



# Single-nucleotide polymorphisms in dopamine receptor D1 are associated with heroin dependence but not impulsive behavior

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**ABSTRACT.** Previous studies suggested that dopamine receptors may be associated with drug dependence and impulsive behavior. In this study, we examined whether dopamine receptor D1 (DRD1) is associated with heroin dependence and the impulsive behavior in patients with heroin dependence. The participants included 367 patients with heroin dependence and 372 healthy controls from a Chinese Han population. We examined the potential association between heroin dependence and 8 single-nucleotide polymorphisms (rs686, rs4867798, rs1799914, rs4532, rs5326, rs265981, rs10078714, rs10078866) of *DRD1*, and the associations between single single-nucleotide polymorphism, haplotypes, and impulsive behavior. Compared with the healthy controls, heroin dependence patients showed a significantly lower frequency of GG homozygotes of rs5326 ( $P = 0.027$ ), significantly lower frequency of the G allele of rs5326 ( $P = 0.007$ , odds ratio = 0.718,

95% confidence interval = 0.565-0.913), and higher frequency of the rs265981 G allele ( $P = 0.0002$ , odds ratio = 1.711, 95% confidence interval = 1.281-2.287). Furthermore, strong linkage disequilibrium was observed in 2 blocks ( $D' > 0.9$ ). However, no association was observed between haplotypes and heroin dependence in the 2 blocks. This genetic behavior correlation study showed that the 2 single-nucleotide polymorphisms, rs5326 and rs265981, were not associated with the impulsive behavior in patients with heroin dependence. These findings indicate that *DRD1* gene polymorphisms are related to heroin dependence in a Chinese Han population and may be informative for future genetic or biological studies on heroin dependence.

**Key words:** Chinese population; Dopamine receptor D1; Heroin dependence; Single-nucleotide polymorphisms

## INTRODUCTION

Heroin dependence is a chronic and relapsing brain disease characterized by drug dependence, tolerance, and compulsive seeking and use despite the harmful consequences (van den Bree et al., 1998). The relapse rate of heroin dependence is high because of its severe withdrawal symptoms, strong craving induction, and compulsive drug-seeking behavior after repeated use. Hence, preventing relapse of heroin dependence is very challenging. The genetic influence on the development of drug addiction has been shown to be substantial, with an estimated range of 40-60% for the inherited risk of drug addiction (Uhl, 2004; Uhl et al., 2008). The identification of vulnerability genes related to heroin dependence would be useful not only for understanding the pathogenesis of heroin dependence but also for preventing its occurrence and relapse.

Five dopamine receptors have been identified and characterized in humans. They are classified into 2 groups: D1-like (D1 and D5) and D2-like (D2, D3, and D4) (Le Foll et al., 2009). The dopamine receptor D1 (DRD1), a member of the dopamine receptor family, belongs to the G protein-coupled receptor superfamily and has 7 membrane-spanning domains (Civelli et al., 1991). DRD1 is involved in various brain functions, including motor control, attention symptoms, and reward and reinforcement mechanisms (Le Foll et al., 2009). DRD1 has also been shown to play an important role in heroin dependence (Gorwood et al., 2012). Administration of 2 DRD1 agonists, SKF 82958 and SKF 81297, produced a leftward shift in the heroin dose-response function in rhesus monkeys trained to self-administer heroin under a progressive-ratio schedule of reinforcement (Rowlett et al., 2007). In contrast, DRD1 blockade decreased heroin intake, but at a dose that produced nonspecific effects (Gerrits et al., 1994). Stimulation of DRD1 by opioid initiates a sequence of molecular events, including c-Fos (Liu et al., 1994),  $\delta$ FosB (Muller and Unterwald, 2005; Zachariou et al., 2006), extracellular receptor kinase (Borgkvist et al., 2008), and cAMP response element-binding (Dudman et al., 2003) activation, which shape neuron structure and functions (Nestler, 2004). Individual differences in impulsive behavior on a 5-choice task of sustained visual attention strongly predict individual variation in the rate of intravenous cocaine self-administration. Specifically, rats exhibiting trait impulsivity on the 5-choice serial reaction-time task showed a greater tendency for escalation of intravenous cocaine self-administration than did their non-

impulsive counterparts. They also observed a significant inverse relationship between D2/3 receptor availability in the ventral striatum and trait impulsivity. These data demonstrated that trait impulsivity predicts drug reinforcement and that dopamine receptor dysfunction in abstinent drug addicts may be partly determined by premorbid factors (Dalley et al., 2007).

