

A Haplotype of the *DRD1* Gene Is Associated With Alcohol Dependence

P. Batel*, H. Houchi*, M. Daoust, N. Ramoz, M. Naassila, and P. Gorwood

Background: The D1 dopamine receptor has been involved in a number of brain functions, including motor control, inattentive symptoms and reward and reinforcement mechanisms. Indeed, *DRD1* antagonists may reduce cocaine-seeking behavior and the acquisition of cocaine-cue associations. The D1.1/r4532 marker of the *DRD1* gene has been associated with a large set of phenotypes including addictive behaviors, but none with alcohol dependence per se.

Methods: We analyzed a population of 134 patients with alcohol dependence, also assessing more homogeneous (severe) phenotypes, comparing this sample with a healthy control population, assessing two SNPs within the *DRD1* gene in order to depict the role of *DRD1* polymorphisms and haplotypes.

Results: The T allele of the rs686 polymorphism within *DRD1* gene was significantly more frequent in patients with alcohol dependence ($p = 0.0008$), with a larger excess for patients with severe dependence ($p = 6 \times 10^{-6}$), and even more for patients with severe complications such as withdrawal seizures ($p = 7 \times 10^{-7}$). A specific haplotype rs686*T-rs4532*G within the *DRD1* gene was significantly more precisely associated with alcohol dependence in our sample ($p = 5 \times 10^{-6}$).

Conclusions: Even though chance finding cannot be ruled out, convergent evidence is given that the *DRD1* gene is a susceptibility gene in alcohol dependence, regarding the fact that relying on more homogeneous phenotypes (i.e., more severe patients) and more informative genetic markers (i.e., haplotypes) reinforce the initial association.

Key Words: Dopamine, Withdrawal, Addiction, Vulnerability, Genetics.

ALCOHOL DEPENDENCE IS a complex disorder with likely additive effects of genetic and environment risk factors (Gorwood et al., 2006). Animal and human studies are in favor of a key role of the mesolimbic dopamine system in the reinforcing effects of alcohol and other drugs of abuse (Koob, 1992; Nestler et al., 1993; Samson and Harris, 1992). In human studies, alcohol dependence has been associated with differences of both dopamine receptors and transporters density (Pfefferbaum et al., 2001; Tupala et al., 2003, 2001). Much attention has been paid to the gene coding for the D2 dopamine receptor (*DRD2*), regarding its large distribution in the brain (Sokoloff et al., 1992) and the initial report

of Blum et al. (1993) showing an increase of one allele of the *DRD2* gene (namely, the A1 allele) in severe alcohol dependent patients compared to controls. While some studies did confirm this association, a large set of studies was negative, leading to the conclusion that this polymorphism could be in fact (i) located in another gene which might have a clearer role (Dubertret et al., 2004; Gelernter et al., 2006); (ii) have a role in a subgroup of patients only (Noble et al., 1994; Gorwood et al., 2000), (iii) or have a minor role that requires the presence of environmental factors (Young et al., 2004; Noble, 1996) or other genes, especially from the dopamine pathways.

The gene coding for the D1 dopamine receptor (*DRD1*) has also been considered as a candidate gene in alcohol dependence, particularly regarding its role within the prefrontal cortex in the modulation of cognitive processes (Rinaldi et al., 2007). D1-type family of G-protein coupled receptors, such as the D1 dopamine receptor, activate adenylyl cyclase and have been involved in a number of brain functions, including motor control (Dreher and Jackson, 1989; Meyer and Shults, 1993), inattentive symptoms of attention-deficit/hyperactive disorder (Misener et al., 2004; Luca et al., 2007) and reward and reinforcement mechanisms (Beninger and Miller, 1998). Indeed, D1 receptor antagonists may reduce cocaine-seeking behavior (Williams and Goldman-Rakic, 1995) and alter the acquisition of cocaine-cue associations, a process which is supposed to have a major role in relapse (Berglund et al., 2006).

From INSERM U675, Faculty of Medicine Bichat (IFR02) (Paris 7) (PB, NR, PG), Paris, France; AP-HP, Unité de Traitement Ambulatoire des Maladies Addictives, Beaujon Hospital (Paris 7) (PB), Clichy, Cedex, France; INSERM ERI24, Faculté de pharmacie (PB, HH, MD, MN), Amiens, France; and AP-HP, Service de Psychiatrie Adulte, Louis Mourier Hospital (Paris 7) (PG), Colombes, Cedex, France.

