The D_2 Dopamine Receptor A_1 Allele and Opioid Dependence: Association With Heroin Use and Response to Methadone Treatment

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A total of 95 Caucasian opioid-dependent patients were followed over a one-year period in an outpatient methadone treatment program. The frequency of the *Taq*I A_1 allele of the D_2 dopamine receptor (*DRD2*) gene was 19.0% in these patients compared with 4.6% in controls free of past and current alcohol and other drug abuse and free of family history of alcohol and other drug abuse ($p = 0.009$). Twenty-two of these patients dropped out of the methadone program (Group A), 54 had a successful treatment (Group B), and 19 had a poor treatment (Group C) outcome. The frequency of the A_1 allele was highest in Group C (42.1%), followed by Group A (22.7%) and was lowest in Group B (9.3%). The more than fourfold higher frequency of the A_1 allele in the poor treatment outcome group compared with the successful treatment outcome group was significant ($p = 0.00002$). Moreover, the average use of heroin (grams/day) during the year prior to study entry was more than twice as great in patients with the A_1^+ allele (A_1/A_1 or A_1/A_2 genotype) than those with the A_1^- allele (A_2/A_2 genotype) (A_1^+ allele = 0.55 ± 0.10, A_1^- allele = 0.25 ± 0.05; $p = 0.003$). The results indicate that *DRD2* variants are predictors of heroin use and subsequent methadone treatment outcome and suggest a pharmacogenetic approach to the treatment of opioid dependence. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 96:592–598, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: opioid dependence; heroin; D_2 dopamine receptor gene; dopamine; methadone; treatment outcome

INTRODUCTION

Opioid dependence represents a significant and growing health and social problem, with heroin being the most commonly abused opiate [Imlah, 1989]. In the United States between 750,000 and 1 million individuals are heroin users [Kreek, 1992]. In Australia 30,000 to 50,000 individuals are estimated to be dependent on heroin, with another 60,000 using heroin on an irregular basis [Commonwealth Department of Community Services and Health, 1988]. Considerable medical, legal, and interpersonal harm, including mortality, is associated with heroin use. The major causes of premature death amongst Australian users are suicide, accidental overdose, and infectious diseases [Commonwealth Department of Human Services and Health, 1995]. Moreover, a high prevalence of criminal activity and psychosocial difficulties are also found among heroin users [Ball and Ross, 1991; Gerstein and Harwood, 1990].

The extent of this serious problem has stimulated considerable interest in the physiological and neurochemical processes involved in opioid dependence. In this respect, there is now growing evidence that opiates and a variety of drugs of abuse (alcohol, cocaine, amphetamine, nicotine, and Δ^9-tetrahydrocannabinol) increase brain dopamine levels and enhance neurotransmission in the nucleus accumbens of animals [Di Chiara and Imperato, 1988; Tanda et al., 1997; Weiss et al., 1993]. Considering the extensive connections of the nucleus accumbens with limbic brain areas involved in emotion [Heimer et al., 1991], the activation of dopamine neurotransmission in the nucleus accumbens is

thought to be involved in the motivational and reward properties of opiates and other drugs of abuse [Tanda et al., 1997; Koob and LeMoal, 1997]. Further support for this notion comes from recent studies of animals that have been genetically manipulated. Mice lacking D_2 dopamine receptors show an absence of opiate rewarding effects [Maldonado et al., 1997]. Another study found in mutant mice lacking D_2 dopamine receptors a markedly reduced alcohol preference and sensitivity when compared with the high alcohol-preferring wild type [Phillips et al., 1998]. Collectively, these data suggest that the mesolimbic dopaminergic pathway, through the D_2 dopamine receptors, is a key neural substrate for opiate- and other drug-related reinforcement and reward.