The *DRDI* gene is located at chromosome 5q35.1 and contains 2 exons separated by a small intron in the 5'-untranslated region (5'-UTR). Polymorphisms within or near *DRDI*, particularly the DdeI polymorphism (rs4532), have been studied widely for their genetic association with other neuropsychiatric diseases (Wong et al., 2000). Although most polymorphisms failed to show an association, some polymorphisms have been shown to be significantly associated with bipolar disorders (Severino et al., 2005; Del Zompo et al., 2007), attention deficit hyperactivity disorder (Misener et al., 2004; Bobb et al., 2005), and alcoholism (Limosin et al., 2003; Kim et al., 2007). Although located in the 5'-UTR of *DRDI*, the rs4532 polymorphism can also affect *DRDI* expression. A preliminary pharmacogenetics study suggested that the rs4532 polymorphism is functionally important (Potkin et al., 2003). However, few studies have examined the association between the *DRDI* gene and opiate addiction. A study by Jacobs et al. (2013) found that polymorphisms in the *DRDI* gene were associated with opiate addiction, despite significant differences in the racial makeup of individual samples. Another study found that *DRDI* gene rs5326 was associated with heroin dependence in African Americans, whereas the association was not significant after correction for multiple testing (Levrant et al., 2009). These findings highlight the importance of determining the role of *DRDI* in genetic predisposition to drug dependence.

In most previous studies, several important single-nucleotide polymorphisms (SNPs), including rs4867798 (5'-UTR), rs265981 (5'-UTR), rs10078714 (promoter), and rs10078866 (promoter), have not been studied, resulting in an ineffective capture of true causative SNPs in the *DRDI* gene because of the weak linkage disequilibrium between them. In the present study, to verify the putative association between *DRDI* SNPs and heroin dependence, we investigated the association between 8 SNPs (rs686, rs4867798, rs1799914, rs4532, rs5326, rs265981, rs10078714, and rs10078866) in the *DRDI* gene and the risk of heroin dependence in a Chinese Han population.

## MATERIAL AND METHODS

### Subjects

A hospital-based case-control study was conducted in 367 patients with heroin dependence (mean  $\pm$  standard deviation age: 39.6  $\pm$  5.6 years) and 372 healthy controls (mean  $\pm$  standard deviation age: 40.3  $\pm$  4.5 years). The patients were recruited from the Methadone Maintenance Treatment Program of the Xi'an Mental Health Center (Xi'an, China). Heroin dependence was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria, medical history, urine test results, and interview responses. A case vignette was prepared to assist with diagnosis, using a semi-structured interview with questions on a) age at initiation and duration of heroin use, b) quantity of drug used over this period, c) route of administration (nasal inhalation or injection), d) whether other substances were used or abused, and e) comorbidity for any other psychiatric disorder. Participants were excluded if they met the DSM-IV criteria for an additional Axis I disorder, had a history of alcohol, cigarette, or amphetamine use according to DSM-IV, were taking other prescribed medications

that could affect the central nervous system, had a history of seizures, hematological diseases, or severe liver or kidney impairment, or were pregnant. Patients with heroin dependence and impulsive behavior were included if they met the following 3 criteria: impulsive behavior towards other people had occurred more than 3 times; the weighted total score of the modified overt aggression scale was more than 5, and the item of the attack of physical strength was more than 1; the total score of the Barratt impulsivity scale-11 was more than 70.

The unrelated healthy subjects were people who underwent health examinations in the First Hospital Affiliated to the Medical College of Xi'an Jiaotong University. Subjects who had substance abuse, participated in other studies, or suffered from chronic brain diseases were excluded. Written informed consent was obtained from all participants. The study protocol was approved by the Ethical Committee of Xi'an Mental Health Center.

### SNP selection

The genomic sequence of the *DRD1* gene spans 8 kb. Most previous studies only analyzed a few SNPs, which was insufficient to cover the gene locus. The present study selected a total of 8 genetic polymorphisms throughout the *DRD1* gene and the 5' and 3' flanking regions. The selected polymorphisms included SNPs that have been shown to be positively associated with nicotine dependence, heroin dependence, and alcoholism in previous studies (Kim et al., 2007; Batel et al., 2008; Gorwood et al., 2012; Peng et al., 2013) and most tag SNPs that were revealed by the genotype data of the Chinese Han population from the HapMap.