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Reprint requests: Dr. P. Batel, Unité de Traitement Ambulatoire des Maladies Addictives (UTAMA), Beaujon Hospital, Polyclinique Jean Beaumann, 100 bld du Général Leclerc 92110 Clichy, France; Fax: 33 (0)1 47 39 87 70; E-mail: philippe.batel@bjn.aphp.fr

*The first two authors equally contributed to this work.

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Among the different polymorphisms of the *DRD1* gene (Cichon et al., 1996), none have been associated with alcohol dependence. However the D1.1 marker/rs4532 SNP, a -48A/G *DdeI* polymorphism in the 5'-UTR of the *DRD1* gene, displayed a modest role in a large set of phenotypes including addictive behaviors (Comings et al., 1997) and we reported an association for patients with alcohol dependence but only if they had high sensation seeking scores (Limosin et al., 2003).

Regarding such heterogeneous or even discrepant results, we tested the role of the *DRD1* gene in alcohol dependence with three purposes that could increase the chances to detect an effect of this gene, if any. Firstly, we analyzed a population of alcohol dependence taking into account the likelihood of phenotypical heterogeneity, therefore also assessing more homogeneous (severe) phenotypes. Secondly, we compared this sample with a healthy control population taking into account the high risk of false-negative diagnosis, in accordance with the high prevalence of addictive disorders in the general population. We therefore relied on a "super normal control population" (with no lifetime addictive morbidity although being above 60 years old). Thirdly, we assessed two SNPs within the *DRD1* gene in order to depict the role of *DRD1* haplotypes, rather than relying on a single marker.

MATERIALS AND METHODS

Samples

As the positive association study from Comings et al. (1997) involved the D1.1/rs4532 marker within the *DRD1* gene in both smoking and gambling behaviors, we used this study to estimate the required sample size. The conclusion of the authors was that the proportion of subjects being homozygous for this polymorphism was 66.1% for smoking patients (compared to 39.3% of controls) and 55.8% for gamblers (compared to 40.3% of controls). With an alpha risk of 5% and a beta power of 90%, 59 patients with alcohol dependence are required according to the first result, and 114 according to the second, in order to be able to show a significant difference of genotype distribution with controls (see Statistics paragraph for sample size computation).

Among the 320 patients seeking treatment for alcohol dependence between January and June 2004 in a center specialized in addictive disorders in Paris suburb, we recruited all patients (i) meeting DSM-IV criteria for alcohol dependence (American Psychiatric Association (APA), 1996); (ii) having Caucasian origins for at least two generations; (iii) not currently polysubstance abusers (DSM-IV criteria, excepting nicotine and cannabis abuse or dependence); (iv) physically able to participate and understand French (for a reliable interview), and (v) agreeing to give a written informed consent. The final sample consisted in 134 Caucasian subjects (94 men and 40 women), with a mean age at interview of 46.2 years old (SD = 9.2 years, ranging from 27 to 69 years).

A control group was recruited at a recreation center for old people, as described elsewhere (Bonnier et al., 2002). Briefly, this "super-normal" group, aged at least 60 years, did not have any lifetime psychiatric nor addictive disorders according to a face-to-face interview (SCID-P). Control subjects were on average 73.6 years old (SD = 8.3), were mostly (54.2%) female, only 4.9% still having a professional activity, and all were Caucasians. Written informed consent was obtained from both patient and control subjects.

Clinical Assessment

All patients were clinically assessed by the same psychiatrist (PB) who was blind for the genotyping. The lifetime addictive diagnoses were made by a face-to-face semi-structured interview, namely the French version of the Diagnostic Interview for Genetic Studies (DIGS). In accordance with the DIGS, all patients were assessed for alcohol misuse (especially ages at onset of all alcohol dependence symptoms), and severity of alcohol dependence, based on physical dependence criteria and presence of alcohol withdrawal seizure episode in the DIGS, but also using a French validated version of the self-administrated questionnaire Michigan Alcoholism Screening Test (Yersin et al., 1989).

Genotyping

Genomic DNA was extracted from buccal swab samples with the Qiagen Kit. The *DRD1* gene markers, D1.7/rs686 (+1403T/C Bsp1286I polymorphisms) and D1.1/rs4532 (a -48 A/G *DdeI* polymorphism), were genotyped by restriction digest as described previously by Cichon et al. (1994).