Human molecular genetic studies are also implicating the dopaminergic system in substance use disorders. The involvement of the D_2 dopamine receptor (*DRD2*) gene was first shown in alcoholism [Blum et al., 1990]. Specifically, the minor *Taq*I A allele (A_1) of the *DRD2* gene was associated with a severe form of alcoholism. Whereas controversy has arisen because some case-control studies reported a lack of significant association of the *DRD2* A1 allele with this disorder, more recent investigations have revealed that the type of controls and alcoholics used are important determinants in this association [Lawford et al., 1997; Neiswanger et al., 1995; Noble et al., 1994c; for a recent review see Noble, 1998]. However, it should be noted that the *DRD2* A_1 allele has clinical pleiotropic effects. Besides alcoholism, this allele has been associated with a variety of other drug use disorders. Among these are cocaine dependence [Noble et al., 1993] and psychostimulant abuse [Persico et al., 1996], nicotine dependence [Noble et al., 1994b; Comings et al., 1996; Spitz et al., 1998] and polysubstance abuse [Comings et al., 1994; O'Hara et al., 1993].

If the *DRD2* gene is involved in various substance use disorders, is it also implicated in opioid dependence? Does methadone treatment outcome in opioid-dependent patients depend, in part, on polymorphism of the *DRD2* gene? Does the extent of heroin use prior to treatment of these patients associate with *DRD2* polymorphism? These are some of the questions that are examined herein. This study was presented at a recent meeting of the Society for Neuroscience [Noble et al., 1998].

METHODS
Subjects

Ninety-five unrelated Caucasian patients attending a methadone clinic for their heroin problem were recruited for the study. Patients were assessed for opioid dependence and polysubstance dependence using *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria. They then underwent a clinical history taking by two medical officers (J.S. and B.L.) as done in previous research [Lawford et al., 1997]. Besides obtaining demographic and ethnic background, this included average daily use of heroin over the year prior to their recruitment into the study and use of other drugs, including alcohol, nicotine, cannabis, ben-

zodiazepines, stimulants (amphetamines, cocaine), and hallucinogens. A follow-up medical chart review was conducted 12 months after initial data collection. Data were coded and included daily dose of methadone used and standardized procedure for assessment of treatment outcome including heroin use (as documented through self-report, medical examination, and random weekly urine screens).

Fifty unrelated Caucasian controls were recruited from several Brisbane hospitals. A history was obtained from these subjects that included demographic and ethnic background. In addition, an assessment was made of current and past use of alcohol, nicotine, and other drugs, as well as first-degree family history of alcohol and other drug abuse. Again, this approach follows that used in previous research [Lawford et al., 1997], which generates reliable and valid data.

The above interviews were conducted blind to the subjects' *DRD2* status. All participants provided informed consent and were able to terminate participation in the study without prejudice. Institutional ethics approval was obtained from the relevant hospitals and clinics involved.

Genotyping

A 10 mL blood sample was drawn from each subject. DNA was extracted using standard techniques and subsequently used as a template for determination of *Taq*I A *DRD2* alleles by polymerase chain reaction [Grandy et al., 1993]. Briefly, and as previously described [Noble et al., 1994a], the amplification of DNA was carried out using a Perkin Elmer Gene Amp 9600 thermocycler. Approximately 500 ng of amplified DNA was then digested with 5 units of *Taq*I restriction enzyme (GIBCO/BRL, Grand Island, NY) at 65°C overnight. The resulting products were analyzed by electrophoresis in a 2.5% agarose gel containing ethidium bromide and visualized under ultraviolet light. The A_1/A_2 genotype is revealed by three fragments: 310 bp, 180 bp, and 130 bp. The A_2/A_2 genotype is indicated by two fragments: 180 bp and 130 bp. The A_1/A_1 genotype is shown by the uncleaved 310 bp fragment.

Data Analysis

Information coded from interview proformas was entered into a computer data base. Chi-square test (Yates corrected) and Fisher's exact test, where appropriate, were employed to compare frequency differences of the *DRD2* A1 allele between the various groups studied. Within the clinical sample, differences among the various treatment groups in previous heroin consumption as a continuous variable (g/day) were examined using one-way analysis of variance (ANOVA). Similarly, chi-square analysis and one-way ANOVA were used to determine response to treatment. A *p*-value of ≤ 0.05 was considered to be statistically significant; ± refers to standard error of the mean (S.E.M.) throughout this paper.

