Available online at www.sciencedirect.com
ScienceDirect
Neuroscience Letters 434 (2008) 88–92
Neuroscience Letters
www.elsevier.com/locate/neulet

Reduced CYP2D6 activity is a negative risk factor for methamphetamine dependence

Kyohei Otani [a], Hiroshi Ujike [a,b,*], Ayumu Sakai [a], Yuko Okahisa [a], Tatsuya Kotaka [a], Toshiya Inada [b,c], Mutsuo Harano [b,d], Tokutaro Komiyama [b,e], Toru Hori [b,f], Mitsuhiko Yamada [b,g], Yoshimoto Sekine [b,h], Nakao Iwata [b,i], Masaomi Iyo [b,j], Ichiro Sora [b,k], Norio Ozaki [b,l], Shigetoshi Kuroda [a]

[a] *Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Shikata-cho 2-5-1, Okayama 700-8558, Japan*
[b] *Japanese Genetics Initiative for Drug Abuse (JGIDA), Japan*
[c] *Institute of Neuropsychiatry, Seiwa Hospital, Tokyo, Japan*
[d] *Department of Neuropsychiatry, Kurume University Graduate School of Medicine, Kurume, Japan*
[e] *Department of Rehabilitation Medicine, Iida Hospital, Iida, Japan*
[f] *Division of Psychiatry, National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Tokyo, Japan*
[g] *National Institute of Mental Health, National Center of Neurology and Psychiatry, Ichikawa, Japan*
[h] *Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, Hamamatsu, Japan*
[i] *Department of Psychiatry, Fujita Health University School of Medicine, Houmei, Japan*
[j] *Department of Psychiatry, Chiba University Graduate School of Medicine, Chiba, Japan*
[k] *Division of Psychobiology, Department of Neuroscience, Tohoku University Graduate School of Medicine, Sendai, Japan*
[l] *Department of Psychiatry and Psychobiology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

Received 28 November 2007; received in revised form 12 January 2008; accepted 15 January 2008

Abstract

Because methamphetamine (METH) is metabolized by CYP2D6 at the first step of hydroxylation and demethylation, it is possible that functional variants of CYP2D6 alter susceptibility to methamphetamine-induced dependence. We genotyped *CYP2D6*1*, **4*, **5*, **10*, and **14* for 202 patients with METH dependence and 337 controls in a Japanese population and found a significant association of the *CYP2D6* gene with METH dependence ($p = 0.0299$). The patients had fewer **10* and **14* alleles, which are hypofunction alleles, than the controls. *CYP2D6* genotypes were divided into three phenotypes: extensive metabolizers, intermediate metabolizers, and poor metabolizers. There was no poor metabolizer among our Japanese subjects, and intermediate metabolizers of CYP2D6 were significantly fewer in methamphetamine-dependent subjects than in controls ($p = 0.0212$), with an odds ratio of 0.62 (95% confidence interval: 0.51–0.76). The present study demonstrated that reduced CYP2D6 activity was a negative risk factor for methamphetamine dependence.

Keywords: CYP2D6; Methamphetamine; Amphetamine; Dependence; Intermediate metabolizer; Case-control association study

Methamphetamine (METH) is an addictive stimulant drug used all over the world, and METH has long been the most popular substance of abuse in Japan [33,40]. Genetic factors may contribute substantially to the development of substance dependence. Family and twin studies have shown that predisposition to drug-taking behaviors and psychological dependence on substances including amphetamines has a strong hereditary component [24,38]. Several genetic risk factors for METH dependence and psychosis, e.g., the dopamine transporter gene [39], μ-opioid receptor gene [18], prodynorphin gene [31], $GABA_A$ receptor γ2 subunit gene [30], and AKT-1 gene [19], have been identified by our

* Corresponding author at: Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Shikata-cho 2-5-1, Okayama 700-8558, Japan. Tel.: +81 86 235 7242; fax: +81 86 235 7246.
E-mail address: hujike@cc.okayama-u.ac.jp (H. Ujike).