Statistics

Power and sample size calculations were computed with the PS Power and Sample Size Calculations software (Dupont and Plummer, 1997). The minimum of case sample size was estimated by using frequencies observed in controls and patients with $\alpha = 5\%$ and $\beta = 90\%$.

Allele frequencies were compared between groups using chi-square test and Fisher's exact test. A significance level of 5% was chosen for the type I error. Odds ratios (ORs) as a measure of association, and their 95% confidential intervals were also computed. Statistical calculations were performed using SPSS 15.0 program (Chicago, IL). Deviations from Hardy-Weinberg equilibrium (HWE) for the two SNPs, their linkage disequilibrium and the frequencies of haplotype blocks were analyzed using the Haploview program v4.0 (Broad Institute, Cambridge, MA) (Barrett et al., 2005). Furthermore, UNPHASED program v3.0 was also used to compute haplotype-based association analysis (Dudbridge, 2003). This program takes account of the phase of markers and allows the assessment of the significance by permutations. Adjusted *p*-values from 1000 permutation tests were calculated by using UNPHASED.

RESULTS

The 134 recruited patients have a high level of alcohol dependence according to both the number of DSM-IV alcohol dependence criteria (Mean = 5.6; SD = 1.5) and the MAST score (Mean = 29; SD = 10.4). Seventy-seven (57%) patients fulfilled at least one criteria for physical dependence and 26 (19.2%) had at least one alcohol withdrawal seizure episode.

We genotyped the two polymorphisms within the *DRD1* gene in a total of 240 samples, including 230 subjects and 10 additional replicates. No discrepancy was found when genotyping the set of replicates. The genotype distribution of both SNPs did not deviate from Hardy-Weinberg equilibrium, for controls ($p > 0.1$) and for patients ($p > 0.2$). Presence of linkage disequilibrium between the two SNPs within the *DRD1* gene was detected ($r^2 = 0.22$). While we recruited more women in the group of controls (54.2%) than in the group of patients (29.1%), the distributions of both SNPs

Table 1. Genotype and Allele-Wise Association Between the *bsp1286* I Polymorphism (rs686) of the *DRD1* Gene and Alcohol Dependence

Sample	Genotype counts										Allele frequency					
	T-T		T-C		C-C		Statistics*			T		C		Statistics*		
	<i>n</i>	<i>n</i> %	<i>n</i>	<i>n</i> %	<i>n</i>	<i>n</i> %	χ^2	df	<i>p</i>	<i>n</i>	<i>n</i> %	<i>n</i>	<i>n</i> %	χ^2	df	<i>p</i>
Controls	96	29 30.21	54 56.25	13 13.54						112	58.33	80	41.67			
Patients	134	67 50.00	53 39.55	14 10.45	9.06	2	0.011			187	69.78	81	30.22	6.44	1	0.011
With physical dependence	76	48 63.16	22 28.95	6 7.89	18.7	2	<0.001			118	77.63	34	22.37	14.26	1	<0.001
With withdrawal seizure	30	23 76.67	7 23.33	0 0.00	21.1	2	<0.001			53	88.33	7	11.67	18.20	1	<0.001
Males	94	50 53.19	35 37.23	9 9.57	10.35	2	0.005			135	71.81	53	28.19	7.58	1	0.006

*All analyses are comparing each group with control genotype and allele frequencies.

Table 2. Genotype and Allele-Wise Association Between the *Ddel* Polymorphism (rs4532) of the *DRD1* Gene and Alcohol Dependence

Samples	Genotype counts										Allele frequency					
	G-G		G-A		A-A		Statistics*			G		A		Statistics*		
	<i>n</i>	<i>n</i> %	<i>n</i>	<i>n</i> %	<i>n</i>	<i>n</i> %	χ^2	df	<i>p</i>	<i>n</i>	<i>n</i> %	<i>n</i>	<i>n</i> %	χ^2	df	<i>p</i>
Controls	96	12 12.50	55 57.29	29 30.21						79	41.15	113	58.85			
Patients	134	25 18.65	56 41.79	53 39.55	3.78	2	0.150			106	39.55	162	60.45	0.118	1	0.731
With physical dependence	76	11 14.47	33 43.42	32 42.11	3.98	2	0.137			55	36.18	97	63.82	0.878	1	0.349
With withdrawal seizure	30	6 20.00	11 36.67	13 43.33	4.33	2	0.115			23	38.33	37	61.67	0.150	1	0.698
Males	94	14 14.89	39 41.49	41 43.62	5.62	2	0.060			67	35.64	121	64.36	1.218	1	0.270

*All analyses are comparing each group with control genotype and allele frequencies.

were not significantly different between males and females, neither in the control group nor in the patient group (Tables 1 and 2). Furthermore, we also observed no significant difference in the distribution of both SNPs between genders in patients whereas an excess of 70.1% men (data not shown).

