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PHARMACOGENETICS

Effects of CYP2D6 polymorphisms on neuroleptic malignant syndrome

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Abstract
Objective Neuroleptic malignant syndrome (NMS) is one of the most serious adverse reactions to antipsychotic medications. We accumulated data on Japanese NMS patients and, in a study designed to examine the effects of drug metabolism on the occurrence of NMS, tested the possibility of association between NMS and *CYP2D6* polymorphisms.
Methods We studied 53 patients who had experienced NMS and 112 healthy individuals. We determined what drugs the patients with NMS had been given and retrospectively identified candidates for drugs causing NMS. We screened the prevalence of *CYP2D6* genotypes using polymerase chain reaction and restriction fragment length polymorphism analyses.
Results The prevalence of **5* alleles in the group of all patients with NMS was higher than that in the controls, though this difference was not statistically significant (10.4% vs. 5.4%; P=0.107; odds ratio (OR) 2.05; 95% confidence interval (CI) 0.87–4.80). No association was found between the frequency of **10* alleles and the occurrence of NMS. We found **4* and duplicated alleles in only one patient each among the patients with NMS. A total of 29 patients appeared to have developed NMS as a result of having taking CYP2D6 substrates. The prevalence of **5* alleles in these 29 patient was significantly higher than that in the controls (15.5% vs. 5.4%; P=0.020; OR 3.25; 95% CI 1.30–8.13).
Conclusion Our findings suggest that the *CYP2D6*5* allele is likely to affect vulnerability to development of NMS.

Keywords Adverse reaction · CYP2D6 · Gene deletion · Neuroleptic malignant syndrome · Polymorphism

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Introduction

Neuroleptic malignant syndrome (NMS) is a well-recognized, severe, and potentially lethal adverse reaction to antipsychotic administration [1]. In addition to neuroleptic drugs, NMS can be caused by antidepressants, lithium carbonate, and other psychotropic agents. NMS is characterized by hyperthermia, extrapyramidal signs, altered consciousness, fluctuating blood pressure, incontinence, and dyspnea, as well as other features [2]. The frequency of its occurrence with conventional antipsychotic agents has been reported to vary from 0.02% to 2.44%, whereas a review of case reports has indicated that atypical antipsychotic agents can cause NMS, which can in some instances be severe enough to be fatal [3]. Caroff et al. and Ananth et al. reported the mortality rate is 4.4–11.3% [4, 5].

CYP2D6, an isozyme among the CYP mono-oxygenases, is responsible for the hepatic metabolism of various psychotropic agents. More than 40 polymorphic alleles that affect enzymatic activity have been described for the *CYP2D6* genes (http://www.imm.ki.se/cypalleles/cyp2d6.htm). The phenotypes of CYP2D6 activity resulting from these polymorphisms can be divided into extensive, poor,

and ultrarapid metabolizers (EM, PM, and UM) according to enzymatic activities [6]. The PM phenotype, lacking CYP2D6 expression, is caused by total gene deletion or single-nucleotide polymorphisms in a gene inherited in an autosomal recessive fashion. Together with the gene deletion allele (**5*), the polymorphic *CYP2D6* alleles **3* and **4* account for most instances of PM phenotype in Caucasians, although **3* and **4* are rare in Eastern Asians. Instead, the **10* allele, which encodes an unstable enzyme with decreased catalytic activity, is relatively frequent in Eastern Asia [7]. The frequency of the **5* allele is similar (4 to 6%) in Caucasian and East Asian populations [6]. Nishida et al. reported that the allelic frequencies of **10*, **5*, **4*, and **3* were 38.1%, 4.5%, 0.2%, and 0%, respectively, in 206 healthy Japanese subjects [8].

The PM phenotype is clinically important, as lack of the associated metabolic pathway may lead to toxicity and adverse reactions upon administration of certain drugs in standard doses [6, 9]. On the other hand, several studies have identified individuals with NMS who possessed *CYP2D6* polymorphisms resulting in defective CYP2D6 activity [10–12]. In this study, we performed systematic screening for *CYP2D6* polymorphisms and assessed genetic associations with the occurrence of NMS in Japanese patients.