0304-3940/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2008.01.033

group, but more, currently unknown, genetic factors are likely.

Several previous studies showed that genetic variability in the enzyme that metabolizes a certain drug was associated with dependence on that drug [17], e.g., alcohol dehydrogenase and aldehyde dehydrogenase genes for alcoholism [5,16,27], *CYP2A6* for nicotine dependence [2,28], and *CYP2D6* for codeine dependence [14]. METH is metabolized by 4-hydroxylation or *N*-demethylation as the first step and then converted to 4-hydroxy METH (4OH-METH) or amphetamine (AMPH); the latter is subsequently metabolized to 4-hydroxy AMPH (4OH-AMPH) by 4-hydroxylation. These metabolites of METH, 4-OH METH, AMPH, 4-OH AMPH, and norephedrine [4,26], are all active and have psychostimulating actions [12]. An experimental study showed that chronic but not acute treatment with AMPH produced accumulation of hydroxylated metabolites in the striatum [10]. Studies of patients with AMPH psychosis showed that the intensity of the psychosis was positively correlated with the amount of basic polar metabolites of AMPH, including 4-OH AMPH and norephedrine, excreted in the urine but not with the AMPH plasma level [1]. The two initial metabolic pathways of METH in humans, 4-hydroxylation and *N*-demethylation, are catalyzed by CYP2D6 [26]. Therefore, it is possible that an alteration of CYP2D6 activity changes the metabolism of METH and synthesis of hydroxylated metabolites and may affect susceptibility to METH dependence.

CYP2D6 is one of the best-known of the polymorphic drug-metabolizing enzymes. CYP2D6 is involved in the metabolism of 20–25% of clinically used drugs and exhibits a clinically relevant gene polymorphism that modifies the pharmacokinetics of nearly 50% of the drugs [20]. Approximately 5–6% of Caucasians are CYP2D6 deficient due to inactivating mutations of the CYP2D6 gene (*CYP2D6*), *CYP2D6*3* (5%), **4* (75%), and **5* (15%) and are termed poor metabolizers (PM) [3,6,7]. In comparison, the ratio of PM among Japanese is less than 1%, comprising mostly *CYP2D6*5* with a few *CYP2D6*4* and **14* genotypes [25,29,36]. However, the allele frequency of *CYP2D6*10* in Japanese (38–51%) [25,29,36] is much higher than that in Caucasians (1–5%), black Africans (6%), and Ethiopians and Saudi Arabians (3–9%) [6]. Individuals with *CYP2D6*10/*10*, which causes decreased CYP2D6 activity, are termed intermediate metabolizers (IM) [22] and account for approximately 15% of Japanese. Therefore, we examined *CYP2D6*1*, **4*, **5*, **10*, **14* in patients with METH dependence in a Japanese population to test our hypothesis that genetic variants of the *CYP2D6* gene could be a genetic factor in susceptibility to METH dependence.

Genotyping was performed on 202 patients with METH dependence (167 males and 35 females; mean age, 36.9 ± 11.8 years; ICD-10-DCR criteria; F15.2), and 337 control subjects (271 males and 66 females; mean age, 37.2 ± 13.1 years) who were age-, gender-, and geographically matched to patients. All subjects in the present study were Japanese, born and living in restricted regions of Japan. The patients were inpatients or outpatients at medical institutions participating in the Japanese Genetics Initiative for Drug Abuse (JGIDA) [39]. The clinical diagnosis was made by two trained psychiatrists according to ICD-10-DCR on the basis of unstructured medical interviews and records. Healthy volunteers were recruited mainly from the medical staff and had no present or past history of major psychiatric disorders, e.g., schizophrenia, bipolar disorder, and drug dependence. This study was approved by the ethics committee of each JGIDA institution. After a complete description of the study to the subjects, written informed consent was obtained.

