Recent studies demonstrated that a genetic variability of β_2AR, Thr164Ile, is closely related to heart failure. In patients with congestive cardiac failure, patients with homozygous genotype Ile/Ile show high mortality compared with those with other genotypes [12]. However, we could not statistically confirm the previous findings, probably because of low frequency of the mutation.

In summary, the α_{2c}Del322–325, β_1Ser49 and β_1Arg389 variants do not appear to be risk factors for CHF due to DCM in a Japanese population, and the α_{2c}Del322–325 variant may be protective. Considering the contradiction with the previous report, it is proposed that there may be a racial difference in the clinical importance of this polymorphism. Further efforts should be made to address any possible racial differences in the responsiveness of heart failure from different causes to β-blockers.

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原　著

N-アセチルトランスフェラーゼ2遺伝子多型に基づいた結核治療の試み

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Tentative Treatments for Tuberculosis Based on *N*-acetyltransferase Gene Polymorphism

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ABSTRACT

During tuberculosis chemotherapy, hepatotoxicity occurs at 10 to 20% of Japanese patients receiving isoniazid (INH) and rifampicin (RFP). Prevention of this adverse reaction is expected to be clinically beneficial. However, the pathological mechanisms involved in liver dysfunction remain to be fully elucidated. Here, we report two cases in which decreased dosage of INH, based on the genotype of NAT2, prevented a relapse of hepatotoxicity without reducing its antituberculous effect. The patients were genotyped as a slow acetylator (SA-type patients). The first case illustrated hepatotoxicity when treated with a regimen of INH 200mg and RFP 150mg twice daily (INH 400mg/day, RFP 300mg/day), but not when treated with a regimen of INH 100mg twice daily and RFP 150mg three times daily (INH

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200mg/day, RFP 450mg/day). This suggests that the daily dose of isoniazid was excessive for this patient, causing hepatotoxicity. In the second case, plasma concentration of INH was optimized by reducing the dosage from 200mg to 100mg twice daily. This reduction was sufficient to prevent recurrence of hepatotoxicity. We propose that the dosage of INH should be determined by NAT2 genotyping. These cases provide the possibility that NAT2 genotyping contributes to individualized medicine for tuberculosis.

Keywords : tuberculosis, pharmacogenetics, *N*-acetyl-transferase 2, individualized medicine, drug-induced hepatotoxity

要　　旨

イソニアジド (INH) とリファンピシン (RFP) を含む結核標準化学療法時には1～2割の患者で肝機能異常が認められる。これは日常診療において最も注意すべき副作用で，その発現機序の解明と，有害事象を未然に防ぐ治療法の確立が求められている。本論文では，治療中に重篤な肝障害を起こした肺結核患者において，N-アセチルトランスフェラーゼ2 (NAT 2) 遺伝子多型に基づいてINHを減量したところ，副作用の再発をみることなく完治した症例を報告する。症例1では肝障害による休薬の後，INH 400mg/day (分2)，RFP 300mg/day (分2) 投与時には肝障害が再発したが，INH 200mg/day (分2)，RFP 450mg/day (分3) では肝障害は発現せず完治した。このことから，この患者の肝障害の原因薬剤はINHであったと推察される。症例2では400mg/day (分2) 投与時には高濃度域に入っていた血中濃度が，200mg/day (分2) に減量することで適切な濃度を推移した。これらの例は，NAT2遺伝子多型に基づいてINH用量を設定することで，副作用を未然に防ぐ適正な結核治療を実現できる可能性を示唆するものである。

索引用語：結核，遺伝子多型，*N*-アセチルトランスフェラーゼ2，個別化適正医療，薬剤性肝障害

I　はじめに

抗結核薬イソニアジド (INH) には肝毒性があり，特にリファンピシン (RFP) 併用時には1～2割の患者で肝機能検査値に異常が認められる。RFPによるINHの肝毒性増強作用の詳細は不明であるが，RFPの酵素誘導作用によりINHから生成する肝毒性代謝物の生成量が増大するためだと推測されている[1)2)]。肝機能異常発現時には，通常，全て休薬後に抗結核薬の再導入を試みる。しかし，肝障害を再発することも多く，適切な指針の立案が求められている。INHの主代謝酵素である*N*-acetyltrans-ferase 2 (NAT2) の酵素活性には個体差が存在し，その表現型はNAT2遺伝子多型によって推定できる。すなわち，野生型の遺伝子 (*NAT2*4*) を2つ持つ人が高い代謝能を持つRapid Acetylator (RA)，野生型と変異型の遺伝子 (*NAT 2*5*, **6*, **7*) を1つずつ持つ人がIntermediate Acetylator (IA)，変異型の遺伝子型を2つ持つ人が低い代謝能を持つSlow Acetylator (SA) となる[3)4)]。著者らはこれまでに，INHとRFPを含む化学療法中にはSA患者で肝障害の起こる危険性が高いことを報告し[5)]，NAT2遺伝子多型に基づいてイソニアジド投与量を設定する結核の個別化治療の可能性を提言している[6)]。本論文では，肝障害の出現したSA患者に対しNAT2遺伝子多型に応じたINHの減量を試み，肝障害の再発を回避できた代表的症例を報告する。

Ⅱ 方　　法

本検討は国立療養所刀根山病院の倫理委員会で承認を受けた後に実施し，十分な説明をした上で文書による同意を得た肺結核入院患者を対象とした。対象患者は INH 400mg/day（分2）と RFP 450mg/day（分1）を含む化学療法で治療を開始した。患者の NAT 2 遺伝子型を判定するとともに，INH の血漿中濃度を測定し，臨床経過観察を行った。肝障害発現後の INH 用量は SA 患者であることを考慮し，INH 100 mg/day（分1）から投薬を再開し，200mg/day（分2）で治療を継続した。

Ⅲ 症　　例

症例 1

患者（31 歳女性）の臨床経過を図 1 に示す。結核治療開始時の INH 量は通常通り 400mg/day（分2）であった。投薬開始 7 日目に血清 AST 967 IU/l，ALT 472 IU/l と肝障害が発現したため，検査値が正常化するまで投薬を中止した。その後 INH の投薬を再開し，400mg/day（分2）まで漸増したが，INH 単剤での治療では肝機能異常は認められなかった。経過が良好であったため，RFP を 150mg/day（分1）より開始し，300mg/day（分2）まで増量した。INH 400mg/day（分2），RFP 300mg/day（分2）での治療に移行したところ，肝障害が再発したため，RFP の投与を中止し，肝機能が正常化するまで INH 400mg/day（分2）で治療を継続した。肝障害再発時の INH 投与後 3 時間の血中濃度は 4.51 μg/ml と高値であった。NAT 2 遺伝子多型判定を行ったところ SA 型（*NAT2*6/*7*）であったため，その結果に基づき INH を 200mg/day（分2）に減量し，RFP を 150mg/day（分1）から 450mg/day（分3）まで逐次増量した。最終的に INH 200mg/day（分2），RFP 450mg/day（分3）の投与量で治療を継続し，肝障害の再発をみることなく完治し退院となった。