RESULTS

Patients and controls were all Australian-born Caucasians of European descent, and none had Aboriginal, Asian, Polynesian, African or other ethnic background.

The 95 patients (66 males and 29 females; mean age 28.4 ± 0.7 years) fulfilled DSM-IV criteria for opioid dependence. Their drug use showed the following pattern. All 95 patients used heroin daily; 87 (91.6%) used nicotine daily; 36 (37.8%) used cannabis daily; 26 (27.4%) used benzodiazepines weekly; 10 (10.5%) consumed alcohol at hazardous drinking levels (40 g/day for males, 20 g/day for females), with two of these being binge drinkers [Australian National Health and Medical Research Council, 1992]; 7 (7.4%) used amphetamines weekly; and 4 (4.2%) used cocaine weekly. None used hallucinogens. While multiple substance use was common, all patients reported heroin as their primary drug of choice and none met DSM-IV criteria for polysubstance dependence.

In the 50 controls (19 males and 31 females, mean age 34.6 years ± 0.9 years), none exceeded current hazardous drinking levels and none were current smokers or illicit drug users, including opiates (Group A). However, this group did include subjects who had past hazardous drinking levels and had first-degree relatives who were alcohol and other drug (AOD) abusers or had neither. Of these 50 subjects, 42 (84.0%) had either first-degree relatives who were AOD abusers or had past hazardous drinking levels or had neither (Group B), 38 (76.0%) had first-degree relatives who were AOD abusers or had neither first-degree relatives who were AOD abusers nor had past hazardous drinking levels (Group C), and 33 (66%) had neither first-degree relatives who were AOD abusers nor had past hazardous drinking levels (Group D).

The genotypes of the 95 opioid-dependent subjects were: A_1/A_1, $n = 1$; A_1/A_2, $n = 34$; A_2/A_2, $n = 60$. The genotypes of the 50 Group A controls were: A_1/A_1, $n = 3$; A_1/A_2, $n = 12$; A_2/A_2, $n = 35$. The genotypes of the 42 Group B controls were: A_1/A_1, $n = 2$; A_1/A_2, $n = 7$; A_2/A_2, $n = 33$. The genotypes of the 38 Group C controls were: A_1/A_1, $n = 0$; A_1/A_2, $n = 5$; A_2/A_2, $n = 33$. Finally, the genotypes of the 33 Group D controls were: A_1/A_1, $n = 0$; A_1/A_2, $n = 3$; A_2/A_2, $n = 30$.

Figure 1 shows the frequency of the *DRD2* A_1 allele in the opioid-dependent group and in the various subsets of the control groups (Groups A to D). No significant differences were found in A_1 allelic frequency when the opioid-dependent subjects were compared with either Group A or Group B controls. However, the opioid-dependent group had a significantly higher frequency of the A_1 allele when compared with either Group C ($\chi^2 = 5.46$, $p = 0.02$) or Group D ($\chi^2 = 6.79$, $p = 0.009$) control.

A test to demonstrate whether there is a significant difference in A_1 allelic frequency among the four control groups (A, B, C, and D) is not possible because these groups are not independent. However, it is feasible to determine statistical difference among the controls if they have independent characteristics. In that respect, of the 50 controls eight were subjects who had first-degree relatives who were AOD abusers and had past hazardous drinking levels (Group 1), four had no first-degree relatives who were AOD abusers but had past hazardous drinking levels (Group 2), five had first-degree relatives who were AOD abusers but had no past hazardous drinking levels (Group 3), and 33
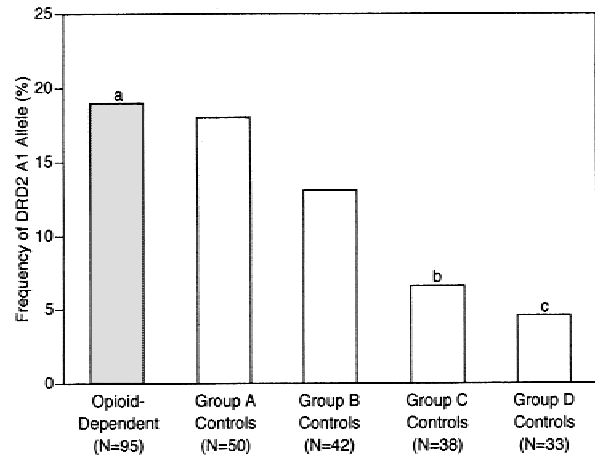