### Genotyping

Genomic DNA was extracted from blood leukocytes using the EZNA™ Blood DNA Midi Kit (Omega Bio-Tek, Norcross, GA, USA) according to the manufacturer protocol. Cases and controls were mixed on the same plates, and a double-blind procedure was performed. Genotyping was carried out for all SNPs using the MassARRAY platform (Sequenom, San Diego, CA, USA). Briefly, SNPs were genotyped using high-throughput matrix-assisted laser desorption ionization time-of-flight mass spectrometry. The resulting spectra were processed using the Typer Analyzer software (Sequenom) and genotype data were generated for the samples. The final genotype call rate of each SNP was >98% and the overall genotyping call rate was 98.6%, indicating the reliability of the data for further statistical analysis.

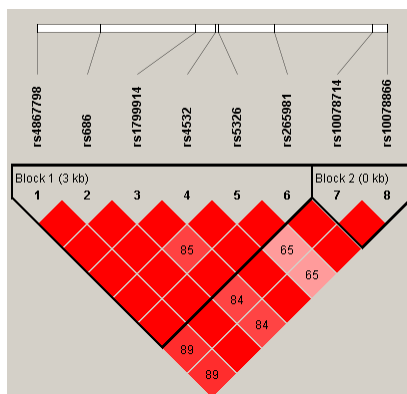
### Statistical analysis

All statistical tests were conducted using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Hardy-Weinberg equilibrium for each SNP was assessed using GENEPOP v4.0 (Rousset and Raymond, 1995). Associations between the case-control status and each polymorphism were assessed using the Fisher exact test or Pearson chi-square test. Unconditional logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) of the independent association between each locus and the presence of heroin dependence. Haplotype blocks were defined according to the criteria developed by Gabriel et al. (2002). Pair-wise linkage disequilibrium (LD) statistics ( $D'$  and  $r^2$ ) and haplotype frequency were calculated, and haplotype blocks were constructed using the Haploview 4.0 (Barrett et al., 2005). To ensure that the LD blocks most closely reflected the population level LD patterns, blocks

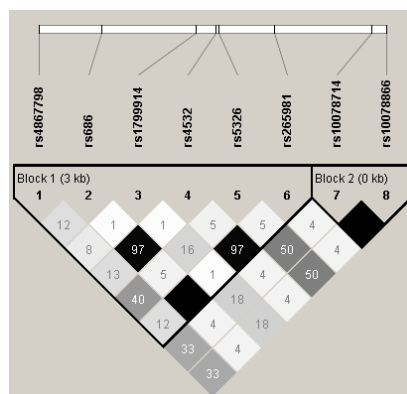
were defined based on the control samples alone. Bonferroni's correction was used to adjust the test level when multiple comparisons were conducted, and the P value was divided by the total number of loci or haplotypes.

**RESULTS**

More than 99% of the samples were genotyped successfully for each SNP, and the replicate experiment for 40 randomly selected samples (5.41%) showed completely consistent genotype data with the original analysis. No significant deviation from Hardy-Weinberg equilibrium was observed for any of the SNPs in the controls and patients with heroin dependence. The analyses of LD of the patient and control groups revealed that 6 SNPs (rs4867798, rs686, rs1799914, rs4532, rs5326, rs265981) and 2 SNPs (rs10078714, rs10078866) were located in haplotype block 1 and block 2 ( $D' > 0.9$ , Figure 1;  $r^2 > 0.8$ , Figure 2), respectively. The genotype distributions, allelic frequencies, and haplotypes in the control and patient groups as well as the results of statistical analysis are provided in Tables 1-4.



**Figure 1.** Linkage disequilibrium plot of the 8 SNPs in the *DRD1* gene. Values in squares are the pairwise calculation of  $D'$ .



**Figure 2.** Linkage disequilibrium plot of the 8 SNPs in the *DRD1* gene. Values in squares are the pairwise calculation of  $r^2$ .

**Table 1.** Genotype and allele frequencies of the *DRD1* gene polymorphisms in cases (N = 367) and controls (N = 372) and the results of their associations with risk of heroin dependence.