We found an association between the rs686 polymorphisms of the *DRD1* gene and alcohol dependence, both for genotype counts and allele frequencies (Table 1). The T allele is more frequently observed in patients than in controls [$p_{\text{adjusted}} = 0.003$; OR = 1.95; 95% CI (1.32–2.87)], the excess of the T allele being more important in the group of patients with physical dependence [$p_{\text{adjusted}} = 0.001$; OR = 2.93; 95% CI (1.83–4.73)], and even more for those with severe complications such as withdrawal seizure [$p_{\text{adjusted}} = 0.001$; OR = 6.41, 95% CI (2.77–14.81)] (Table 1). In accordance with the hypothesis of a specific role of the T allele in patients with more severe dependence, the MAST score, and the number of DSM-IV symptoms were higher in patients with the T allele ($p = 0.007$ and $p = 0.001$ respectively). More precisely, the MAST score and the number of DSM IV symptoms were increased with the number of the T allele ($r = 0.197$, $df = 128$, $p = 0.026$ and $r = 0.252$, $df = 128$, $p = 0.004$ respectively). Finally, we found a significant overrepresentation of the T allele in male patients compared to male controls [OR = 2.43, 95% CI (1.44–4.11); $p_{\text{adjusted}} = 0.002$]. No difference in the distribution of rs686 was observed in female patients compared to female controls (data not shown).

The distribution of the other SNP, rs4532, within the *DRD1* gene was not significantly different between patients and controls, nor in the different subgroups of patients

(Table 2). Using the number of 134 cases, 96 controls and the proportions of subjects being homozygous for the rs686 and rs4532 polymorphisms, we found a power of this sample of 98% and 62%, respectively.

Assessing the role of both these markers in linkage disequilibrium, we found that the rs686-rs4532 haplotype was strongly associated with alcohol dependence, with a global p of 5×10^{-6} . In particular, there is a significant excess of the T-G haplotype block (UNPHASED: Transmitted = 53.85 vs. Not Transmitted = 9.36, $\chi^2 = 21.856$, $df = 1$, $p = 0.000003$; Haploview: T = 51.5 vs. NT = 13.1, $\chi^2 = 14.21$, $df = 1$, $p = 0.0002$). This haplotype was 4.06 more frequently observed in patients than in controls [95% CI (1.75–9.42)]. This association is mainly relying on the rs686 polymorphism ($p_{\text{adjusted}} = 0.003$) in accordance with the fact that the rs4532 polymorphism of the *DRD1* gene was not associated with alcohol dependence when considered alone.

DISCUSSION

Comparing 134 patients with alcohol dependence to 96 super-normal controls, all with Caucasian origin, showed that the T allele of rs686 within *DRD1* gene was more frequent in patients with alcohol dependence, with a larger excess for patients with severe dependence, and even more for patients with severe complications such as withdrawal seizures. Analyzing another SNP within the same gene and in linkage disequilibrium with the latter, allowed to show that it is a haplotype rs686*T-rs4532*G within the *DRD1* gene that is

associated with alcohol dependence in our sample, the informativity of this haplotype mainly relying on the rs686 polymorphism.

Eight studies tested the hypothesis of a role of different polymorphisms of the *DRD1* gene in alcohol dependence (Comings et al., 1997; Heinz et al., 2004; Hietala et al., 1997; Kim et al., 2007; Limosin et al., 2003; Liu et al., 1995; Sander et al., 1995; Thompson et al., 1998), with no excess of one allele in patients versus in controls in studies using a case-control approach devoted to alcohol dependence (Hietala et al., 1997; Kim et al., 2007; Sander et al., 1995; Thompson et al., 1998). The most logic conclusion should be, therefore, that the present association is explained by chance finding, as it is frequently the case in case-control genetic studies (Gorwood, 1999). Nevertheless, two types of reasoning interfere with the likelihood of such conclusion, concerning on the one hand statistical power and on the other hand the specificity of the involved phenotype.