Fig. 1.   Frequency of the *DRD2* A_1 allele in opioid-dependent subjects and in various control groups (A–D). Group A included 50 subjects, none of whom exceeded current hazardous drinking levels and none were current smokers or illicit drug users. However, this group did include subjects who had past hazardous drinking levels and had first-degree relatives who were alcohol and other drugs (AOD) abusers. Group B included 42 of the 50 subjects who had either first-degree relatives who were AOD abusers or had past hazardous drinking levels or neither. Group C included 38 of 50 subjects who had first-degree relatives who were AOD abusers or had neither first-degree relatives who were AOD abusers nor had past hazardous drinking levels. Group D included 33 of 50 subjects who had neither first-degree relatives who were AOD abusers nor had past hazardous drinking levels. a vs. b, $p = 0.02$; a vs. c, $p = 0.009$.

had no first-degree relatives who were AOD abusers and had no past hazardous drinking levels (Group 4). The frequencies of the A_1 allele in Groups 1, 2, 3, and 4, respectively, were 43.8, 75.0, 20.0, and 4.6%, with a significant difference being found among them ($\chi^2 = 32.9$, $p < 10^{-6}$). More specific comparisons among the four groups showed a significant A_1 allelic frequency difference between Group 1 and 4 ($p = 2.58 \times 10^{-4}$) and between Group 2 and 4 ($p = 1.17 \times 10^{-5}$), but not between the other groups compared. These findings show that the frequency of the A1 allele differs significantly among the various control groups studied, with the lowest frequency being observed in the highly screened Group 4 (or Group D) controls.

At one-year follow-up, methadone treatment outcome was ascertained by medical chart review of the opioid-dependent patients. This was done blind to the patients' *DRD2* allelic status or to their heroin use prior to entry into the study. Successful treatment outcome in these patients was defined by one of the following criteria: (1) continued use of methadone with both reliable attendance at the clinic and heroin use abolished or markedly reduced, (2) completed planned methadone treatment without returning to heroin use, (3) uneventful transfer to another methadone treatment program. Poor treatment outcome in these patients included one of the following criteria: (1) leaving the methadone program precipitously and not returning for treatment, (2) continued abuse of heroin on at least a weekly basis despite methadone treatment. Of the 95 opioid-dependent patients, 54 (56.8%) had a successful treatment outcome, 19 (20.0%) had a poor treatment outcome and 22 (23.2%) failed to engage in methadone treatment following their initial assessment (drop-outs).

The genotypes of the patients with successful treatment outcome were: $A_1/A_1 = 0$; $A_1/A_2 = 10$; $A_2/A_2 = 44$. Those who were drop-outs had the following genotypes: $A_1/A_1 = 0$; $A_1/A_2 = 10$; $A_2/A_2 = 12$. Patients with poor treatment outcome had the following genotypes: $A_1/A_1 = 1$; $A_1/A_2 = 14$; $A_2/A_2 = 4$.