Variable	Location	N	MAF	Group	Genotype (N, %)			Allele (N, %)		P <sup>a</sup>	P <sup>b</sup>	P <sup>c</sup>
					AA	AG	GG	A	G			
rs686	3'UTR	372	0.188	Control	241 (64.78)	122 (32.80)	9 (2.42)	604 (81.18)	140 (18.82)	0.95	0.428	0.308
		367		Case	285 (77.66)	77 (20.98)	5 (1.36)	647 (88.15)	87 (11.85)			
rs4867798	5'UTR	372	0.457	Control	110 (29.57)	184 (49.46)	78 (20.97)	404 (54.30)	340 (45.70)	0.16	0.428	0.308
		364		Case	103 (28.30)	170 (46.70)	91 (25.00)	376 (51.65)	352 (48.35)			
rs1799914	Exon 1	372	0.054	Control	333 (89.52)	38 (10.22)	1 (0.27)	704 (94.62)	40 (5.38)	0.94	0.395	0.209
		367		Case	319 (86.92)	45 (12.26)	3 (0.82)	683 (93.05)	51 (6.95)			
rs4532	5'UTR	372	0.163	Control	260 (69.89)	103 (27.69)	9 (2.42)	623 (83.74)	121 (16.26)	0.75	0.073	0.023
		367		Case	283 (77.11)	79 (21.53)	5 (1.36)	645 (87.87)	89 (12.13)			
rs5326	5'UTR	372	0.210	Control	236 (63.44)	116 (31.18)	20 (5.38)	588 (79.03)	156 (20.97)	0.25	0.027	0.007
		367		Case	198 (53.95)	140 (38.15)	29 (7.90)	536 (73.02)	198 (26.98)			
rs265981	5'UTR	372	0.188	Control	242 (65.05)	121 (32.53)	9 (2.42)	605 (81.32)	139 (18.68)	0.17	0.001	0.0002
		367		Case	285 (77.66)	77 (20.98)	5 (1.36)	647 (88.15)	87 (11.85)			
rs10078714	Promoter	372	0.219	Control	228 (61.29)	124 (33.33)	20 (5.38)	580 (77.96)	164 (22.04)	0.56	0.298	0.136
		367		Case	210 (57.22)	128 (34.88)	29 (7.90)	548 (74.66)	186 (25.34)			
rs10078866	Promoter	372	0.219	Control	228 (61.29)	125 (33.60)	19 (5.11)	581 (78.09)	163 (21.91)	0.73	0.244	0.120
		367		Case	210 (57.22)	128 (34.88)	29 (7.90)	548 (74.66)	186 (25.34)			

<sup>a</sup>P values for Hardy-Weinberg equilibrium in controls. <sup>b</sup>P values for genotype frequency difference. <sup>c</sup>P values for allele frequency difference. Alpha value is adjusted by Bonferroni's correction and statistically significant results (P < 0.00625). MAF, minimum allele frequency.

**Table 2.** *DRD1* haplotype in block 1 frequencies and the results of their associations with risk of heroin dependence.

Haplotype <sup>a</sup>	ID						Gene-counting (frequency <sup>b</sup> %)		P value <sup>c</sup>
	rs4867798	rs686	rs1799914	rs4532	rs5326	rs265981	Cases	Controls	
HAP1	T	A	G	T	G	G	146.4	134.3	0.305
HAP2	C	A	G	T	G	G	75.6	89.7	0.256
HAP3	T	G	G	C	G	A	43.7	60.6	0.086
HAP4	C	A	G	T	A	G	76.0	58.0	0.071

<sup>a</sup>Haplotypes with frequency <0.05 were excluded. <sup>b</sup>Based on comparison of frequency distribution of all haplotypes for the combination of SNPs. <sup>c</sup>Alpha value is adjusted by Bonferroni's correction and statistically significant results (P < 0.008).

**Table 3.** *DRD1* haplotype in block 2 frequencies and the results of their associations with risk of heroin dependence.

Haplotype	ID		Gene-counting (frequency <sup>a</sup> %)		P value <sup>b</sup>
	rs10078714	rs10078866	Cases	Controls	
HAP1	A	A	274.1	290.5	0.283
HAP2	G	G	92.9	81.5	0.283

<sup>a</sup>Based on comparison of frequency distribution of all haplotypes for the combination of SNPs. <sup>b</sup>Alpha value is adjusted by Bonferroni's correction and statistically significant results (P < 0.025).