症例 2

患者（69 歳女性）の臨床経過を図 2（a）に，INH 減量前後の血中濃度を図 2（b）に示す。INH 400mg/day（分2）を含む結核標準治療を

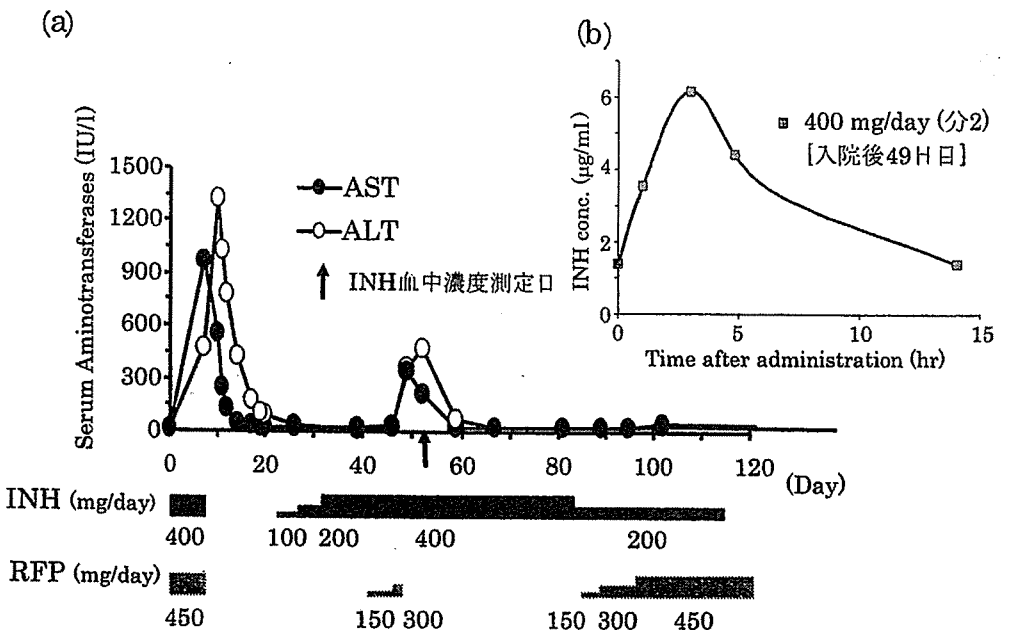

図 1　症例 1 の臨床経過
(a)入院後の AST，ALT の推移および INH と RFP の投与量推移
(b)入院後 49 日目の INH 血中濃度

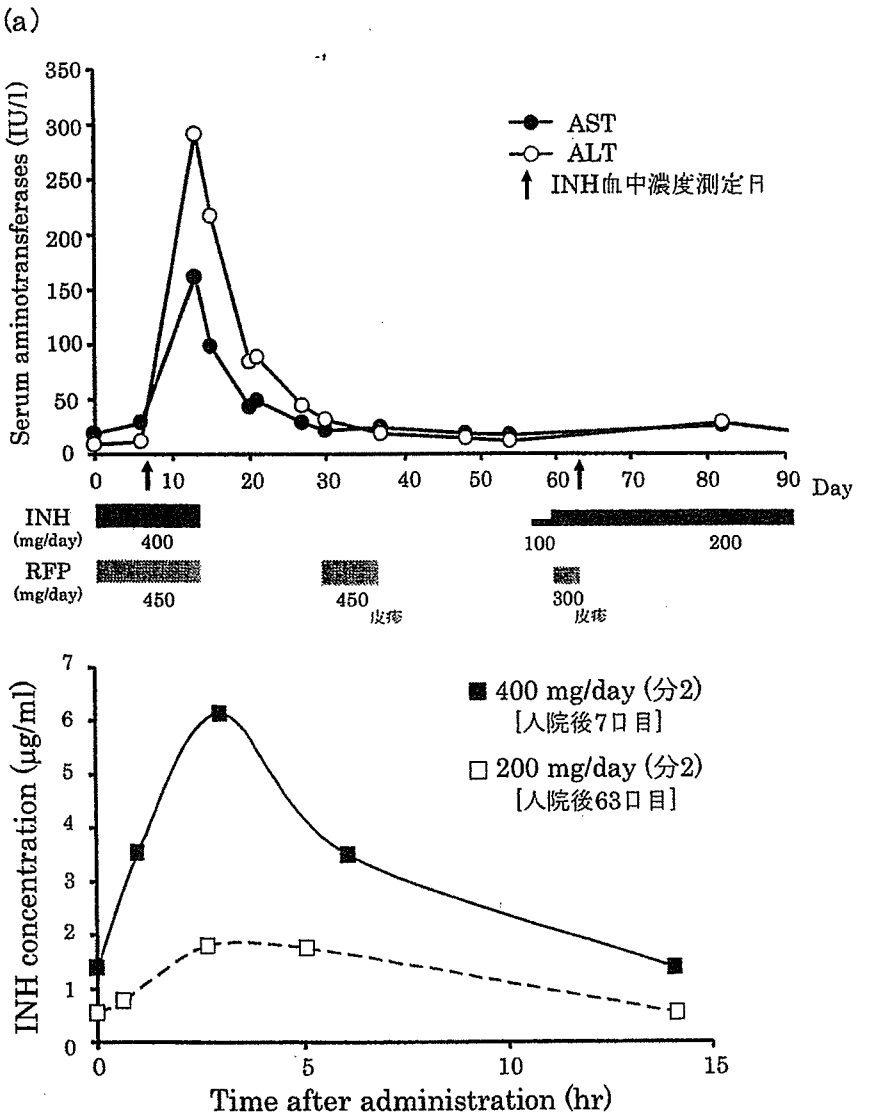

図2　症例2の臨床経過
(a) 入院後のAST, ALTの推移およびINHとRFPの投与量推移
(b) 入院7日目と入院63日目のINH血中濃度

開始した。投薬開始7日目にNAT2遺伝子多型を判定したところSA型 (*NAT2*6/*6*) であった。同時にINH血中濃度を測定したところ投与後2時間値は6.14μg/mlと高値であったが，肝機能検査値に異常が認められなかったためそのまま投薬を続けた。投薬開始14日後には血清AST 162 IU/l，ALT 292 IU/lと肝障害が発現したため，投薬を中止した。休薬後3日目より，肝障害の少ないレボフロキサシン投薬を開始した[8]。さらに，RFPの追加を試みたが薬疹が見られたため，RFPの投薬を中止した。その後，NAT2判定結果を基にINH 100mg/day (分1) より投薬を再開し，5日後に200mg/day (分2) に増量した。投薬再開後6日目における投与後1.5時間の血中濃度は1.79μg/mlとなり，肝機能検査値にも異常はみられなかった。薬疹が発現したためRFPの投薬を中止して，そのまま治療を継続したところ，肝障害の

再発をみることなく完治し退院となった。

Ⅳ 考　　察

症例1は，INHが肝障害の起因薬剤であり，通常の投与量がSA患者では過量であることを示す典型例である。結核治療薬を再導入したときに再現した肝機能検査値の上昇程度が1回目に比べて小さいことから，アレルギー性肝障害ではなく中毒性肝障害だと判断される。また，胆汁うっ滞性肝障害の特徴であるアルカリフォスファターゼやビリルビンの上昇を認めなかったことから，RFPに起因するものとは考え難い。今回，NAT2遺伝子型に基づいてINHを減量した結果，本SA患者は副作用をみることなくINHとRFPを含む化学療法を完結することができた。

INHを1日1回300mg投与した時，投与後1～2時間の血中濃度は3～5μg/mlが望ましいとされている[7]が，1日2回投与の時の有効血中濃度に関する報告はない。我々は，これまでの研究成績に基づき，INH 400mg/day（分2）とRFP 450mg/day（分1）を併用する場合には，服薬2時間後の血中INH濃度が3μg/mlを超えると肝機能障害の出現する危険性が高くなると考えている。INHの用量変更前後の血中濃度を実測した症例2では，400mg/day（分2）で中毒域に達していたINH濃度が，200mg/day（分2）にすると適切な血中濃度で推移することが確認された。これらの症例は，いずれも代謝能の低いSAであり，INH 400mg/day（分2）が過量投与となったために肝障害が引き起こされたと考えられる。

以上，NAT2遺伝子多型に基づくINHの減量が，SA患者における肝障害の再発防止に役立った実例を報告した。これらは，結核治療を未然に防ぐ結核治療の個別適正化に，NAT2遺伝子多型が極めて有用な情報となり得ることを示している。

