings et al. [14] e	3	17	15.0
Comings et al. [14] a	21	67	23.9	Blum et al. [8] e	6	25	19.4
Smith et al. [64] b	6	14	30.0	Smith et al. [64] f	8	28	22.2
Amadéo et al. [2] a	5	18	21.7	Amadéo et al. [2] e	2	18	10.0
Noble et al. [55] c	17	32	34.7	Noble et al. [55] g	4	16	20.0
Lawford et al. [37] d	14	32	30.4	Neiswanger et al. [41] h	4	26	13.3
				Lawford et al. [37] i	3	27	10.0
Total subjects (n = 635)	124	275	31.1*		37	199	15.7*

Note: A1⁺ allele subjects include A1A1 or A1A2 genotypes; A1⁻ allele subjects include A2A2 genotype only. a: Alcoholics and drug abusers not excluded; b: Alcohol and other drug abusers not excluded; c: Alcoholics excluded but not drug abusers or cigarette smokers; d: Alcohol abusers not excluded; e: Alcoholics excluded; f: Alcoholics and drug abusers excluded; g: Alcoholics, drug abusers and smokers excluded; h: Alcoholics and subjects with family history of alcoholism excluded; i: Alcohol abusers and subjects with family history of alcoholism excluded; †: Excludes CEPH subjects included in [14]; * The prevalence of the A1⁺ allele was significantly higher in A Controls than in B Controls: ($\chi^2 = 17.8$, 95% confidence limits: 1.58 and 3.73, odds ratio = 2.43, $P = 2.49 \times 10^{-5}$).

prevalence of this allele being also significantly higher in unassessed than assessed controls. Moreover, the more severe alcoholics (*table II*) had a threefold higher prevalence of the A1 allele than the assessed controls (*table III*), a difference that was highly significant ($P < 10^{-10}$). However, the prevalence of the A1 allele in the less severe alcoholics (*table II*) was virtually identical to that of the unassessed controls (*table III*), 32.0% vs. 31.1%, a difference that was not significant.

THE DRD2 GENE IN OTHER SUBSTANCE USE DISORDERS

Other substances of abuse, like alcohol, enhance brain dopamine levels and exert their reinforcing properties through the dopaminergic system of the mesocorticolimbic pathways of the brain (for review, see [35, 74]). This commonality in the actions of substances of abuse raises the question as to whether the DRD2 gene is also implicated in substance use disorders other than alcoholism.

In a study of Caucasian polysubstance abusers (cigarettes, alcohol, heroin, cocaine, marijuana, amphetamines and other drugs), the prevalences of the *TaqI* A1 allele and the *TaqI* B1 allele were significantly higher in these subjects when compared to controls [56, 64]. (It should be noted that the *TaqI* A alleles, A1 and A2, are produced by mutations in the 3' untranslated region of the DRD2 gene, whereas the *TaqI* B alleles, B1 and B2, are produced by mutations closer to the 5' regulatory region of this gene. However, these two loci are in linkage disequilibrium, i.e., certain alleles at one locus appear together on the same chromosome with certain alleles at the other locus more often than would be expected by chance, based on population allele frequencies.) These associations remained significant, even after alcohol abusers were removed from the polysubstance abusing group. Other investigators [18] similarly studied the DRD2 gene in Caucasian polysubstance abusers. They also found A1 allelic prevalence to be significantly higher in these subjects than controls. Moreover, A1 allelic prevalence was significantly higher in more severe than less severe polysubstance abusers. In another study, the *TaqI* A and *TaqI* B DRD2 alleles have been examined in Caucasian cocaine-dependent subjects [47]. The prevalence of the A1 allele was significantly higher in these subjects than in non-substance-abusing controls, as was the B1 allele. These associations remained significant, even after alcohol co-dependent subjects were

removed from the sample of cocaine-dependent subjects. Similarly, the prevalences of the A1 and B1 alleles were significantly higher in Caucasian psychostimulant- (cocaine, amphetamine) preferring abusers than controls [59].

The role of the DRD2 gene has also been studied in smoking (nicotine-dependent) subjects. In one study of Caucasians drawn from the general population, the prevalence of the A1 allele progressively increased in the order of non-smokers, ex-smokers and active smokers [54]. Moreover, A1 allelic prevalence was found to be significantly higher in active smokers and ex-smokers when each are compared to the non-smoking controls. Another study [15] examined smokers attending a smoking cessation clinic. A1 allelic prevalence was found to be significantly higher in the active smokers than in the nonalcoholic, non-drug-abusing controls. Furthermore, a very recent case-control study ascertained the DRD2 alleles and smoking status in lung cancer patients [65]. The prevalence of the B1 allele was significantly higher in the smokers than in the non-smokers. Moreover, the age of onset of smoking in the smokers was significantly younger in subjects who carried either the A1 or the B1 allele. In addition, subjects with the A1 and/or B1 alleles made fewer attempts to quit smoking than those who lacked these alleles, indicating a greater difficulty in abstaining. A recent editorial [44] reviews the role of the DRD2 gene in smoking behavior.