Genomic DNA was extracted from peripheral leukocytes using standard procedures. The *CYP2D6*5* genotype was identified using long-PCR analysis according to the method of Johansson et al. [21]. Those of *CYP2D6*4* (G1840A), *CYP2D6*10* (C188T), and *CYP2D6*14* (G169A) were identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) according to the methods of Heim and Meyer [15] and Wang et al. [41,42]. We did not examine other CYP2D6 alleles, e.g., **3*, and **2xN* alleles, in the present study because it has been demonstrated that the frequency of those alleles is below 0.7% in the Japanese population [25,29,36]. The frequency of **2* in the Japanese population is high, but we did not identify it because it has no effect on CYP2D6 activity. We carried out genotyping in a blinded fashion with control and patient samples randomly mixed. Allele frequencies were calculated using the allele-counting method. Genotype deviation from Hardy–Weinberg equilibrium was assessed by χ^2 goodness-of-fit test. The statistical significance of case-control associations was evaluated by χ^2 test, Fisher's extract test, and the CLUMP program (ver 2.3) [34]. A T4 value was adopted as the *p*-value by CLUMP analysis. Statistical significance was accepted at $p < 0.05$.

The genotype distribution of patients with METH dependence and controls is shown in Table 1. We identified six *CYP2D6* genotypes in the Japanese subjects in the present study, *CYP2D6*1/*1*, **1/*5*, **1/*10*, **5/*10*, **10/*10*, and **10/*14*, whereas no *CYP2D6*4* allele or no *CYP2D6*1/*14*, **5/*5*, **5/*14*, **14/*14* genotype was found in either patients with METH dependence or controls. Genotype distributions of the patients and controls did not deviate from Hardy-Weinberg equi-

Table 1
CYP2D6 genotypes of patients with methamphetamine dependence and controls

Subjects	*N*	CYP2D6 genotypes						*p*
		*1/*1	*1/*5	*1/*10	*5/*10	*10/*10	*10/*14	
Patients	202	74(36.6)	6(3.0)	77(38.1)	4(2.0)	41(20.3)	0(0.0)	0.121
Controls	337	98(28.9)	16(4.7)	121(36.0)	12(3.6)	88(26.2)	2(0.6)	

p-Value was generated by CLUMP ver 2.3 using 10,000 simulations.

Table 2
CYP2D6 allele frequencies of patients with methamphetamine dependence and controls

Subjects	*N*	CYP2D6 alleles				*p*
		*1	*5	*10	*14	
Patients	404	231(57.2)	10(2.5)	163(40.3)	0(0.0)	0.0299
Controls	672	329(48.9)	28(4.2)	313(46.6)	2(0.3)	

p-Value was generated by CLUMP ver 2.3 using 10,000 simulations.

librium (patients: $G = 2.75$, d.f. = 4. $p = 0.60$; controls: $G = 7.92$, d.f. = 6, $p = 0.24$). The frequency of *CYP2D6*1/*1*, a wild-type genotype, was 36.9% in patients with METH dependence, and was higher than that in controls, 28.9%. In contrast, *CYP2D6*10/*10* and **5/*10* genotypes were observed in 20.3% and 2.0% of patients, respectively, which were lower than those in controls, 26.2% and 3.6%, respectively. However, the difference in the *CYP2D6* genotype distribution between controls and patients with METH dependence was not statistically significant ($p = 0.121$).

The allele distributions of *CYP2D6* in patients and controls are shown in Table 2. The frequency of the wild-type allele, **1*, was 48.9% in controls, which was less than that of patients, 57.2%. The frequencies of **5* and **10* alleles in controls were 4.2% and 46.6%, respectively, which were higher than those in patients, 2.5% and 40.3%, respectively. Only two subjects had the **14* allele, and they were controls (0.3%). The distribution of allele frequencies of the *CYP2D6* gene differed significantly between patients with METH dependence and controls ($p = 0.0299$).