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Controlled clinical comparison of paroxetine and fluvoxamine considering the serotonin transporter promoter polymorphism

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The present study aimed to compare the effects of two currently used selective serotonin reuptake inhibitors (SSRIs) in Japan taking the individual background in 5-HTT gene-linked polymorphic region (5HTTLPR) genotype into account. Clinical responses to paroxetine and fluvoxamine were evaluated by total and cluster depressive symptoms for 81 Japanese patients who were diagnosed with major depression. Patients with the l allele had a greater percentage reduction on the total score ($P=0.059$) and somatic anxiety items ($P=0.026$) of the 21-item Hamilton Depression Rating Scale (HAM-D) score compared to s/s genotype carriers. Paroxetine was significantly more effective than fluvoxamine in the s/s carriers, as evaluated on the percentage reduction in total score ($P=0.012$) and core ($P=0.049$) HAM-D after 4 weeks of medication, but not in the l/s carriers. These findings suggest that the genetic test may be useful in investigating the efficacy of the two SSRIs, and that normalization by the 5HTTLPR genotypes may lead to improvement of the precision of comparative analysis. *Int Clin Psychopharmacol* **20:151–156 © 2005 Lippincott Williams & Wilkins.**

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Keywords: Depression, fluvoxamine, paroxetine, serotonin transporter, SSRIs, treatment response

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Introduction

Recent advances in pharmacotherapy for affective disorders have reduced morbidity and improved depressive symptoms for millions of individuals worldwide. Many kinds of antidepressant drugs are available but selective serotonin reuptake inhibitors (SSRIs) are the first-line in the treatment of major depressive disorders (MDD) because of their efficacy and favourable side-effect profiles. However, not all patients benefit from SSRI treatment, with partial or zero responses being observed for 29–46% of MDD patients (Fava, 2000).

The inter-individual variation in clinical response to antidepressant treatment might result mainly from two factors: (i) differences in the efficacy of antidepressants and (ii) the influence of the genetic profile of an individual.

The primary mode of action for SSRIs relates to binding to the serotonin transporter (5-HTT) which inhibits its capacity to transport serotonin and modulate serotonergic activity. There are a number of differences between paroxetine and fluvoxamine, including the relative level of selectivity for inhibiting serotonin reuptake and pharmacokinetic characteristics (Jonson, 1991; Horton *et al.*, 1993; Hiemke and Hartter, 2000; Kirchheiner *et al.*, 2001). The serotonergic pathway is a candidate in the search for liability genes because SSRIs block 5-HTT as a first step of their action. It has been demonstrated that the long (l) and short (s) variants in the 5-HTT gene-linked polymorphic region (5HTTLPR) have different transcriptional efficiencies. Basal transcriptional activity of the l variant is more than twice that of the s variant, with differences in 5-HTT mRNA synthesis, 5-HTT expression and 5-HT cellular uptake (Heils *et al.*, 1996; Lesch *et al.*, 1996). In many studies, the efficacy and time of onset of SSRIs have been associated with variations in 5HTTLPR polymorphism (Smeraldi *et al.*, 1998; Pollock *et al.*, 2000; Zanardi *et al.*, 2000; Yu *et al.*, 2002).

We hypothesized that a genetic background such as 5HTTLPR would be a potential confounder in studies comparing the clinical efficacy of SSRIs. Although there are prospective studies comparing the efficacy of the SSRIs paroxetine and fluvoxamine (Ansseau *et al.*, 1994; Kevin and Feiger, 1997), the individual genetic background has not been considered in a comparative study. The frequencies of the s and l alleles in Japanese subjects

are approximately 79% and 21% (Kunugi *et al.*, 1997), respectively, which suggests that most Japanese have s/s genotypes.

In the present study, we examined the association between the 5HTTLPR polymorphism and SSRI treatment response, and compared the difference in efficacy between paroxetine and fluvoxamine in the same genotype carriers in Japanese population.

Materials and methods

Study population

The study was performed between January 2002 and January 2004 at the Department of Neuropsychiatry in Kansai Medical University. The study was approved by the ethics committee of Kansai Medical University and Osaka University. Informed consent was obtained from all participants before entry into the study. Eighty-one patients meeting DSM-IV (American Psychiatric Association, 1994) diagnosis of major depressive disorder (excluding bipolar disorder) were included in the study. All patients were Japanese and were either fresh cases or were individuals who had discontinued antidepressants for more than 10 days before participation in the study. Exclusion criteria were additional diagnoses on Axis 1 and Axis 2, pregnancy, and major medical and neurological disorders.

Study design

The trial was an open-label study with two parallel groups of patients randomly assigned to either paroxetine or fluvoxamine. Paroxetine or fluvoxamine was administered at an initial dose of 20 mg/day or 50 mg/day, respectively, in the evening. The dose could be increased up to 40 mg/day for paroxetine in the evening and 150 mg/day for fluvoxamine (50 mg in the morning and 100 mg in the evening) in the case of a lack of response. In this study, 'lack of response' was defined as a 40% or less reduction of the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967) score. Patients who had been receiving benzodiazepines for at least 10 days before entering the study were permitted to continue these agents, providing that the dose remained unchanged throughout the study period. A low-dose sleep-inducing hypnotic agent, either brotizolam or triazolam, was permitted for severe insomnia as an additional medication.

Clinical assessment

Treatment efficacy was evaluated by administering the HAM-D before and after 2, 4 and 6 weeks of antidepressant treatment. To evaluate specific cluster of depressive symptoms, HAM-D items were grouped according to the following factors: core (items 1, 2, 7, 8, 10, 13), sleep (items 4, 5, 6), activity (items 7, 8), psychic anxiety (items 9, 10), somatic anxiety (items 11, 12, 13) and delusion (items 2, 15, 20), in accordance with Serretti *et al.* (1999). Therapeutic response was evaluated by the rate of 'responders', defined as an at least 50% decrease after medication and 'remitters' were defined as subjects having a HAM-D total score of 7 or less points, and by the percentage score reduction [(baseline score − 2, 4 and 6-week score) × 100/baseline score] in the 21-item, and subcategory HAM-D scores. HAM-D score evaluations were administered at weekly intervals by trained raters (M.K. and M.W.), who were blind to genotyping. The same rater conducted admission and subsequent ratings for a patient wherever possible.

Plasma levels of paroxetine and fluvoxamine were determined by high-performance liquid chromatography after at least 2 weeks of stable dosage to confirm compliance. Those individuals who showed extremely high or low plasma concentrations were excluded from analysis (Lucca *et al.*, 1994). Genomic DNA was extracted from whole blood, target DNA was amplified by polymerase chain reaction (PCR), and 5-HTT genotype was detected according to (Deckert *et al.*, 1997).

Statistical analysis

The age, sex, and baseline total and subcategory HAM-D scores of each group were evaluated using Student's *t*-test. Wilcoxon Rank Sum test was performed with total and subcategory HAM-D scores reduction. Rates of 'responders' and 'remitters' were analysed using the chi-square test. $P < 0.05$ was considered statistically significant for all tests. Data are presented as mean ± SD.