Methods

We studied 53 patients (29 men and 24 women) who had experienced NMS. The patients had been recruited from several hospitals since 1996. NMS was diagnosed according to the criteria of Pope et al. [13]. Psychiatric diagnoses were made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*). Our control subjects were 112 healthy individuals without psychiatric diagnoses (33 men and 79 women). We recruited control subjects from personnel in hospitals and students, and we carried out the Mini-International Neuropsychiatric Interview (MINI) to exclude psychiatric patients. All subjects were Japanese and unrelated. We presented all NMS patients and healthy controls that we have accumulated so far. The prevalence of *CYP2D6*3, *4,* and **10* in a part of our samples were previously reported elsewhere [7, 14].

We determined the drugs that the patients with NMS had been given and retrospectively identified candidates for drugs causing NMS. If NMS occurred after increase of an antipsychotic drug, we regarded the drug as a candidate. If sudden discontinuation of antipsychotics or antiparkinsonian drugs caused NMS, we mentioned it in the Table 1. In the other cases, we listed all psychotic drugs the patients were given.

This study was approved by the ethics committee of the Yokohama City University School of Medicine. Written informed consent was obtained from all of the patients and control subjects.

Genetic analysis

Genomic DNA was extracted from peripheral white blood cells from all patients and control subjects using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA) according to manufacturer guidelines. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analyses were performed to screen for **10* and **4* alleles according to the method of Wang et al. [15] and Kawanishi et al. [14]. Long PCR was performed to screen for *CYP2D6* gene deletion allele (*CYP2D6*5*) and duplicated alleles according to the method of Lundqvist et al. [16] for duplication and that of Johansson et al. [17] and Wennerholm et al. [18] for deletion using two sets of oligonucleotide primers in each PCR reaction. Alleles for which neither **10*, **5*, **4* nor duplicated alleles could be identified were classified as *CYP2D6*1* (wild-type) alleles. Genetic analyses were performed by an investigator unaware of which subjects had developed NMS.

Statistical analysis

Statistical analyses were performed using the χ^2 tests with Fisher's exact test. Statistical tests were two-tailed, with P values less than 0.05 considered significant. These analyses were performed using SPSS 11.0 for Windows (SPSS Japan, Tokyo).

Results

Table 1 shows characteristics of the patients with NMS. Mean age at the first NMS episode was 50.8 years [standard deviation (SD)=16.8). NMS relapsed in ten patients. The principal diagnoses were schizophrenia in 41 cases; mood disorders in four; delusional disorder, alcohol dependence, drug dependence, dementia, steroid-induced psychotic disorder, psychotic disorder due to viral encephalitis, autism, and personality disorder in one case each. CYP2D6 genotypes and allele frequencies of the NMS patients and control subjects are given in Table 2. The observed frequency of **5* alleles in patients with NMS was higher than that in controls, though the difference between groups was not statistically significant [10.4% vs. 5.4%; P=0.107; odds ratio (OR) 2.05; 95% confidence interval (CI) 0.87–4.80). No association was found between **10* alleles and the occurrence of NMS. The**4* and duplicated

Table 1 Characteristics of the patients with neuroleptic malignant syndrome (NMS)