Then we divided *CYP2D6* genotypes into three functional phenotypes, EM, IM, and PM, according to as the level of enzyme activity. The definition of the three phenotypes follows the modified method described by Someya et al. [35]. They defined the heterozygote of a wild and inactivating allele, e.g., *CYP2D6*1/*5* as IM because they did not find a significant difference in *CYP2D6* activity between *CYP2D6*10/*10* and *CYP2D6*1/*5*. Briefly, EM comprise *CYP2D6*1/*1* and **1/*10*, IM comprise of *CYP2D6*10/*10*, **1/*5*, **5/*10*, *10/*14, and PM comprise *CYP2D6*5/*5*, **5/*14*, and **14/*14*. No subject with the PM phenotype was observed in the subjects of the present study. The patients with METH dependence had significantly fewer IM and more EM ($p = 0.0212$, Table 3). The odds ratio of IM for METH dependence was 0.62 (95% confidence interval: 0.51–0.76).

We found that the distributions of *CYP2D6* allele and phenotype frequency were significantly associated with susceptibility to METH dependence. Hypofunction alleles of *CYP2D6*, *10 and *14, and IM phenotypes comprising *CYP2D6*10/*10*, **1/*5*, **5/*10*, *10/*14 were fewer in the patients than in the controls. Intermediate metabolism of CYP2D6 was identified as a negative risk factor for development of METH dependence, and reduced the risk of METH dependence to about six out of ten. CYP2D6 catalyzes the first step in the metabolism of METH, 4-hydroxylation of the aromatic ring and *N*-demethylation [26], which produces several kinds of metabolites, e.g., 4-OH METH, 4-OH AMPH, and norephedrine. The ratios of these metabolites excreted in urine were different among human, rat, and guinea pig species [8]. In humans, the major metabolites of METH in urine are the unchanged drug and 4-OH METH, and the minor ones are hippuric acid, norephedrine, 4-OH AMPH, and 4-OH norephedrine. Hydroxylated metabolites of METH were shown to be active neurochemically and behaviorally like the parent compound. OH-METH and OH-AMPH inhibited uptake of noradrenaline in chopped cerebral cortex [43], uptake of dopamine into striatal homogenates [9], and induced release of noradrenaline and dopamine from striatal homogenates [13]. The potency of 4-OH AMPH in inhibition and release of dopamine from the striatum was almost equivalent to that of AMPH. These hydroxylated metabolites themselves had propensity to induce hyperlocomotion and stereotyped behaviors [37], indicating psychostimulating and psychotomimetic activities, and also to enhance abnormal behaviors induced by the parent drugs [11]. These metabolites were taken up by dopaminergic terminals [23] and accumulated greatly in synaptic terminals of the striatum and hypothalamus after chronic administration of METH or AMPH because the half life of hydroxylated AMPH is 1.5 days in rat brain, whereas the half-life of AMPH is 45 min. Therefore, hydroxylated metabolites of METH could preferentially contribute to the development of dependence or the psychotic disorder induced by METH in the chronic phase of METH abuse. This speculation seems to be consistent with a clinical observation by Anggard et al. [1], who noted that the intensity of the psychosis of patients with AMPH dependence is more closely related to the urinary levels of hydroxylated metabolites than to the plasma levels of AMPH.

Ramamoorthy et al. [32] showed that the intrinsic clearance rate of (+)- and (−)-METH in 4-hydroxylation by *10 of CYP2D6 was 30- and 67-fold slower than the wild-type *1 *in vitro*. Thus, it can be expected that, *in vivo*, an individual who is a CYP2D6 IM, for example, the *10/*10 genotype, would display much lower levels of hydroxylated metabolites of METH after abuse of METH, resulting in less accumulation of the hydroxylated metabolites of METH in the brain and more rapid excretion of unchanged METH in the urine. This pharmacokinetic change of METH by CYP2D6 IM could result in relative insuscepti-

Table 3
Phenotypes of patients with methamphetamine dependence and controls

Subjects	*N*	CYP2D6 phenotypes		*p*
		EM	IM	
Patients	202	151(74.8)	51(25.2)	0.0212
Controls	336	218(64.9)	118(35.1)	

No poor metabolizer was found. EM, extensive metabolizer; IM, intermediate metabolizer.

bility to development of dependence on the drug. However, our findings need to be confirmed in larger samples because our sample size may not be large enough to exclude possibilities of population stratification and type 1 and 2 errors. Confirmation in different populations, e.g., Caucasian should be very useful because there are poor metabolizers of CYP2D6, who must show the least dependence to methamphetamine. In addition, examination of the *CYP2D6* gene in patients who abuse methylendioxymethamphetamine, another widely abused drug, should be informative because it is also a substrate for CYP2D6.