Results

A total of 81 patients (male/female: 45/36; paroxetine/fluvoxamine: 42/39; mean ± SD age: 44.8 ± 14.9 years) were enrolled in the study. Sixty-four patients completed the 6-week study. Seventeen patients withdrew during the course of the study. The genotype distribution for the 5HTTLPR polymorphisms and the dropout rate for 81 MDD patients are shown in Table 1. The l allele carriers showed a more favourable response to SSRIs than the s/s carriers, as evaluated on the basis of total ($P = 0.058$), and somatic anxiety ($P = 0.026$) HAM-D score percentage reduction after 4 weeks of medication. There were two l/l carriers receiving paroxetine, but no l/l carrier receiving fluvoxamine. Both l/l carriers receiving paroxetine were in remission after 2 weeks of medication. Because the two patients with the l/l genotype had relatively early response and remission to SSRI, the two patients were

Table 1 Genotype distribution of the 5HTTLPR

	l/l	l/s	s/s
Entering the study	3 (3.7)	27 (33.3)	51 (63.0)
Dropout	1 (5.9)	5 (29.4)	11 (64.7)
By adverse events/unknown reasons	1/0	2/3	5/6
Completing the study	2 (3.1)	22 (34.4)	40 (62.5)

Data are *n* (%). l, long allele of the 5HTTLPR; s, short allele of the 5HTTLPR.

Table 2 **Demographic data and therapeutic response between paroxetine and fluvoxamine in the same genotype group**

5-HTTLPR genotypes	l/s			s/s		
	Paroxetine ($n=13$)	Fluvoxamine ($n=9$)	P	Paroxetine ($n=16$)	Fluvoxamine ($n=24$)	P
Sex (Male/Female)	8/5	6/3	0.817	9/7	11/13	0.519
Age	42.4 ± 12.7	45.1 ± 16.1	0.678	41.4 ± 15.8	47.6 ± 16.1	0.237
0W						
Core	8.5 ± 1.8	12.0 ± 4.0	0.034	9.8 ± 2.4	10.2 ± 2.7	0.665
Sleep	2.8 ± 1.3	2.8 ± 2.0	0.991	2.7 ± 1.7	3.3 ± 1.8	0.580
Activity	3.2 ± 1.1	4.7 ± 1.6	0.034	3.7 ± 1.2	3.7 ± 1.5	0.961
Psychic anxiety	2.3 ± 0.9	3.7 ± 1.2	0.013	3.3 ± 1.1	3.6 ± 1.4	0.345
Somatic anxiety	3.4 ± 1.7	4.7 ± 2.0	0.134	2.8 ± 1.2	4.0 ± 1.6	0.012
Delusion	2.1 ± 1.0	2.2 ± 2.3	0.862	2.0 ± 1.5	1.7 ± 1.8	0.589
HAM-D 21 total	20.0 ± 4.2	26.0 ± 7.9	0.060	21.7 ± 5.6	24.0 ± 7.7	0.270
2W	HAM-D score change (%)					
Core	16.0 ± 11.8	25.4 ± 23.0	0.157	21.4 ± 19.3	16.5 ± 19.5	0.165
Sleep	66.0 ± 34.5	80.0 ± 38.5	0.145	60.8 ± 38.5	66.4 ± 35.0	0.328
Activity	10.5 ± 14.2	23.1 ± 23.6	0.099	16.8 ± 21.9	11.2 ± 21.0	0.151
Psychic anxiety	6.4 ± 16.0	25.9 ± 27.8	0.026*	23.5 ± 26.7	25.2 ± 29.3	0.477
Somatic anxiety	21.7 ± 22.1	25.2 ± 35.6	0.457	20.3 ± 31.2	22.7 ± 30.7	0.351
Delusion	15.4 ± 29.2	29.0 ± 41.3	0.216	29.4 ± 42.1	11.8 ± 26.5	0.102
HAM-D 21 total	26.8 ± 15.9	31.3 ± 24.9	0.308	30.1 ± 19.5	26.2 ± 17.7	0.241
Responders/non-responders	1/12	2/7	0.730	2/14	3/21	0.626
Remitters/non-remitters	1/12	1/8	0.631	1/15	2/22	0.713
4W	HAM-D score change (%)					
Core	53.3 ± 29.2	52.3 ± 27.4	0.473	52.2 ± 21.9	40.4 ± 25.2	0.049*
Sleep	75.0 ± 34.5	91.3 ± 18.1	0.159	82.6 ± 31.3	77.0 ± 31.9	0.232
Activity	50.5 ± 35.0	45.1 ± 29.5	0.319	51.1 ± 20.9	36.2 ± 28.0	0.052
Psychic anxiety	44.2 ± 41.6	63.1 ± 31.2	0.146	51.8 ± 22.2	45.2 ± 30.3	0.246
Somatic anxiety	65.5 ± 35.8	54.1 ± 31.1	0.170	50.0 ± 35.5	40.4 ± 39.4	0.236
Delusion	41.7 ± 36.3	70.0 ± 44.7	0.086	58.3 ± 45.1	40.7 ± 40.0	0.125
HAM-D 21 total	59.5 ± 26.2	61.6 ± 23.5	0.395	62.0 ± 16.5	47.6 ± 23.3	0.012*
Responders/non-responders	10/3	8/1	0.878	14/2	11/13	0.020*
Remitters/non-remitters	7/6	3/6	0.607	9/7	5/19	0.021*
6W	HAM-D score change (%)					
Core	71.6 ± 30.4	58.7 ± 30.7	0.135	67.7 ± 26.3	56.0 ± 29.0	0.107
Sleep	88.9 ± 29.6	81.3 ± 53.0	0.134	92.8 ± 18.1	77.7 ± 35.4	0.076
Activity	58.8 ± 41.1	50.6 ± 30.0	0.239	75.9 ± 26.1	57.0 ± 38.0	0.068
Psychic anxiety	74.4 ± 38.3	70.6 ± 35.3	0.331	67.1 ± 26.6	55.9 ± 28.6	0.117
Somatic anxiety	77.9 ± 28.9	60.1 ± 35.3	0.127	61.5 ± 37.9	52.8 ± 36.9	0.241
Delusion	58.3 ± 41.4	70.0 ± 44.7	0.267	68.3 ± 44.8	63.2 ± 40.3	0.278
HAM-D 21 total	73.5 ± 27.6	65.7 ± 24.6	0.332	74.9 ± 20.3	60.4 ± 24.2	0.017*
Responders/non-responders	12/1	8/1	0.631	14/2	16/8	0.264
Remitters/non-remitters	9/4	4/5	0.471	12/4	9/15	0.045*

Data are mean ± SD. Responders were defined as at least 50% decrease in the Hamilton Depression Rating Scale (HAM-D) total score. Remitters were defined as subjects having a HAM-D total score of 7 or less points. HAM-D score change (%) = (baseline score − 2, 4, and 6- weeks score) × 100/baseline score.
*$P<0.05$.

excluded from the next investigation. Table 2 shows the results of 62 MDD patients except for l/l carriers in 5HTTLPR. No significant differences were found for age or sex between the two SSRIs in each 5HTTLPR genotype group. There were also no significant differences between the two SSRIs in each genotype group for the baseline total HAM-D score. Marginal significant differences were noted in somatic anxiety ($P = 0.013$) in the group of s/s carriers and in the core ($P = 0.034$) and psychic anxiety ($P = 0.026$) in the group of l/s carriers between the two SSRIs. Plasma levels (mean ± SD) of paroxetine and fluvoxamine were 36.0 ± 35.3 and 37.2 ± 35.4 ng/ml and the mean doses were 22.4 ± 5.8 and 84.8 ± 34.2 mg/day, respectively, after 4 weeks of the medication. There was no significant difference between plasma levels of the l/s and s/s genotype groups. No significant differences between the paroxetine group and fluvoxamine group were found for total HAM-D or sub-HAM-D score percentage reduction in the l/s carriers at 2, 4 and 6 weeks. The rates of 'responders' and 'remitters' of the l/s carriers were also similar between the two SSRIs at 2, 4 and 6 weeks. On the other hand, patients with the s/s genotype had a significantly better response to paroxetine than fluvoxamine, as evaluated by the total ($P = 0.012$), and core ($P = 0.049$) HAM-D score percentage reduction after 4 weeks of medication, and the total ($P = 0.017$) HAM-D score percentage reduction after 6 weeks of medication. There were more 'remitters' in the paroxetine-treated group compared to fluvoxamine after both 4 weeks ($P = 0.021$) and 6 weeks of medication ($P = 0.045$) in the s/s carriers. There were also more 'responders' in the paroxetine-treated group than the fluvoxamine group after 4 weeks of medication ($P = 0.020$) but there was no significant difference at 6 weeks ($P = 0.264$).