Figure 2 shows the frequency of the *DRD2* A_1 allele in the three treatment outcome groups. A_1 allelic frequency was 9.3% in the successful treatment outcome group, 22.7% in the drop-out group, and 42.1% in the poor treatment outcome group. There was a significant difference in A_1 allelic frequency among these three groups ($\chi^2 = 20.3$, $p = 3.90 \times 10^{-5}$). Specific group comparisons showed that, compared with the successful treatment outcome group, frequency of the A_1 allele was significantly higher in both the drop-out group ($\chi^2 = 3.85$, $p = 0.05$) and the poor treatment outcome group ($\chi^2 = 18.5$, $p = 0.00002$). However, there was no significant difference in A_1 allelic frequency between the drop-out and the poor treatment outcome groups ($\chi^2 = 2.70$, $p = 0.10$). Furthermore, the treatment failure group (drop-outs and poor treatment outcome group combined) had a significantly higher frequency of the A_1 allele than the successful treatment outcome group ($\chi^2 = 13.9$, $p = 0.0002$).

The mean daily dose of methadone prescribed to the opioid-dependent patients who remained in the present program was 52.5 mg. This is similar to the mean daily dose of 47.3 mg methadone used in 1928 opioid-dependent patients at six clinics in the United States [Ball and Ross, 1991]. However, it is possible that the poor treatment outcome group could have received lower maintenance doses of methadone than the successful treatment outcome group, accounting for their poor treatment outcome. This possibility was examined. The results showed that the poor treatment outcome group ($n = 19$) received 54.3 ± 5.7 mg/day of methadone, while the successful treatment outcome group ($n = 54$) received 51.9 ± 4.8 mg/day of methadone. A one-way ANOVA indicated that there was no significant difference in methadone dose between these two groups ($F = 0.81$, N.S.). It is also possible that
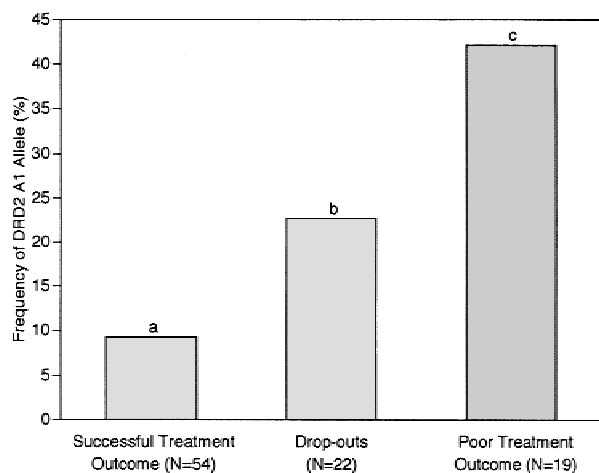

Fig. 2. Frequency of the *DRD2* A_1 allele in various opioid-dependent treatment groups. a vs. b, $\chi^2 = 3.85$, $p = 0.05$; a vs. c, $\chi^2 = 18.5$, $p = 0.00002$.

patients with A_1^+ allele (A_1/A_1 or A_1/A_2 genotype) could have received lower maintenance doses of methadone than patients with the A_1^- allele (A_2/A_2 genotype), accounting for their poor treatment outcome. This possibility was also examined. The results showed that patients with the A_1^+ allele ($n = 25$) received 57.5 ± 5.7 mg/day of methadone whereas patients with the A_1^- allele ($n = 48$) received 49.9 ± 5.0 mg/day of methadone. A one-way ANOVA showed that this difference was also not statistically significant ($F = 0.90$, N.S.).

The mean daily heroin consumption, during the year prior to entry into the study, and its relationship to *DRD2* allelic status and treatment outcome was next ascertained. Table I shows that the A_1^+ allelic group had consumed more than twice the mean daily amount of heroin than the A_1^- allelic group (0.55 ± 0.10 g/d vs. 0.25 ± 0.05 g/d, $F = 9.42$, $p = 0.003$). When treatment outcome was considered in the patient sample without regard to allelic status, the treatment failure group (drop-outs and poor treatment outcome group combined) had consumed a greater amount of heroin than the successful treatment outcome group (0.48 ± 0.08 g/d vs. 0.27 ± 0.06 g/d, $F = 4.78$, $p = 0.03$). When treatment outcome and *DRD2* allelic status were considered together, the mean daily amount of heroin consumed within the successful treatment outcome group was not significantly different between the A_1^+ and the A_1^- allelic subgroups (0.35 ± 0.20 g/d vs. 0.25 ± 0.07 g/d, $F = 0.35$, $p = 0.56$). However, heroin consumption within the treatment failure group was more than twice as great in the A_1^+ allelic subgroup than in the A_1^- allelic subgroup (0.63 ± 0.11 g/d vs. 0.25 ± 0.06 g/d, $F = 7.15$, $p = 0.01$).