Acknowledgements

We are grateful to Dr. Yutaro Suzuki from Niigata University for technical advice on *CYP2D6* genotyping. This work was partly supported by the Zikei Institute of Psychiatry (Okayama, Japan) and Grants-in-Aid from the Japanese Ministry of Health, Labor and Welfare.

References

[1] E. Anggard, L.E. Jonsson, A.L. Hogmark, L.M. Gunne, Amphetamine metabolism in amphetamine psychosis, Clin. Pharmacol. Ther. 14 (1973) 870–880.
[2] T. Arinami, H. Ishiguro, E.S. Onaivi, Polymorphisms in genes involved in neurotransmission in relation to smoking, Eur. J. Pharmacol. 410 (2000) 215–226.
[3] L. Bertilsson, M.L. Dahl, P. Dalen, A. Al-Shurbaji, Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs, Br. J. Clin. Pharmacol. 53 (2002) 111–122.
[4] R.E. Billings, P.J. Murphy, R.E. McMahon, J. Ashmore, Aromatic hydroxylation of amphetamine with rat liver microsomes, perfused liver, and isolated hepatocytes, Biochem. Pharmacol. 27 (1978) 2525–2529.
[5] W.F. Bosron, T.K. Li, Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism, Hepatology 6 (1986) 502–510.
[6] L.D. Bradford, CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants, Pharmacogenomics 3 (2002) 229–243.
[7] F. Broly, A. Gaedigk, M. Heim, M. Eichelbaum, K. Morike, U.A. Meyer, Debrisoquine/sparteine hydroxylation genotype and phenotype: analysis of common mutations and alleles of CYP2D6 in a European population, DNA Cell Biol. 10 (1991) 545–558.
[8] J. Caldwell, L.G. Dring, R.T. Williams, Metabolism of (14C)methamphetamine in man, the guinea pig and the rat, Biochem. J. 129 (1972) 11–22.
[9] A.K. Cho, B.J. Hodshon, B. Lindeke, J. Jonsson, The *p*-hydroxylation of amphetamine and phentermine by rat liver microsomes, Xenobiotica 5 (1975) 531–538.
[10] D.F. Dougan, A.M. Duffield, P.H. Duffield, D.N. Wade, Stereoselective accumulation of hydroxylated metabolites of amphetamine in rat striatum and hypothalamus, Br. J. Pharmacol. 88 (1986) 285–290.
[11] D.F. Dougan, S.L. Labrie, P.D. Paull, P.H. Duffield, D.N. Wade, Evidence that alpha-methyl-*p*-tyramine is implicated in behavioural augmentation to amphetamine, Gen. Pharmacol. 17 (1986) 453–456.
[12] D.F. Dougan, D.N. Wade, P. Duffield, How metabolites may augment some psychostimulant actions of amphetamine, TiPS 8 (1987) 277–280.
[13] J.F. Fischer, A.K. Cho, Chemical release of dopamine from striatal homogenates: evidence for an exchange diffusion model, J. Pharmacol. Exp. Ther. 208 (1979) 203–209.
[14] Y. Gasche, Y. Daali, M. Fathi, A. Chiappe, S. Cottini, P. Dayer, J. Desmeules, Codeine intoxication associated with ultrarapid CYP2D6 metabolism, N. Engl. J. Med. 351 (2004) 2827–2831.
[15] M. Heim, U.A. Meyer, Genotyping of poor metabolisers of debrisoquine by allele-specific PCR amplification, Lancet 336 (1990) 529–532.
[16] S. Higuchi, S. Matsushita, M. Murayama, S. Takagi, M. Hayashida, Alcohol and aldehyde dehydrogenase polymorphisms and the risk for alcoholism, Am. J. Psychiatry 152 (1995) 1219–1221.
[17] N. Hiroi, S. Agatsuma, Genetic susceptibility to substance dependence, Mol. Psychiatry 10 (2005) 336–344.
[18] S. Ide, H. Kobayashi, H. Ujike, N. Ozaki, Y. Sekine, T. Inada, M. Harano, T. Komiyama, M. Yamada, M. Iyo, N. Iwata, K. Tanaka, H. Shen, K. Iwahashi, M. Itokawa, M. Minami, M. Satoh, K. Ikeda, I. Sora, Linkage disequilibrium and association with methamphetamine dependence/psychosis of mu-opioid receptor gene polymorphisms, Pharmacogenomics J. 6 (2006) 179–188.