A very recent study followed opioid-dependent subjects treated with methadone in an outpatient setting [51]. The frequency of the DRD2 A1 allele was significantly higher in these patients than controls free of current and past alcohol/drug abuse. Mean daily heroin consumption was twice as great in A1⁺ (A1/A1 and A1/A2 genotypes) than A1⁻ (A2/A2 genotype) allelic patients during the year prior to 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 over the one-year course of methadone administration. These findings suggest DRD2 genotypic differences in pretreatment heroin use and post-treatment outcome in opioid-dependent subjects.

The reinforcing properties of food have also led to an examination of the involvement of DRD2 polymorphisms in obesity. Haplotype 4 of the DRD2 gene was found to be associated with increasing risk for obesity [16]. In another study, the DRD2 A1 allele was

present in 45.2% of obese subjects [52], 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 DRD2 genes have been examined in relationship to obesity [17]. 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 effect of gender on the relationships among DRD2 alleles, obesity, and smoking status [49]. Female smokers who carried either the A1 or the Intron 6/Exon 7 1 allele of the DRD2 had a significantly lower BMI than those who lacked these alleles. However, this pattern was reversed in male smokers. These findings suggest that smoking lowers BMI in A1 or Intron 6/Exon 7 1 allele females, but not in males.

DRD2 PHENOTYPES

Given the growing body of evidence supporting association between DRD2 polymorphisms and various substance use disorders, the question is raised whether such mutations have phenotypic correlates. In the absence of such correlates, it may be inferred that the said mutations have no functional significance. In an attempt to answer this question, a variety of approaches have been utilized. These include pharmacologic, metabolic, neurophysiological, neuropsychological, stress, personality, and treatment studies.

Pharmacologic studies

Postmortem caudate nucleus samples obtained from 33 alcoholics and 33 nonalcoholics were ascertained for D₂ dopamine receptor binding [48]. Using [³H]spiperone as the D₂ dopamine receptor binding ligand, two important D₂ dopamine receptor binding characteristics were obtained: B_{max} (the number of binding receptors) and K_d (binding affinity). In the 29 brain samples with the A1⁺ allele, the B_{max} was found to be significantly reduced (by almost 30%) when compared with the B_{max} of the 37 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 nonalco-

holic samples, or between the A1⁻ allelic alcoholic and nonalcoholic samples. Moreover, a significant progressively reduced B_{max} was observed in the A2/A2, A1/A2 and A1/A1 genotypes, respectively, ($P = 0.01$). However, no significant difference was observed in the K_d between A1⁺ and A1⁻ allelic samples (either unadjusted or covariate adjusted for B_{max}).

A recent confirmation, in the UK, of the above study has been obtained on brain autopsy samples of 44 individuals [68]. 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 A1 allele ($n = 19$) compared with those homozygous for the DRD2 A2 allele ($n = 25$).

A very recent study [63] determined D₂ dopamine receptor binding density (B_{max}), affinity (K_d) and availability (B_{max}/K_d) in 54 healthy Finnish volunteers using positron emission tomography (PET) and [¹¹C]raclopride in order to ascertain whether the A1 allele is 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 A1/A2 group ($n = 17$) compared with the A2/A2 group ($n = 37$). However, there was 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 [36] determined in 70 living subjects (47 healthy controls and 23 schizophrenics) striatal D₂ dopamine receptor binding potential using the D₂ dopamine receptor radiotracer [¹²³I]BZM. In the total population studied, there was no significant difference in D₂ dopamine receptor binding potential between A1⁺ ($n = 27$) and A1⁻ allelic ($n = 43$) subjects. However, when the controls and schizophrenics were separately examined, 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. Since the above two studies [36, 63] appeared simultaneously in the same journal issue, an editorial [33] reviewed the merits of these studies. It

suggests that the study using [^{123}I]BZM [36] had insufficient power to detect a significant difference between $A1^+$ and $A1^-$ allelic controls. Moreover, since schizophrenics showed a trend in the opposite direction, the results on D_2 dopamine receptor binding potential and allelic association may have been confounded in these subjects by prior neuroleptic treatment.

Metabolic studies

PET studies have identified brain metabolic deficits in alcoholics and other drug abusers. In abstinent alcoholics, compared to nonalcoholic controls, hypometabolism was found in various brain areas using as tracers [^{11}C]glucose [73] and 2-deoxy-2- [^{18}F]fluoro-D-glucose (FDG) [1]. FDG studies of cocaine abusers [71, 72] have also shown hypometabolism in a number of brain areas that remained even after several months post-detoxification. However, it has not been determined whether some of these deficits were a consequence of prolonged substance abuse or due to a preexisting condition.