Eighteen patients (42.9%) in the paroxetine group and 11 patients (28.2%) in the fluvoxamine group reported at least one adverse event during the study. The most frequently reported adverse events in both groups were

Table 3 Adverse events

	Paroxetine group (n=42)	Fluvoxamine group (n=39)
Gastrointestinal symptoms	6 (14.3)	6 (15.4)
Sexual dysfunction	7 (16.7)	5 (12.8)
Psychotic symptoms	4 (9.5)	0 (0)
Vertigo	2 (4.8)	1 (2.6)
Headache	0 (0)	2 (5.3)
Other adverse events	2 (4.8)	3 (7.7)
Total	18 (42.9)	11 (28.2)

Data are n (%). Total equals the number of patients reporting at least one adverse event.

Table 4 Adverse events from 5HTTLPR perspective

	l/l (n=3)	l/s (n=27)	s/s (n=51)
Gastrointestinal symptoms	2 (66.7)	3 (11.1)	7 (13.7)
Sexual dysfunction	0 (0)	5 (18.5)	7 (13.7)
Vertigo	1 (33.3)	1 (3.7)	1 (2.0)
Headache	0 (0)	1 (3.7)	1 (2.0)
Psychotic symptoms	0 (0)	2 (7.4)	2 (3.9)
Other adverse events	1 (33.3)	0 (0)	4 (7.8)
Total	2 (66.7)	11 (40.7)	16 (31.4)

Data are n (%). l, long allele of the 5HTTLPR; s, short allele of the 5HTTLPR. Total equals the number of patients reporting at least one adverse event.

related to gastrointestinal symptoms and sexual dysfunction (Table 3). Psychotic symptoms were reported only in patients who received paroxetine, and headache was reported only in two patients who received fluvoxamine. Regarding adverse events from the 5HTTLPR perspective, two (66.7%) out of three patients with the l/l genotype, 11 (40.7%) of 27 patients with the l/s genotype, and 16 (31.4%) of 51 patients with the s/s genotype reported at least one adverse event (Table 4). Eight patients experienced adverse events that led to premature dropout from the study: six patients (14%) with paroxetine and two patients (5%) with fluvoxamine. All of these symptoms causing dropout occurred within 8 days after medication. Nine patients could not complete the 6-week study for unknown reasons. Reasons for the dropouts are summarized in Table 5.

Discussion

In this study of a Japanese sample population, we demonstrated that l allele carriers had a more favourable response to SSRI treatments than s/s carriers. The two patients with the l/l genotype achieved remission at an early date, within 2 weeks. This finding confirms previous Western reports and one Chinese report (Smeraldi *et al.*, 1998; Pollock *et al.*, 2000; Zanardi *et al.*, 2000; Yu *et al.*, 2002). Variations in 5HTTLPR polymorphism are thought to exert a major influence on the efficacy and time of onset of SSRIs in the treatment of MDD. In our study, we were able to compare clinical response to paroxetine and fluvoxamine in patients with depression, regardless of the influence of variations in the 5HTTLPR polymorphism by investigating patients with the l/s

Table 5 Adverse events leading to dropout

	Paroxetine group (n=42)	Fluvoxamine group (n=39)
Gastrointestinal symptoms	3 (7.1)	1 (2.6)
Psychotic symptoms	2 (4.8)	0 (0)
Dyspnea	0 (0)	1 (2.6)
Memory failure	1 (2.4)	0 (0)
Unknown reasons	5 (11.9)	4 (10.3)
Total	11 (26.2)	6 (15.4)

Data are n (%).

genotype and the s/s genotype of 5HTTLPR. The l/s genotype carriers for both the paroxetine group and the fluvoxamine group had an approximately 60% reduction in total HAM-D score after 4 weeks of medication. There were no significant differences between the paroxetine group and the fluvoxamine group for the total HAM-D and sub-HAM-D score percentage reduction, and the rates of 'responders' and 'remitters' at 2, 4 and 6 weeks in patients with the l/s genotype.

Interestingly, patients with the s/s genotype receiving paroxetine had a significantly better response than those receiving fluvoxamine after 4 or 6 weeks of medication. Patients treated with paroxetine reached an approximately 60% reduction in total HAM-D score after 4 weeks of medication, but patients treated with fluvoxamine did not reach the same percentage reduction until 6 weeks of medication. That is, l/s genotype carriers had a better response than s/s genotype carriers to fluvoxamine, although most of the patients with paroxetine had a good response regardless of genotype.

Concerning the adverse events, the present study did not find significant differences between the two drugs in the overall number of patients reporting adverse events ($P = 0.246$). In both groups, the adverse events most frequently reported were gastrointestinal symptoms and sexual dysfunction. These results reflect the characteristic profile of adverse events seen with SSRIs (Goldstein and Goodnick, 1998). The results showed no significant differences between the two drugs in the overall number of patients ($P = 0.282$) and the dropout rate does not appear to have been related to the dosage of SSRIs because all eight patients dropped out of the study during the initial dose period before dose increase was permitted. The relationship between adverse events and 5HTTLPR genotypes remains to be clarified due to the small number of patients with the l/l genotype, and the similar rate of adverse events between l/s and s/s carriers. There was no association between the number of dropouts and the genotype.

The plasma levels of the SSRIs were relatively low compared to previous studies (Pollock *et al.*, 2000; Yoshida *et al.*, 2002). This is probably a consequence of the dose

escalation protocol. The mean doses of paroxetine (22.4 ± 5.8 mg/day) and fluvoxamine (84.8 ± 34.2 mg/day) after 4 weeks of medication were appropriate considering their equivalent dosage as described in some previous reports (Fava and Davidson, 1996; Ali, 1998). Furthermore, plasma levels were unlikely to be associated with the rates of 'responders' or genotype variants of 5HTTLPR.

Our study was an open-label design with a consequent risk of bias, especially in the clinical evaluation. However, the main focus of this study was genetic background as a potential confounder in the clinical efficacy of SSRIs, and it was hoped that experienced raters would be relatively free from bias.

To our knowledge, this study is the first trial to compare SSRIs in relation to a genetic factor, 5HTTLPR. Previous prospective studies have demonstrated no significant differences in clinical response to treatment of depression between paroxetine and fluvoxamine (Ansseau *et al.*, 1994; Kevin and Feiger, 1997). Our finding of the earlier efficacy of paroxetine compared to fluvoxamine is not consistent with these previous studies. There are two possible explanations for the different findings. First, compared with the Japanese, Chinese and Korean populations, the l allele frequency in Caucasian American populations is much higher (Kunugi *et al.*, 1997; Smeraldi *et al.*, 1998; Pollock *et al.*, 2000; Yu *et al.*, 2002). All the previous clinical studies were carried out in Caucasian American populations. Therefore, most of the patients in those studies may be expected to be l/l or l/s genotype carriers. The present study found no significant differences in clinical responses between paroxetine and fluvoxamine in patients with the l/s genotype. If the genotype distribution among Japanese were similar to that of Caucasian American populations, the results of this study might have been similar to findings in the previous clinical studies. Second, the imbalance of 5HTTLPR variants between the two SSRIs might have led to the negative results in the previous studies because no genetic variants were considered.