[19] M. Ikeda, N. Iwata, T. Suzuki, T. Kitajima, Y. Yamanouchi, Y. Kinoshiya, Y. Sekine, M. Iyo, M. Harano, T. Komiyama, M. Yamada, I. Sora, H. Ujike, T. Inada, N. Ozaki, Positive association of AKT1 haplotype to Japanese methamphetamine use disorder, Int. J. Neuropsychopharmacol. 9 (2006) 77–81.
[20] M. Ingelman-Sundberg, Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity, Pharmacogenomics J. 5 (2005) 6–13.
[21] I. Johansson, E. Lundqvist, M.L. Dahl, M. Ingelman-Sundberg, PCR-based genotyping for duplicated and deleted CYP2D6 genes, Pharmacogenetics 6 (1996) 351–355.
[22] I. Johansson, M. Oscarson, Q.Y. Yue, L. Bertilsson, F. Sjoqvist, M. Ingelman-Sundberg, Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation, Mol. Pharmacol. 46 (1994) 452–459.
[23] A. Jori, S. Caccia, A. Guiso, M. Ballabio, S. Garattini, Selective storage of *p*-hydroxy-D-amphetamine in the dopaminergic nerve terminals, Biochem. Pharmacol. 28 (1979) 1205–1207.
[24] K.S. Kendler, C.A. Prescott, J. Myers, M.C. Neale, The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women, Arch. Gen. Psychiatry 60 (2003) 929–937.
[25] T. Kubota, Y. Yamaura, N. Ohkawa, H. Hara, K. Chiba, Frequencies of CYP2D6 mutant alleles in a normal Japanese population and metabolic activity of dextromethorphan *O*-demethylation in different CYP2D6 genotypes, Br. J. Clin. Pharmacol. 50 (2000) 31–34.
[26] L.Y. Lin, E.W. Di Stefano, D.A. Schmitz, L. Hsu, S.W. Ellis, M.S. Lennard, G.T. Tucker, A.K. Cho, Oxidation of methamphetamine and methylenedioxymethamphetamine by CYP2D6, Drug Metab. Dispos. 25 (1997) 1059–1064.
[27] Y. Maezawa, M. Yamauchi, G. Toda, H. Suzuki, S. Sakurai, Alcohol-metabolizing enzyme polymorphisms and alcoholism in Japan, Alcohol Clin. Exp. Res. 19 (1995) 951–954.
[28] V. Malaiyandi, E.M. Sellers, R.F. Tyndale, Implications of CYP2A6 genetic variation for smoking behaviors and nicotine dependence, Clin. Pharmacol. Ther. 77 (2005) 145–158.
[29] Y. Nishida, T. Fukuda, I. Yamamoto, J. Azuma, CYP2D6 genotypes in a Japanese population: low frequencies of CYP2D6 gene duplication but high frequency of CYP2D6*10, Pharmacogenetics 10 (2000) 567–570.
[30] T. Nishiyama, M. Ikeda, N. Iwata, T. Suzuki, T. Kitajima, Y. Yamanouchi, Y. Sekine, M. Iyo, M. Harano, T. Komiyama, M. Yamada, I. Sora, H. Ujike, T. Inada, T. Furukawa, N. Ozaki, Haplotype association between GABAA receptor gamma2 subunit gene (GABRG2) and methamphetamine use disorder, Pharmacogenomics J. 5 (2005) 89–95.
[31] A. Nomura, H. Ujike, Y. Tanaka, K. Otani, Y. Morita, M. Kishimoto, A. Morio, M. Harano, T. Inada, M. Yamada, T. Komiyama, Y. Sekine, N. Iwata, I. Sora, M. Iyo, N. Ozaki, S. Kuroda, Genetic variant of prodynorphin gene is risk factor for methamphetamine dependence, Neurosci. Lett. 400 (2006) 158–162.
[32] Y. Ramamoorthy, R.F. Tyndale, E.M. Sellers, Cytochrome P450 2D6.1 and cytochrome P450 2D6.10 differ in catalytic activity for multiple substrates, Pharmacogenetics 11 (2001) 477–487.
[33] M. Sato, Y. Numachi, T. Hamamura, Relapse of paranoid psychotic state in methamphetamine model of schizophrenia, Schizophr. Bull. 18 (1992) 115–122.
[34] P.C. Sham, D. Curtis, Monte Carlo tests for associations between disease and alleles at highly polymorphic loci, Ann. Hum. Genet. 59 (1995) 97–105.