Number	Sex (M/F)	Age of first NMS onset	Times of NMS	Diagnosis	Genotype	Possible causative drugs of NMS occurrence [1]
1	M	54	1	Schizophrenia	*1/*1	HPD
2	F	45	1	Schizophrenia	*1/*10	Bromperidol
3	M	46	1	Schizophrenia	*1/*10	Unknown
4	M	30	1	Schizophrenia	*1/*5	Fluphenazine
5	M	41	3	Schizophrenia	*10/*10	[a]Mosapramine, [b]HPD, [c]risperidone
6	F	72	2	Schizophrenia	*1/*10	[a]HPD, [b]sulpiride
7	M	40	1	Schizophrenia	*1/*1	Risperidone, thioridazine
8	M	59	2	Schizophrenia	*5/*10	[a]HPD, [b]HPD
9	M	76	1	Schizophrenia	*1/*5	Amoxapine, CPZ
10	M	43	2	Alcohol dependence	*1/*1	[a]Levomepromazine, [b]unknown
11	F	24	2	Schizophrenia	*1/*1	[a]Sulpiride, [b]CPZ, sultopride
12	M	28	1	Schizophrenia	*1/*1	HPD
13	F	60	1	Mood disorder	*1/*10	Amoxapine, amitriptyline
14	M	16	1	Schizophrenia	*10/*10	HPD
15	F	26	2	Schizophrenia	*1/*10	[a]HPD, propericyazine, [b]thioridazine
16	F	24	1	Schizophrenia	*1/*1	Bromperidol, discontinuation of biperiden
17	F	20	1	Schizophrenia	*1/*1	Risperidone
18	M	55	4	Psychotic disorder due to viral encephalitis	*1/*1	[a]Li , [b]unknown, [c]Li, HPD, [d]levomepromazine
19	M	30	1	Schizophrenia	*1/*10	Nemonapride
20	F	62	2	Schizophrenia	*4/*10	[a]Bromperidol, [b]Discontinuation of neuroleptics
21	M	57	1	Mood disorder	*1/*1	Amitriptyline, levomepromazine
22	F	74	1	Schizophrenia	*1/*10	HPD
23	M	48	1	Mood disorder	*1/*1	Mianserin
24	F	31	1	Schizophrenia	*5/*10	Risperidone, olanzapine
25	F	32	1	Schizophrenia	*10/*10	HPD
26	M	21	1	Schizophrenia	*10/*10	HPD
27	F	62	1	Schizophrenia	*1/*1	Discontinuation of HPD and bromperidol
28	F	38	1	Personality disorder	*1/*1	Sultopride
29	M	30	1	Drug dependence	*1/*1	Mianserin, levomepromazine
30	F	51	1	Schizophrenia	*1/*10	Risperidone, perospirone
31	F	31	1	Schizophrenia	*1/*5	Levomepromazine, propericyazine, perospirone
32	M	34	1	Schizophrenia	*10/*10	HPD
33	M	73	1	Schizophrenia	*10/*10	Risperidone, tiapride
34	M	19	1	Schizophrenia	*1XN/*1	Quetiapine
35	F	38	1	Schizophrenia	*1/*1	HPD, CPZ
36	M	21	1	Schizophrenia	*1/*1	Zotepine, bromperidol
37	F	65	1	Schizophrenia	*1/*1	Risperidone, nemonapride, CPZ
38	M	9	1	Autism	*1/*5	HPD
39	M	66	1	Dementia	*1/*5	Quetiapine
40	F	68	1	Mood disorder	*1/*1	Reduced amantadine
41	F	54	2	Schizophrenia	*1/*5	[a]HPD, CPZ, levomepromazine, sulpiride, tiapride, [b]CPZ
42	F	58	2	Steroid-induced psychotic disorder	*10/*10	[a]Perospirone [b]reduced bromocriptine
43	M	47	1	Schizophrenia	*1/*1	HPD
44	M	21	1	Schizophrenia	*1/*10	Sultopride
45	M	34	1	Schizophrenia	*1/*1	Sultopride, zotepine
46	M	49	1	Schizophrenia	*1/*5	Risperidone, quetiapine
47	M	26	1	Schizophrenia	*10/*10	Discontinuation of antipsychotics
48	M	66	1	Schizophrenia	*1/*1	Risperidone, zotepine

Table 1 (continued)

Number	Sex (M/F)	Age of first NMS onset	Times of NMS	Diagnosis	Genotype	Possible causative drugs of NMS occurrence [1]
49	M	58	1	Schizophrenia	*5/*10	HPD
50	F	71	1	Schizophrenia	*1/*10	Levomepromazine
51	F	56	1	Delusional disorder	*10/*10	Quetiapine
52	F	35	1	Schizophrenia	*1/*5	Risperidone, levomepromazine
53	F	71	1	Schizophrenia	*1/*10	Zotepine

[1] *HPD* haloperidol, *CPZ* chlorpromazine, *Li* lithium carbonate
[a], [b], [c], and [d] indicate the first, second, third, and fourth episodes of NMS, respectively.

alleles were found in only one patient each among the NMS group.