The above 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 DRD2 $A1$ allele. However, to establish inherent differences in brain glucose metabolism between $A1^+$ and $A1^-$ allelic subjects, it is necessary to exclude the possible CNS toxic effects of the alcohol/drug abuse state on this measure. To initiate such a study, brain FDG metabolism was compared in healthy nonalcohol/nondrug-abusing subjects who had either the $A1^+$ or the $A1^-$ allele [50].

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 indicate that subjects who carry the $A1^+$ allele and express lower levels of D_2 dopamine receptors [48, 63, 68] have reduced GMRs in brain regions closely associated with the prefrontal system and interconnected cortical and subcortical structures that are normally rich in dopamine receptors. These structures are known to participate in a variety of complex cognitive and motivational states. The present observations support phenotypic differences, based on brain glucose metabolism, between $A1^+$ and $A1^-$ allelic subjects.

Neurophysiological studies

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 neurophysiological 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's disease), prolonged P300 latency and/or decreased P300 amplitude have been associated with decreased CNS dopaminergic activity. To determine whether a relationship exists between P300 characteristics and DRD2 alleles, a sample of 98 young Caucasian boys was studied [45]. This sample consisted of three groups of children: a) 32 sons of active (nonabstinent) alcoholic (SAA) fathers; b) 36 sons of recovering (abstinent) alcoholic (SRA) fathers; and c) 30 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 large main effect of allele ($A1^+ = 455 + 12$ ms, $A1^- = 412 + 8$ ms, $P = 0.004$), 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 $A2$ homo-

gygotes ($P = 0.01$) [7]. However, no significant difference 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 [22]. 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 [32].

These studies suggest that in a neurophysiological marker, the P300, which has a strong dopaminergic component in its generation, reduced dopaminergic tone is observed in subjects who carry the DRD2 A1 allele.

Neuropsychological studies

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, since 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 182 alcohol- and other drug-naive young sons of active alcoholic, recovered alcoholic, and nonalcoholic fathers was studied [5]. 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 found in the sons of the active alcoholic group who carried the A1⁺ allele, and the best score 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 and cognitive functioning studies

Twin studies suggest that genes and environmental factors each influence approximately equally the vulnerability for developing alcoholism. What these environmental factors are, remains to be clearly deter-

mined. However, it has been suggested that stress is one of the environmental factors that increases alcohol and drug abuse. Interestingly, animal studies have shown that the mesocorticolimbic dopaminergic neurons are involved in the control of cognitive processes and are activated by stress. Moreover, differences in brain dopamine metabolism have been found in animals in response to stress. Put together, these findings raise the question of whether stress differentially affects cognitive functioning in A1⁺ and A1⁻ allelic individuals.

In an attempt to answer this question, the interactions of family stress score, A1⁺ and A1⁻ allelic status and cognitive marker characteristics (visuospatial functioning and P300 amplitude and latency) were determined in 168 alcohol- and drug-naive young boys [6]. In boys with the A1⁺ allele, the family stress score was negatively and significantly correlated with Benton's Line Orientation score and the P300 amplitude. However, no such significant correlations were found in boys with the A1⁻ allele. Moreover, the interaction of the A1⁺ allele and the family stress score produced significant regression coefficients in both the Line Orientation score ($P = 0.002$) and the P300 amplitude ($P = 0.04$). Together, these two cognitive markers accounted for 37% of the variance in the family stress score of the A1⁺ allelic boys ($P = 0.0002$) but less than 1% in the A1⁻ allelic boys ($P > 0.9$). This study provides the first evidence of a specific gene-environment interaction involving human cognitive functioning and suggests that stress differentially affects cognitive functioning in A1⁺ and A1⁻ allelic subjects.

Personality studies

It has been hypothesized that Novelty Seeking (NS) behavior, as determined by the Tridimensional Personality Questionnaire (TPQ), has a dopaminergic component [12]. In support of this hypothesis, a positive association was reported [21] 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 [4] reported a study, using another questionnaire, and found a similar association. However, these findings were not replicated by some other investigators [34, 40]. In fact, a significant negative association was found between NS score and the DRD4 7R allele [40], leading to the suggestion that a reevaluation is indicated of the DRD4 gene in this personality domain.

In a recent study [53], the relationship of NS of the TPQ to polymorphisms of both the DRD2 and DRD4 genes was determined in 119 healthy Caucasian boys, who had not 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 with boys lacking any of these alleles. Boys with the DRD4 7R allele had also a higher NS score that just achieved a statistically significant level ($P = .049$), than those without this allele. However, the greatest difference in NS score 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. However, the combined DRD2 and DRD4 polymorphisms contribute more markedly to this behavior than when these two gene polymorphisms are individually considered.