DISCUSSION

Little attention has been directed to the molecular genetic factors that might influence the acquisition and prognosis of opioid dependence. The present study demonstrates that a significant association of the *DRD2* A_1 allele occurred with this drug problem only when the comparative controls excluded present and past alcohol and other drug (including nicotine) abusers. Since previous studies have revealed that alcohol- and other drug-related problems share a common diathesis with the *DRD2* A_1 allele (see Introduction), the importance of using controls free of these problems has been previously stressed [Lawford et al., 1997; Noble et al., 1994c]. Moreover, exclusion from controls of subjects with a positive family history of alcoholism and other drug problems has also been suggested in *DRD2* case-control studies [Neiswanger et al., 1995]. Thus, A_1 allelic association with opioid dependence is further strengthened when controls included not only subjects free of present and past alcohol and other drug abuse but also subjects free of family history of alcohol and other drug abuse. The involvement of the *DRD2* gene in opioid dependence and in other drug use disorders supports the view that the *DRD2* is not a specific "opiate" gene but rather it is a reinforcement or reward gene [Noble et al., 1994b; Noble, 1996].

Effective methadone programs can expect success rates of 60 to 70% for opioid-dependent patients while

TABLE I. Heroin Consumption,[1] Treatment Outcome,[2] and DRD2 Allelic Status[3]

Treatment outcome	A_1^+ Allele	A_1^- Allele	A_1^+ and A_1^- Alleles
Success	0.35 ± 0.20 ($n = 10$)[e]	0.25 ± 0.07 ($n = 44$)[f]	0.27 ± 0.06 ($n = 54$)[c]
Failure	0.63 ± 0.11 ($n = 25$)[g]	0.25 ± 0.06 ($n = 16$)[h]	0.48 ± 0.08 ($n = 41$)[d]
All subjects	0.55 ± 0.10 ($n = 35$)[a]	0.25 ± 0.05 ($n = 60$)[b]	0.36 ± 0.05 ($n = 95$)

[1]Mean ± S.E.M. grams heroin consumed per day during the year prior to entry into the methadone program.
[2]Treatment failure group includes both the poor treatment outcome group ($n = 19$) and drop-outs ($n = 22$).
[3]A_1^+ allele: A_1/A_1 and A_1/A_2 genotypes; A_1^- allele: A_2/A_2 genotype.
Notes: [a] vs. [b], F = 9.42, $p = 0.003$; [c] vs. [d], F = 4.78; $p = 0.03$; [e] vs. [f], F = 0.35, $p = 0.56$; [g] vs. [h], F = 7.15, $p = 0.01$.

they remain in treatment [Ball and Ross, 1991]. In the present study, a success rate of 74% was found in the patients who remained in the methadone program. Moreover, success rate was strongly associated with *DRD2* allelic status. Specifically, the poor treatment outcome group had more than a fourfold higher frequency of the A_1 allele than the successful treatment outcome group, with drop-outs having an intermediate frequency. Neither treatment outcome nor *DRD2* allelic status was differentiated by the methadone dose consumed. These observations suggest that in opioid-dependent patients who are engaged in a methadone treatment program, a poor prognosis is expected for carriers of the *DRD2* A_1 allele.