**Table 4.** Impulsive behavior association with genotypes rs5326 and rs265981.

Variable	High-impulsive		Low-impulsive		P value <sup>a</sup>	OR, 95%CI
	N	%	N	%		
rs5326						
GG	59	57.3	139	84.8	0.424	1.206, 0.762-1.908
GA+AA	44	42.7	125	15.2		
rs265981						
GG	57	74.0	228	78.6	0.390	0.775, 0.433-1.386
GA+AA	20	26.0	62	21.4		

Compared with the healthy controls, patients with heroin dependence had a significantly lower frequency of GG homozygotes of rs5326 (P = 0.027), a significantly lower frequency of the G allele of rs5326 (P = 0.007, OR = 0.718, 95%CI = 0.565-0.913), and a higher frequency of the rs265981 G allele (P = 0.0002, OR = 1.711, 95%CI = 1.281-2.287). The rs5326 showed a nominal significant P-value for association (P < 0.05), but did not pass the threshold value (P < 0.00625). Strong LD was observed in the 2 blocks (D' >0.9). However, we observed no association between haplotype and heroin dependence in the 2 blocks. The genetic behavior correlation study showed that 2 SNPs, rs5326 and rs265981, were not associated with impulsive behavior of the patients with heroin dependence.

## DISCUSSION

Drug-induced persistent neuroadaptation in reward-related learning and memory processes, which leads to hypersensitivity to drug-associated cues, impulsive decision-making, and abnormal learned behaviors, is the neurobiological basis for the transition to dependence

(Nestler, 2004; Kauer and Malenka, 2007). Postmortem analysis revealed the regulatory effects of *DRD1* variation on its mRNA expression in the striatum, which were blunted by chronic opioid abuse (Kauer and Malenka, 2007). Our results demonstrate that a genetic change in *DRD1* is linked to heroin dependence in humans, and extends the list of variants that may affect the development of heroin dependence (Jacobs et al., 2013; Peng et al., 2013).

Several studies have reported that *DRD1* gene polymorphisms are associated with alcohol dependence (Limosin et al., 2003; Kim et al., 2007; Batel et al., 2008), nicotine dependence (Vink et al., 2006; Huang et al., 2008; Levran et al., 2009), nicotine metabolite ratio (Lee et al., 2012), stimulant dependence (Liu et al., 2006), and a series of addictive behaviors (Comings et al., 1997). This may be because *DRD1* plays different roles in the dependence to different drugs or because of population differences. A previous study found that *DRD1* gene rs5326 was associated with heroin dependence in African Americans (Levran et al., 2009). However, the association was not significant after correction for multiple testing (Levran et al., 2009). In this study, significant differences were found in the distribution of genotype and allele frequencies in *DRD1* gene rs5326 between heroin-dependent subjects and healthy controls, and the rs5326 polymorphism showed a nominal significant P-value for association ( $P < 0.05$ ), but did not pass the threshold value ( $P < 0.00625$ ). Among patients with heroin dependence, subjects with rs5326 CC genotypes developed heroin dependence more rapidly than those without rs5326 CC genotypes (Peng et al., 2013). The results indicated that *DRD1* gene polymorphisms may not be important in the susceptibility to heroin dependence in the Chinese Han population, but may be associated with the rapidity of heroin dependence development from first drug use. These *DRD1* gene variations can change the mRNA secondary structure, which may affect the stability, processing, or subcellular targeting of the mRNA transcript and thereby alter splicing, transcription, and translation efficiency (Ramos et al., 2004). In this case-control association study, the G alleles of rs265981 were strongly associated with an increased risk of heroin dependence. This is the first report to identify a significant association between *DRD1* gene rs265981 and heroin dependence. In previous studies, *DRD1* polymorphisms have also been shown to be associated with substance dependence (Kim et al., 2007; Huang et al., 2008), addictive behavior (da Silva Lobo et al., 2007), and psychiatric diseases (Hettinger et al., 2008; Zhu et al., 2011). In this study, 2 SNPs (rs4532, rs686) were not associated with heroin dependence. These differences may be correlated to alterations in hormone levels, neuronal system adaptations, the pharmacokinetics of substances of abuse (Russo et al., 2003), or differences in ethnic groups. To some extent, this finding further supports a role of *DRD1* polymorphism in drug dependence.

In conclusion, these findings will be useful for future studies aimed at identifying functional polymorphisms within or close to the *DRD1* gene using a systemic approach in a larger sample set. Our results agree with the dopamine hypothesis developed to understand the chronic effects of heroin on the brain. This study increases the understanding of the neurobiological mechanisms of heroin and may be used to develop better treatment strategies against heroin dependence.

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