We hypothesize that the reasons for a better response to paroxetine than fluvoxamine in the s/s genotype carriers, and the good response to both SSRIs in the l/s genotype carriers, are related to the differences in the potential to inhibit serotonin (5-HT) uptake of each SSRI. Paroxetine ($K_i = 0.1 \pm 0.01$) is a more potent 5-HT reuptake inhibitor than fluvoxamine ($K = 3.6 \pm 0.9$) in the human brain (Horton *et al.*, 1993). In terms of transcriptional activity, the l variant more than twice as active as the s variant, with differences in 5-HTT mRNA synthesis, 5-HTT expression and 5-HT cellular uptake (Heils *et al.*, 1996; Lesch *et al.*, 1996). Overall, the l/s carriers appeared to have a better response to SSRIs than the s/s carriers, which was consistent with the previous reports in Western and Chinese subjects. Thus, paroxetine was effective in patients regardless of 5HTTLPR variants, even in the s/s genotype carriers, with a high potential to inhibit 5-HT reuptake. However, fluvoxamine led to a different response between l/s and s/s carriers because of its lower potential to inhibit 5-HT than paroxetine.

We have presented a strategy for clinical comparisons that are independent of any possible effects of 5-HTTLPR genetic variants. However, many different genes might modulate therapeutic antidepressant effects (Serretti and Artioli, 2004) and further investigation of other possible genetic factors contributing to the effect of SSRIs is necessary. Finally, studies with a larger number of subjects are needed to confirm the effects on clinical response to SSRIs.

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Regular Article

The Frequency of Candidate Alleles for CYP2D6 Genotyping in the Japanese Population with an Additional Respect to the −1584C to G Substitution

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Summary: The −1584C/G single nucleotide polymorphism (SNP) in the promoter region of *CYP2D6* was suggested to have the potential to influence CYP2D6 activity. In this report, we demonstrated the frequencies of −1584C to G substitution-related alleles, such as *CYP2D6*2*, *CYP2D6*21*, *CYP2D6*35* and *CYP2D6*41*, in the Japanese population. The frequencies of *CYP2D6*2*, **41* and **21* were 0.102, 0.026 and 0.005, respectively. We also showed a relationship between the SNP and other common alleles, *CYP2D6*4*, **5*, **10*, **14* and **18*. Interestingly, the SNP was detected in all three subjects carrying *CYP2D6*14*. This finding suggests the −1584G is included in the *CYP2D6*14* allele, which is a null-allele characteristic to the Japanese population. This report presents practical information on *CYP2D6* alleles that should be considered in the pharmacokinetic study of CYP2D6 substrates in the Japanese population.

Key words: CYP2D6; frequency; *CYP2D6*41*; *CYP2D6*35*; *CYP2D6*21*; Japanese

Introduction

CYP2D6 metabolizes many clinically important drugs including antidepressants, neuroleptics, β-blockers and antiarrhythmics.[1] There is a wide interethnic variation in the frequency of the *CYP2D6* genotypes. In a previous study, we reported the frequencies of *CYP2D6* genotypes in a Japanese population.[2] However, some alleles have since been reported which were not included in our study.

In the present study, we focused on the −1584C/G substitution, because the subjects with −1584G were suggested to have higher CYP2D6 enzyme activity than those with −1584C.[3] The locations of the mutations in common *CYP2D6* alleles are displayed in **Fig. 1** according to the CYP nomenclature committee (http://www.imm.ki.se/CYPalleles/cyp2d6.htm), with some modifications. Since the single nucleotide polymorphism (SNP) in −1584 seems to be mainly associated with *CYP2D6*2*, the committee has designated *CYP2D6*2* with −1584G as *CYP2D6*2A* and *CYP2D6*2* with −1584C as *CYP2D6*41*, according to Zanger *et al.*[3] Recent studies have suggested that individuals with *CYP2D6*41* have lower CYP2D6 enzymatic activity *in vivo* than those with *CYP2D6*2A*,[4] possibly as a consequence of lower expression of CYP2D6 protein.[3] The −1584G substitution is also found in the *CYP2D6*35* allele, which has a 31G to A substitution in addition to the SNPs of the *CYP2D6*2* allele, but does not have the gene conversion mutation from *CYP2D7* in intron 1 of *CYP2D6*. Although the allele has been identified in many duplication-negative "Ultra rapid" metabolizers,[5] the activity of recombinant CYP2D6.35 is comparable to that of the wild-type.[6] Furthermore, the −1584G is found in the *CYP2D6*21* allele. However, these effective alleles have been classified as *CYP2D6*2* according to previous detection criteria. Therefore, the consideration of these alleles may result in a better understanding of the phenotype-genotype correlation.

In view of the importance of the −1584C/G substitution-related alleles in the Japanese population, we examined the frequencies of *CYP2D6*41* and **35*, possibly included in *CYP2D6*2*, **21* and other alleles in the present study.

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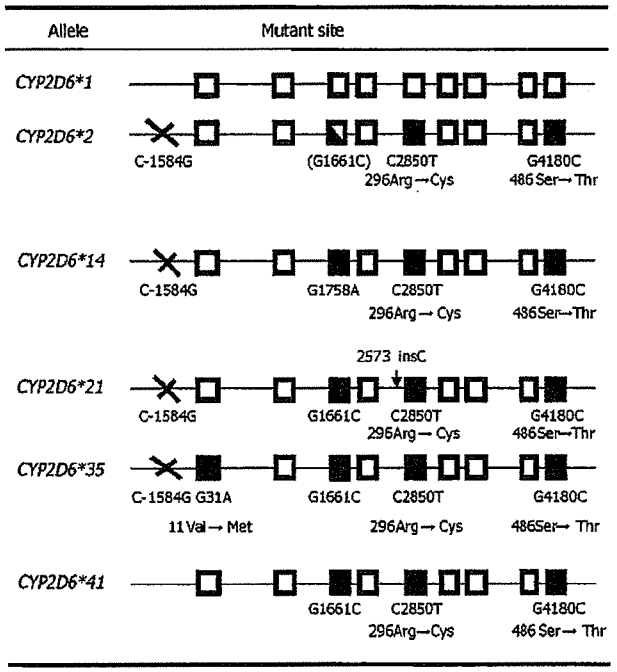

Fig. 1. Schematic representation of the position of mutations on the *CYP2D6* allele
The nature of the mutations and the positions where nucleotide changes occur are indicated. The structures are illustrated with closed boxes (exon containing at least one mutation) and open boxes (exon with wild-type sequence). The position of mutations is in accordance with the numbering used in the CYP2D6 allele nomenclature (http://www.imm.ki.se/CYPalleles/cyp2d6.htm).

Methods

All subjects in the present study were healthy males who had enrolled for several clinical trials. We regenotyped 206 subjects whose data had previously been reported.[2] An additional 79 subjects were newly included, and consequently a total of 285 subjects were examined for the *CYP2D6* genotype. This study was approved by the ethic committees of Osaka University. Written informed consent for genetic analysis was obtained from all subjects. Genomic DNA was isolated from peripheral lymphocytes from each subject.