[35] T. Someya, Y. Suzuki, K. Shimoda, G. Hirokane, S. Morita, A. Yokono, Y. Inoue, S. Takahashi, The effect of cytochrome P450 2D6 genotypes on haloperidol metabolism: a preliminary study in a psychiatric population, Psychiatry Clin. Neurosci. 53 (1999) 593–597.
[36] T. Tateishi, M. Chida, N. Ariyoshi, Y. Mizorogi, T. Kamataki, S. Kobayashi, Analysis of the CYP2D6 gene in relation to dextromethorphan *O*-demethylation capacity in a Japanese population, Clin. Pharmacol. Ther. 65 (1999) 570–575.
[37] W.A. Taylor, F. Sulser, Effects of amphetamine and its hydroxylated metabolites on central noradrenergic mechanisms, J. Pharmacol. Exp. Ther. 185 (1973) 620–632.
[38] M.T. Tsuang, J.L. Bar, R.M. Harley, M.J. Lyons, The Harvard Twin Study of Substance Abuse: what we have learned, Harv. Rev. Psychiatry 9 (2001) 267–279.
[39] H. Ujike, M. Harano, T. Inada, M. Yamada, T. Komiyama, Y. Sekine, I. Sora, M. Iyo, T. Katsu, A. Nomura, K. Nakata, N. Ozaki, Nine- or fewer repeat alleles in VNTR polymorphism of the dopamine transporter gene is a strong risk factor for prolonged methamphetamine psychosis, Pharmacogenomics J. 3 (2003) 242–247.
[40] H. Ujike, M. Sato, Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis, Ann. N. Y. Acad. Sci. 1025 (2004) 279–287.
[41] S.L. Wang, J.D. Huang, M.D. Lai, B.H. Liu, M.L. Lai, Molecular basis of genetic variation in debrisoquin hydroxylation in Chinese subjects: polymorphism in RFLP and DNA sequence of CYP2D6, Clin. Pharmacol. Ther. 53 (1993) 410–418.
[42] S.L. Wang, M.D. Lai, J.D. Huang, G169R mutation diminishes the metabolic activity of CYP2D6 in Chinese, Drug Metab. Dispos. 27 (1999) 385–388.
[43] G.R. Wenger, C.O. Rutledge, A comparison of the effects of amphetamine and its metabolites, *p*-hydroxyamphetamine and *p*-hydroxynorephedrine, on uptake, release and catabolism of 3H-norepinephrine in cerebral cortex of rat brain, J. Pharmacol. Exp. Ther. 189 (1974) 725–732.