To estimate the clinical effects of deletion, NMS patients were classified into those whose NMS-causative drugs had been CYP2D6 substrates. A total of 29 patients had been given CYP2D6 substrates (risperidone, olanzapine, fluphenazine, thioridazine, haloperidol, chlorpromazine, amitriptyline, or mianserin [9]) (Table 1). The prevalence of **5* alleles in these 29 patients was significantly higher than that in controls (15.5% vs. 5.4%; P=0.020; OR 3.25; 95% CI 1.30–8.13).

Discussion

Since NMS was first proposed as a clinical entity in the 1960s, various case descriptions and clinical studies of it have been reported from psychiatric and neurologic units, though the mechanisms underlying NMS remain unclear. Dopaminergic systems of the central nervous system appear likely to be involved in the onset of NMS, as all neuroleptics known to cause NMS act as dopamine receptor antagonists [1]. Certain predisposing conditions such as dehydration, malnutrition, exhaustion, infection, and organic brain diseases are risk factors for the development of NMS [19–23]. High or rapidly increasing antipsychotic doses, large numbers of intramuscular injections, and psychomotor agitation are additional risk factors that tend to be interrelated [19, 20]. On the other hand, NMS often recurs despite absence of acquired risk factors. In addition, occurrences of familial NMS have been reported. Deuschl et al. reported NMS in twin brothers with schizophrenia [24], and Otani et al. described familial occurrence involving a mother and her two daughters [25]. Furthermore, patients who have experienced NMS remain at increased risk for its occurrence [1, 26–29]. These findings suggest that constitutional factors under genetic control play roles in the onset of NMS, which has spurred mutation analyses and genetic association studies. Although minimization of risk factors and increased awareness of NMS could decrease its incidence, and detection of prodromal symptoms could decrease the morbidity of NMS, prediction and prevention are still difficult, as there are individual differences in responses to drugs, and no biological marker is available to identify individuals who are inherently at increased risk for NMS.

Recent findings of pharmacogenetic studies have indicated that polymorphisms of the *CYP2D6* gene are associated with interindividual differences in drug responses. PM individuals who are homozygous for either point mutations in or deletion of the *CYP2D6* gene are unable to metabolize CYP2D6 substrates, resulting in higher plasma drug concentrations. The PM phenotype is clinically important, as lack of the associated metabolic pathway may lead to toxicity and adverse reactions upon administration of drugs in standard doses [6, 9]. Dose effect of the *CYP2D6* gene has been shown to be associated with CYP2D6 activity, and this activity is decreased in individ-

Table 2 CYP2D6 genotypes and allele frequencies in patients with neuroleptic malignant syndrome (NMS) and control patients (%)

	Controls (n=112)	Patients with NMS (n=53)	Patients with NMS caused by drugs including CYP2D6 substrates (n=29)
Genotypes			
*1/*1	46 (41.1)	20 (37.7)	11 (37.9)
*1/*10	32 (28.6)	11 (20.8)	4 (13.8)
*10/*10	21 (18.8)	9 (17.0)	5 (17.2)
*1/*5	8 (7.1)	8 (15.1)	6 (20.7)
*5/*10	4 (3.6)	3 (5.7)	3 (10.3)
*4/*10	0	1 (1.9)	0
*1XN/*1	1 (0.9)	1 (1.9)	0
Alleles			
*1	133/224 (59.4)	60/106 (56.6)	32/58 (55.2)
*10	78/224 (34.8)	33/106 (31.1)	17/58 (29.3)
*5	12/224 (5.4)	11/106 (10.4)	9/58 (15.5)[a]
*4	0	1/106 (0.9)	0
*1XN	1/224 (0.4)	1/106 (0.9)	0

[a] $\chi 2$, Fisher's exact test, $p<0.05$

uals heterozygous for deletion [6]. Several studies have suggested that adverse reactions to neuroleptics are associated with decreased or deficient CYP2D6 activity. PM is more prevalent among patients with than those without drug-induced extrapyramidal symptoms [30, 31]. For example, tardive dyskinesia (TD) has been linked to decreased CYP2D6 activity. Kapitany et al. genotyped patients with schizophrenia for the **3*, **4,* and **5* alleles and found that frequency of TD was higher in patients heterozygous for these alleles [32]. Ohmori et al. also found an association between TD and the **10* allele in Japanese patients with schizophrenia [33]. Similar conclusions were obtained in another study [30, 34].