In our previous study, each *CYP2D6* genotype was defined from the results of PCR-RFLP methods for 100C/T, 1846G/A, 2850C/T and 4180G/C[2] and from the results of *Xba*I and *Eco*RI-RFLP methods or the long-PCR method for the *CYP2D6*5* allele.[7,8]

A PCR-RFLP method for the −1584C to G substitution was developed for it's direct detection. A mismatch PCR-RFLP assay was based on a recognition site for the restriction enzyme *Sma*I by utilizing an oligonucleotide mismatch primer (CYP2D6*41 Mut.R; 5′-TTG TAT TTT TTG TAG AGC CC -3′; the letter with the underline is the mismatch nucleotide). This antisense primer introduces a *Sma*I recognition site by extension when a cytosine is present at the first base. In contrast, in the present of a guanine no recognition site for *Sma*I is introduced. The PCR reaction was carried out in a 25-microl reaction volume containing 1.5 mM $MgCl_2$, 10 mM Tris/HCl (pH 8.3), 0.2 mM of each dNTP, 10 pmol of each primer (CYP2D6*41F; 5′-TTC AAG ACC AGC CTG GAC AAC -3′ and CYP2D6*41Mut.R), 30 ng genomic DNA and 1U AmpliTaqGold™DNA polymerase (Applied Biosystems). An initial denaturation step at 95°C for 10 min was followed by 35 cycles of 95°C for 30 sec, 60°C for 1 min and 72°C for 30 sec, and a final elongation step of 72°C for 5 min. PCR products were then digested with *Sma*I and separated on 4% agarose gel. Product from the −1584C allele was not cut and remained 53 bp in length, while the −1584G allele was cut into 32 and 21 bp.

The 31G/A substitution was detected to find the *CYP2D6*35* allele according to Lovlie *et al.*[5] In brief, a 341-bp fragment covering the SNP was amplified by a set of primers (CYP-511; 5′-AGG TTC ACT CAC AGC AGA GGG-3′ and CYP-518; 5′-CCT GGT CGA AGC AGT ATG GTG-3′), then digested with *Nla*III. The wildtype (31G) was cut into 305 and 36 bp fragments, while the mutant (31A) allele generated 193, 112 and 36 bp fragments. The PCR reaction product was purified and directly sequenced by DNA sequencer ABI 310 using dye-terminater chemistry to confirm the nucleotide substitution and search for other related substitutions. Then, to determine the haplotype, the fragment was cloned using the TOPO TA cloning kit (Invitrogen) according to the manufacturer's instructions. Additionally, after genotyping, some clones with insertions were randomly selected and directly sequenced.

The presence of the *CYP2D6*21* allele was determined by an allele specific PCR method using genotyping kit "-SNP Typing Kit-Cytochrome P450 2D6*21 (2573C insert)" (TOYOBO, Japan) according to the manufacturer's instructions.

Results

The −1584G alleles were detected in the subjects previously determined as having the *CYP2D6*2* genotype. The frequency of −1584G substitution in the Japanese population was estimated to be 0.114 and *CYP2D6*41* allelic frequency 0.026 (**Table 1**).

Interestingly, there were four unusual subjects among all of the subjects with the −1584G allele. One subject was heterozygous for −1584G and had substitutions classified as *CYP2D6*1/*10*. Two subjects were also heterozygous for −1584G although both had *CYP2D6*1/*14*. The last was homozygous for −1584G in spite of *CYP2D6*2/*14* carrier according to the previous classification.

The insertion of cytosine at 2573 was detected in three

Table 1. The allele frequency of *CYP2D6* in Japanese compared with frequencies in other ethnic populations

(Number of subjects)	Allele frequency (95% confidential interval; lower/upper)				
	−1584C	−1584G			
	*CYP2D6*41*	*CYP2D6*2*	*CYP2D6*2×n*	*CYP2D6*21*	*CYP2D6*35*
Japanese (n=285)	0.026 (0.016/0.043)	0.102 (0.082/0.132)	—#	0.005 (0.002/0.015)	0.000 (0.000/0.005)
Caucasian (n=203)[9]	0.094	0.172	—	—	0.074
Caucasian (n=206)[10]	0.102	0.187	0.010	—	—
African-American (n=193)[9]	0.114	0.047	—	—	0.010

Allelic frequency of *CYP2D6*2*×n and *CYP2D6*1*×n was reported to be 0.01 (n=206)[2].

subjects, which indicates that they had the *CYP2D6*21* allele. Consistent with the allelic information on *CYP2D6*21*, the heterozygous for −1584G was detected from all three. Therefore, one subject was genotyped as *CYP2D6*10/*21* and the other two as *CYP2D6*1/*21*. As a result, the frequency of *CYP2D6*21* allele was estimated to be 0.005 in the present study.

One subject was found to be heterozygous for the 31G to A substitution with *CYP2D6*1/*10* according to the previous classification. In the same subject, we also detected an allele carrying 100T and 31A by subcloning analysis. However, the allelic information on *CYP2D6*35* showed no link between the 31A and the 100T. Therefore, we did not consider the subject to be a *CYP2D6*35* carrier, but provisionally as a *CYP2D6*1/*10* carrier, which may be a new type of allele related to *CYP2D6*10* with 31A.

Discussion

In the past, we have classified *CYP2D6*2* as the wild-type enzymic status according to the phenotype test. However, we have, on occasion, encountered subjects with a lower enzyme activity than that expected of the *CYP2D6*2* genotype. In the Caucasian population, subjects with −1584G substitutions including *CYP2D6*2* have been reported to achieve higher CYP2D6 activity *in vivo* than those with −1584C, possibly as a consequence of greater expression of the CYP2D6 protein.[3,4] In addition, irrespective of the genotype, individuals with −1584C/C expressed less CYP2D6 protein than individuals with at least one −1584G allele.[3] There has been no study concerning the −1584C/G substitution in the Japanese population.

In the present study, we confirmed that the −1584G allele was also detected in the Japanese population although its frequency is lower than in other ethnic groups (**Table 1**). Therefore, our results did not disprove the presence of a possible inconsistency between the phenotype and genotype of CYP2D6 found in several previous studies for Japanese, regarding the effect of this SNP on the activity of CYP2D6.

We also examined the 31G to A substitution for presence of *CYP2D6*35* as a related-allele with the −1584C/G substitution. In this study, the heterozygous for 31A was found in only one subject with *CYP2D6*1/*10*. We subcloned the sample and detected the **10* allele with the 31A mutation as a minor novel allele. This was not regarded as *CYP2D6*35*. Although the 31G/A substitution is not likely to influence CYP2D6 enzyme activity and protein expression level *in vitro*,[6] the *CYP2D6*35* allele is found in many ultra rapid metabolizers.[5,9] The present findings suggest that *CYP2D6*35* allele frequency in the Japanese population is very low, compared with some other ethnic populations, which is consistent with the fact that the ultra rapid metabolizers are rare in Japanese[2] and occur in less than about 10% of Caucasians.

The result from four unusual subjects suggests that the −1584G substitution might be associated with *CYP2D6*14* and possibly *CYP2D6*1* or **10* in addition to *CYP2D6*2*, **21* and **35*. Zanger *et al.* also mentioned that one subject with *CYP2D6*1/*1* possessing −1584G was detected in their study,[3] supporting the present result. On the other hand, Gaedigk *et al.* suggested that CYP2D6 poor metabolizers (PMs) can be detected by the selection of −1584G carriers, as −1584G is exclusively linked to functional allelic variants.[9] Their study seems to be of value for the simple clinical use of the SNP information. However, the connection between the **14* allele and the −1584G substitution was found in the present study in addition to **21*. Since *CYP2D6*14* is a null-allele characteristic to the Japanese population, these connections may limit the genotyping strategy to Japanese.

In conclusion, we examined the distribution of −1584C/G substitutions in the Japanese population mainly associated with *CYP2D6*2*, and found the frequency showed interethnic variation. Since the −1584C/G substitution-related alleles potentially effect CYP2D6 enzyme activity, these alleles should be consi-

dered in *CYP2D6* genotyping. The present study found that the −1584C/G substitution has a potential link to other alleles, and further studies on the related alleles in various ethnic populations are necessary.