Most would assume that opioid-dependent subjects who prior to treatment had consumed high amounts of heroin are generally more likely to fail in a methadone program than those who had consumed low amounts of this opiate. This assumption was borne out in the present study. The results showed that the treatment failure group had consumed almost twice the daily amount of heroin at entry into the study than the treatment success group. However, it has not been known whether prior heroin consumption was related to *DRD2* allelic status. The present findings showed that A_1^+ allelic carriers had consumed more than twice the daily amount of heroin than those who carried the A_1^- allele. Moreover, when treatment outcome was considered, A_1^+ allelic patients, in both the treatment success and the treatment failure group, had consumed more heroin than A_1^- allelic patients, although the difference was statistically significant only in the treatment failure group. These findings suggest that both prior heroin consumption and *DRD2* allelic status are important indicators of treatment outcome.

It is now recognized that alcoholics are a heterogeneous group consisting of at least two types: (1) a less severe, "environmental" type characterized by an ability to abstain, and (2) a more severe, "genetic" type characterized by an inability to abstain [Babor et al., 1992; Cloninger, 1987]. Recent analyses of a large number of alcoholics, drawn from different studies, showed the frequency of the *DRD2* A_1 allele to be significantly higher in the more than the less severe alcoholics [Lawford et al., 1997; Noble, 1998]. A similar typology may be applied to opioid-dependent subjects. The A_1^+, in contrast to the A_1^- allelic opioid-dependent group had not only used greater amounts of heroin prior to study entry, but they also showed an inability to abstain even while receiving standard methadone therapy. Moreover, another study [Lawford et al.,

1999] found A_1^+ allelic individuals to be more likely to be infected with hepatitis C than their A_1^- allelic counterparts and exhibited persistent drug-seeking behavior. Interestingly, methadone nonresponders have been shown to have more heroin use and criminal activity, and earned significantly more income through illegal means than methadone responders [Cacciola et al., 1998; Perneger et al., 1998]. Thus, whereas a minority of the patients in the present methadone program showed a poor prognosis and carried the *DRD2* A_1 allele, their inability to abstain presents for them and society a disproportionately high degree of harm.

Why do individuals with the *DRD2* A_1 allele consume more heroin and have a poorer treatment outcome than those who carry the A_1^- allele? The answer to this question remains yet to be determined. However, there is emerging evidence that A_1^+ allelic carriers have reduced brain dopaminergic function. An early brain autopsy study [Noble et al., 1991], using [^{3}H]spiperone as the D_2 dopamine receptor binding ligand, found a significant reduction (~30%) in the number of D_2 dopamine receptors (B_{max}) in the caudate nucleus of A_1^+ compared to A_1^- allelic subjects. Moreover, a significant progressive decline in B_{max} was found across A_2/A_2, A_1/A_2, A_1/A_1 genotypes, in that order. However, no difference in D_2 dopamine receptor binding affinity (K_d) was found between A_1^+ and A_1^- allelic subjects. This study has been recently confirmed in the United Kingdom where binding of the specific D_2 dopamine receptor ligand [^{3}H]raclopride was measured by autoradiography [Thompson et al., 1997]. The results showed a 30–40% reduction in D_2 dopamine receptor density in the striatum of individuals with the A_1^+ allele compared with those with the A_1^- allele. Furthermore, an in vivo study of healthy Finnish volunteers [Pohjalainen et al., 1998] adds further support to reduced brain dopaminergic function in A_1^+ allelic subjects. Using [^{11}C]raclopride and positron emission tomography, a statistically significant decrease in D_2 dopamine receptor availability, reflecting a reduction in receptor density, was observed in the striatum of A_1^+ compared with A_1^- allelic subjects. However, there was again no difference in K_d between the two groups.

Given that a dopaminergic deficit prevails in subjects with the *DRD2* A_1 allele, it may be hypothesized that subjects with this genetic variant may compensate for the inherent deficiency of their dopaminergic system by using opiates and other drugs, agents known to increase brain dopamine levels. Stimulation by dopamine of A_1^+ allelic subjects' fewer D_2 dopamine receptors could provide enhanced feelings of reward and plea-

sure. Continued abuse of opiates could then lead to dependence and other complications. This is a hypothesized mechanism and only incremental future research can determine its validity.