Firstly, the risk of false positive is difficult to limit, especially as the size of samples are mainly designed to avoid the type I error. Nevertheless, the present sample is of the same range of the majority of studies testing the *DRD1* gene in alcohol dependence, apart from the one used in Kim et al. (2007) study. Furthermore, the negative findings concerning the rs4532 polymorphism of the *DRD1* gene in alcohol dependence already reported by Kim et al. (2007) is indeed replicated, as the association we detected concerns another polymorphism of the gene, therefore our positive association was specific, and not in contradiction with the possibility to detect an absence of role for a specific SNP. Both type I and type II errors were in fact taken into account for the estimation of the required sample size. Thus, our sample size gives a power of 97% for the rs686. Furthermore, we also applied permutation tests showing that observed significant associations were powerful, robust and likely not due to chance finding.

Secondly, the specificity of this sample may explain why a role of the *DRD1* gene in alcohol dependence was detected for the first time. No allele of the *DRD1* gene was previously found in excess in patients with alcohol dependence compared to controls, but this is not the case for intermediate traits. High MAST score (Comings et al., 1997), important AUDIT score (Kim et al., 2007) and elevated sensation seeking scores (Limosin et al., 2003) were associated with the rs4532 polymorphism of the *DRD1* gene, in various types of patients. This raises the possibility that the *DRD1* gene could play an indirect role in alcohol dependence through severity rather than presence of alcohol dependence, or in at-risk related temperaments. This is convergent with our results based on a severe sample, where the aspects of alcohol dependence severity (presence of physical dependence and withdrawal seizures) are associated with a stronger role of the T allele (or the TT genotype) of rs686 overrepresented in patients of this study. Furthermore, inattentive symptoms of the attention-deficit/hyperactivity disorder (ADHD) in families with reading disabilities were

associated with different markers of the *DRD1* gene, the association being detected for rs4532, and even more important for rs686. As ADHD is doubling the risk for different addictive disorders including alcohol dependence (Biederman et al., 2006), and, when detected, is associated with a higher severity of alcohol dependence (Kim et al., 2006), the following hypothesis can be proposed. The T allele of the rs686 within *DRD1* gene may be a nonspecific risk factor for a trait related to attention deficit and impulsivity (2 highly interconnected traits, Malloy-Diniz et al., 2007) which may increase the risk for earlier initiation, higher consumptions of alcohol and/or more deleterious consumption of alcohol, increasing the risk for alcohol dependence, and when detected, the risk for severe complications. This hypothesis is reinforced by the now clearer role of the D1 dopamine receptor in both mesolimbic structures underlying alcohol reinforcement (Zhang et al., 2006) and circuits and pathways involved in attention-deficit/hyperactivity disorder (Arnsten, 2006). Such hypothesis, whether it is relevant or not, could be being worth tested more directly before any firm conclusion.

Some limits should be raised in this study. First of all, the best way to prove an association, when detected, is to replicate it in an independent sample. Before such replication, all associations should be taken with caution. Secondly, even if there is a rational in the scientific literature linking dopamine D1 receptor, impulsivity, inattention and alcohol dependence, such relationship could not be directly tested in our sample, as ADHD was not assessed. Lastly, only two SNPs were tested for the *DRD1* gene. As these SNPs were in linkage disequilibrium, in our sample and in others (Luca et al., 2007), more tagging SNPs should be used to further precise which part of the *DRD1* gene is really involved. According to the SNP databases from HAPMAP and NCBI, more than 30 SNPs encompass the 3.5 kb of the *DRD1* gene. They are all in linkage disequilibrium. Up to now, none of them was reported as having functional consequences. In the present study, we found a larger effect of the associated haplotype rs686*T-rs4532*G (OR = 4.06) than of the T allele of rs686 (OR = 1.95), although part of their 95% confidence interval is overlapping. This observation therefore suggests that it is the rs686*T-rs4532*G haplotype, rather than the rs686 SNP per se, which is a marker of the vulnerability to alcohol dependence. We nevertheless cannot rule out the hypothesis that the associated haplotype contains, or is in linkage disequilibrium, with another yet unknown marker more directly involved.

CONCLUSION

Even though chance finding cannot be ruled out, convergent evidence is given that the *DRD1* gene is a susceptibility gene in alcohol dependence, regarding the fact that relying on more homogeneous phenotypes (i.e., more severe patients) and more informative genetic markers (i.e., haplotypes) reinforce the initial association.

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