Genetic association studies also have sought to identify *CYP2D6* polymorphisms affecting susceptibility to NMS. We also reported the finding of homozygosity for the *CYP2D6*10* allele in two psychiatric patients who had previous episodes of NMS, although we failed to identify an association between the **3*, **4*, or **10* allele and NMS in previous studies [7, 11, 14]. Recently, we reported two NMS patients with schizophrenia who were found to possess a *CYP2D6* gene-deletion allele [12].

Thus, in the study reported here, we reexamined the possibility of an association between CYP2D6 polymorphisms including the **5* allele and NMS in 53 patients with NMS. We found that the prevalence of **5* alleles in the 29 patients whose NMS-causative drugs were CYP2D6 substrates was significantly higher than that in controls (15.5% vs. 5.4%; P=0.020), though we did not find a significant difference in prevalence of **5* alleles between the group of patients with NMS and controls (10.4% vs. 5.4%; P=0.107).

On the other hand, no association was found between NMS and **10* or **10/*10* genotypes. The frequency of genotype of either **5/*10, *4/*10, *10/*10,* or **1/*5* tended to be higher in NMS patients whose NMS-causative drugs were CYP2D6 substrates than that in controls (P= 0.076). Kubota et al. found that no difference was observed in metabolic activity of dextromethorphan O-demethylation between individuals with **10/*10* and **1/*5* genotypes [35]. Mihara et al. reported that the steady-state plasma concentrations of equal doses of risperidone were not significantly different between **10/*10* and **5/wt* [36]. Another study investigating haloperidol metabolism indicated that **5* might have stronger impact than **10* [37]. The two polymorphic alleles, **10* and **5*, possibly have different impacts in drug metabolism.

CYP2D6 substrates taken by patients with a **5* allele were metabolized at a reduced rate, resulting in higher plasma levels of the CYP2D6 substrate; it is the same condition as that brought on by known risk factors of NMS: rapidly increasing or greater numbers of intramuscular injections of neuroleptic drugs. We speculate that accumulation or high plasma concentrations of CYP2D6 substrates may have induced cellular toxicity and/or aberrant neurotransmission linked to the pathogenesis of NMS. Screening for at least the *CYP2D6*5* allele before initiating antipsychotic therapy including CYP2D6 substrates might be useful in identifying subjects at risk of developing NMS.

The following limitations to our study should be noted: we did not know whether sulpiride, sultopride, levomepromazine, propericyazine, and mosapramine are CYP2D6 substrates; we did not consider causes of NMS other than medications because physical conditions of the patients were not fully investigated in this study; and we lacked laboratory data concerning serum concentrations of antipsychotics because this study was retrospective and we could measure only a few serum concentrations of antipsychotics, given the constraints of the Japanese health insurance system.

NMS may be a heterogeneous condition with respect to etiology. We believe that by themselves, *CYP2D6* gene polymorphisms such as the **5* allele cannot explain all occurrences of NMS. Systemic analyses involving functional genetic polymorphisms of drug targets, such as dopamine receptors [38], may also be needed to improve understanding of this disorder. Our findings do suggest, though, that the *CYP2D6*5* allele is likely to affect vulnerability to development of NMS. Although 53 patients is a small number for an association study, NMS occurs only rarely, and this number is the greatest in a genetic study of NMS to date. Whereas our sample size has been the greatest for an association study regarding NMS to date, it is still small. Larger case-control studies will be needed to assess the effects of *CYP2D6* gene polymorphisms on the occurrence of NMS.

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