Treatment studies

If the A1⁺ allelic subjects have reduced numbers of brain D₂ dopamine receptors [48, 63, 68] and diminished CNS dopaminergic tone [5, 45], 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 83 hospitalized alcoholics over a six-week period [38]. Besides ascertaining *TaqI* A 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⁺). However, no significant differences were found in decreased depression among the four groups. Additionally, the retention rate of the A1⁺ allelic alcoholics receiving bromocriptine during the six-week trial was greater than the other three groups and significantly higher when compared to A1⁺ allelic alcoholics receiving placebo (PLA A1⁺).

This study indicates that alcoholics who carry the A1⁺ allele are more amenable to treatment by a dopaminergic agent than alcoholics who lack this allele. It suggests that DRD2 genotypes differentially influence treatment outcome.

COMMENTS

The DRD2 has been one of the most, if not the most, intensively and extensively studied gene in alcoholism and other substance use disorders. Population-based studies of Caucasians of European ancestry, derived from U.S., European and Australian centers, show a strong association of the DRD2 A1 allele with alcoholism. Given that no significant A1 allelic variations are known to exist among Europeans of different nationalities, but a significant association of this allele is found with alcoholics of 'mixed' European background and also with more 'pure' European alcoholics (e.g., French [2] and Finnish [31]), it is highly unlikely that unplanned stratification bias is a valid explanation for this association. Moreover, when 16 studies of subjects of European ancestry, consisting of about 1,000 alcoholics and 1,000 controls, conducted in different settings by a variety of investigators are analyzed, the overall robust genotypic difference between alcoholics and controls, and the significantly higher prevalence and frequency of the A1 allele in alcoholics compared to controls, can no longer be attributed to chance. Still, the evidence gathered thus far does not indicate that DRD2 is an alcoholism gene per se. Rather, the clinical pleiotropic effects of the DRD2 A1 allele, as manifested by its association with a variety of substance use disorders, suggest that the DRD2 is a reinforcement or reward gene [54].

Evidence that the DRD2 gene is implicated in alcohol- and other drug-related behaviors also comes from animal models. Quantitative trait locus (QTL) analyses, using recombinant inbred mouse strains, localized QTLs for alcohol drinking preference in the region of the DRD2 [61, 62]. A QTL in this region linked to alcohol preference drinking has been recently confirmed by two other laboratories [23, 67]. Moreover, another recent study [60] showed that alcohol preference and sensitivity are markedly reduced in mice specifically lacking functional D₂ dopamine receptors. Interestingly, an earlier study [39] found an absence of opiate-rewarding effects in mice lacking D₂ dopamine receptors. These findings demonstrate the importance of the dopamine signaling pathway via D₂ dopamine receptors in ethanol- and opiate-related behaviors, and support the view that the DRD2 is a reward gene.

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 and/or other drug abusers had a twofold greater and significantly higher prevalence of the A1 allele than controls that did exclude these subjects. 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. However, no such allelic difference would be expected if less severe alcoholics are compared to controls that do not exclude alcohol and other drug abusers.

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

The empirical evidence reviewed herein does suggest that variants of the DRD2 are expressed as different phenotypes. Specifically, subjects carrying the DRD2 A1 allele have reduced brain D₂ dopamine receptors. Moreover, that reduced brain dopaminergic activity characterizes A1 allelic subjects is also derived from a variety of multidisciplinary approaches including those obtained from metabolic, neurophysiological, neuropsychological, stress, personality and treatment studies.

Given that a dopaminergic deficit prevails in subjects with the DRD2 A1 allele, it may be hypothesized that subjects with this allele may compensate for the deficiency of their dopaminergic system by the use of alcohol and other substances, agents known to increase brain dopamine levels. Stimulation by dopamine of A1 allelic subjects' fewer D₂ dopamine receptors could provide enhanced feelings of reward and pleasure. Continued substance abuse can then lead to dependence and other complications. This is a hypothesized mechanism and only incremental future research can determine its validity.

It has been estimated, from twin and other studies, that of the diathesis for severe substance use disorders, 60% is genetically determined and 40% is environmen-

tally determined [70]. Of the genetic diathesis, 27% is attributed to the DRD2 gene and 33% is attributed to other genes [70]. Thus, while the DRD2 remains a major gene in substance use disorders, other genes are yet to be identified. Knowledge of these genes and their functional significance will enhance the understanding of the underlying biological mechanisms that subserve alcoholism and other substance use disorders. Furthermore, it could lead to more rational prevention and treatment approaches for a major problem in society.

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