If opioid-dependent subjects with the *DRD2* A$_1$ allele represent a more severe "genetic" type of addict whose problems are not amenable to conventional methadone treatment, how might such molecular genetic identification offer the opportunity for more successful treatment approaches?

Brain dialysis studies have shown that methadone, like morphine, dose-dependently increases dopamine levels in the caudate nucleus and nucleus accumbens of animals [Di Chiara and Imperato, 1988]. Moreover, the effects on brain dopamine levels were greater and more sustained at higher doses of these opiates. If higher doses of methadone can bring about a greater and more prolonged stimulation of the brain dopaminergic reward pathway, a consideration may then be given for using methadone at doses above those used in conventional programs for subjects who carry the *DRD2* A$_1$ allele. It is interesting to note that an Australian study has shown heroin addicts to be nearly three times as likely to die outside a methadone maintenance program as in it [Caplehorn et al., 1994]. Moreover, it found that a higher compared with a lower daily dose of methadone (120 mg vs. 80 mg) resulted in patients remaining twice as long in the treatment program. An American study found a higher daily dose of methadone (80 mg vs. 30 mg) significantly enhanced patient retention [Ling et al., 1996]. Put together, these findings suggest that a daily dose of 80 mg methadone or higher may be targeted to opioid-dependent subjects who carry the *DRD2* A$_1$ allele.

Another approach may entail the administration of injectable heroin to opioid-dependent patients who carry the *DRD2* A1 allele. Although the use of heroin in refractory heroin addicts, most often combined with a low dose of methadone, has resulted in a favorable outcome in some randomized trials outside the United States, it remains controversial [for review see Bammer et al., 1999]. This approach was not sanctioned in the United States until recently when the National Institute on Drug Abuse approved and funded trials of injectable heroin to opioid-dependent patients at various research centers [Wren, 1999].

Yet another possible approach would be to use nonopioidergic pharmacological agents that stimulate D$_2$ dopamine receptors of opioid-dependent subjects with the *DRD2* A$_1$ allele. Such a study has already been done on alcoholic patients [Lawford et al., 1995; Noble et al., 1995]. In a double-blind study, the effects of a D$_2$ dopamine receptor agonist, bromocriptine (BRO) and placebo (PLA) on treatment outcome were ascertained. The results showed that in the four groups of alcoholics studied (BRO A$_1$⁺, BRO A$_1$⁻, PLA A$_1$⁺, PLA A$_1$⁻), the greatest and most significant decreases in craving and anxiety and the best retention rate were found in A$_1$ allelic alcoholics who were treated with bromocriptine (BRO A$_1$⁺). A similar pharmacogenetic approach using a D$_2$ dopamine receptor full or partial agonist could be used in *DRD2* A$_1$ allelic opioid-dependent subjects.

Ongoing addictive behavior is typically a complex and protracted process with A$_1$ allelic opioid-dependent subjects facing particular difficulty as a result of their brain physiology. It is suggested that this recalcitrant group might require a stronger pharmacological treatment than current methadone maintenance programs provide. In addition to this, enhancing their retention in treatment programs and minimizing their heroin use may be further aided by intense psychosocial services [McLellan et al., 1993; Yancowitz et al., 1991].

The results of this study should be interpreted in the context of several limitations. First, the findings need to be replicated in a larger number of opioid-dependent subjects than used herein. Second, the population studied was Caucasian and primarily male; as such its validity to other racial/ethnic groups and females has not been established. Third, a follow-up period of one year was used; studies over longer periods of time will be required to determine whether treatment outcome is still associated with *DRD2* allelic status.

In conclusion, the present study implicates the *DRD2* gene in opioid dependence. The *DRD2* A$_1$ allele was positively related to prior heroin consumption and was negatively related to treatment success. Failure of traditional methadone treatment in *DRD2* A$_1$ allelic subjects suggests a more powerful pharmacological approach is required that targets this more severe "genetic" type of addiction.

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