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フォーラム

遺伝子多型情報に基づく投与指針作成に向けて—CYP2C9—

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東純一[*1]

1．はじめに

薬の応答性には大きな個体差が存在し，同じ薬を同量服用しても，効果や副作用が大きく異なることがある．このような個体差を考慮した個別化医療の実現は，より安全で有効な治療を可能にするうえで重要である．

薬物応答性の個体差の原因の1つに，薬物代謝酵素であるチトクロムP450（CYP450）の遺伝子多型がある．CYP分子種の中で，CYP2Cファミリーは CYPで代謝される医薬品の約20%の代謝に関わっており，*CYP2C9*，*CYP2C19* 遺伝子多型の医薬品に及ぼす影響が数多く報告されている．個別化医療の実現には遺伝子多型の情報の活用が有効であると考えられるが，臨床試験のデザイン，すなわち対象者や治療法などの違いにより，エビデンスが一致しないことも多く，それらの報告を臨床現場へそのままの形で応用することは難しいのが現状である．

本稿では，*CYP2C9* 遺伝子多型について，得られているエビデンスを系統的に整理し，独自の視点で遺伝子多型情報の臨床応用の可能性を論ずる．

2．CYP2C9の遺伝子多型と薬物

CYP2C9には，**2* から **23* までの多型が報告されている(2005年6月20日更新)[1]．欧米人では**2*，**3* の頻度がそれぞれ10%前後，3～8%程度であるのに対し，日本人では，*CYP2C9*2* および **4* から **23* は出現頻度が非常に低いか，もしくは詳細に検討されておらず，エビデンスの観点からアレル頻度で約2%存在する**3* を考慮することが重要である．

CYP2C9はワーファリン（warfarin）やフェニトイン（phenytoin）といった治療域が狭い薬物をはじめ，スルホニル尿素（sulfonylurea，SU），ロサルタン（losartan），フルバスタチン（fluvastatin），ジクロフェナク（diclofenac）などの非ステロイド性抗炎症薬（nonsteroidal anti-inflammatory drugs，NSAIDs）の代謝に関わっている．

以下に，これらの薬物について，*CYP2C9*3* 保有者に対する投与量やその反応性など臨床応用の際に留意すべき点を整理した．

1）ワーファリン（warfarin）

ワーファリンは治療域が狭いうえに，薬に対する感受性の個人差が大きいことが知られている．この個人差の原因の1つとして，ワーファリンの主たる代謝を担うCYP2C9の遺伝子多型が挙げられる[2]．

これまでの報告の多くは，ワーファリン血中濃度が定常状態に到達後の維持量について検討したものである．日本人の場合，*CYP2C9*1/*3* を有する患者の維持量は**1/*1* の患者の約50%，*CYP2C9*3/*3* を有する患者（n=1）では**1/*1* の患者の約13%であると報告されている[3,4]．欧米人では *CYP2C9*1/*3* の維持量が**1/*1* の約80%という報告もあり[4,5]，人種差の存在が示唆される．

一方，目標international normalized ratio（INR）を2～3に設定した治療におけるワーファリン導入期では，*CYP2C9*3* を有する患者の投与量が**1/*1* の患者の投与量に比して60%程度に減少している(Fig. 1-A)[6]．

ワーファリン服用による出血の副作用は，維持期よりも導入期（3カ月以内）で1.75倍起こりやすいと報告されている[7]．その導入期に，*CYP2C9* 遺伝子多型が副作用のリスクファクターになると報告されている．しかし，維持期における *CYP2C9* 多型のリスクについては見解が分かれており，多型がリスクファクターになる[8]という報告と関係ない[5]という両方の見解が示されている．関係ないとする後者の論文ではINRのみによるリスク評価にとどまり，実際の出血

Key words：CYP2C9, warfarin, phenytoin, polymorphism, individualized medicine
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頻度については述べられていない点を考慮しなければならない．また，副作用の出現頻度と多型のリスク評価は，INR等のモニター間隔にも依存すると考えられる．

導入時における多型による副作用のリスクについての論文を引用し列挙する．

例1）66歳白人男性（73 kg）に2日間，ワーファリン10 mgを投与したところ，INRが9.7まで上昇し，最終的に1.0 mg/2 dayの維持量で落ち着いた．この患者の*CYP2C9*遺伝子型は**3/*3*であった[9]．

例2）ワーファリン維持量が1.5 mg/day以下で落ち着いた低用量群では，ワーファリン導入時にINR>4となる患者の割合がコントロール群（無作為抽出群）の3.2倍であり，この群では*CYP2C9*多型保有者の割合が高かった[10]．

例3）虚血性心疾患のリスクが高い男性233人に対し，目標INRを1.5に設定しワーファリンを初回投与量2.5 mgで予防投与を開始した際，*CYP2C9*3/*3*の患者の2例中2例ともに，ワーファリン投与開始3カ月以内に出血の副作用が観察された[11]．

例4）185人の患者を対象とした治療において，*CYP2C9*の多型を有する患者では，出血の発現率が**1/*1*より高く，とくに治療開始初期（3カ月）でその傾向は顕著であった[8]．

例5）ワーファリン導入時（24日以内）に白人患者125人中，INR>3となる患者の割合は*CYP2C9*3*を有する患者では67%（14/21）であり，**1/*1*の33%（25/75）に比して2倍であった[6]．

出版バイアスの存在を考慮する必要はあるが，上記のように，*CYP2C9*3*を有する患者にはとくに慎重に投与する必要がある．

さらに，高齢者では維持量が少ないと報告されている．高齢（66歳以上）かつ*CYP2C9*3*を有する患者のワーファリン維持量は，65歳以下で**1/*1*の患者の約28%であり[12]，多型とともに年齢を考慮した投与が必要と考えられる．

日本人と欧米人の常用量に乖離があり（*CYP2C9 *1/*1*同士で比較した場合：日本人3.4～4 mg/day[3,13]，欧米人5.0～6.5 mg/day[5,8,12]），また，治療時の目標INRも欧米人が2～3であるのに対し日本人が1.5～2.5と，日本人のほうが低い[4,14]．その原因として，日本人と欧米人の体格差とともに，血液凝固因子や[13,15]やワーファリンの標的分子であるvitamin K epoxide reductase遺伝子（*VKORC1*）の多型[16~18]が報告されている．これらの多型には人種差があり，アジア人ではワーファリンの感受性が高くなるアレルが欧米人と比較して大多数である．上記の例は，ほとんどが白人を対象とした試験であることを考慮する必要があり，ワーファリン量の絶対値を単純に日本人と比較することはできない．しかし，薬物代謝酵素*CYP2C9*多型の影響により血中濃度が変動することは明白であり，多型の影響がワーファリン量に与える相対的な影響は参考にすべきであると考えられる．

日本人の大多数である**1/*1*に比して*CYP2C9*3*を有する患者にワーファリンを投与する際には注意を要する．とくに導入初期（1～3カ月）の出血傾向には注意したい．

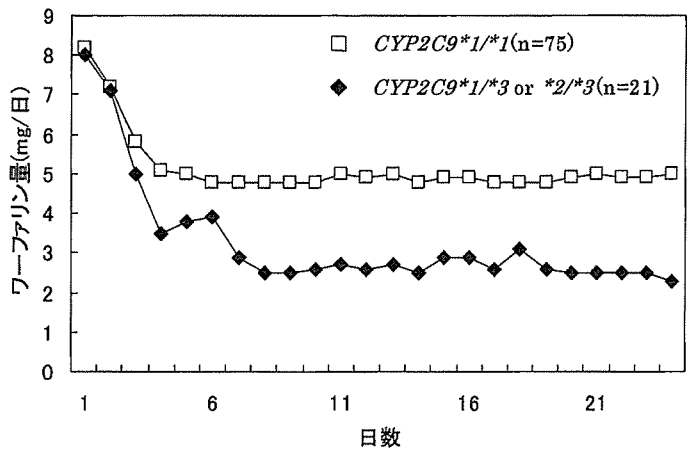
2）フェニトイン（phenytoin）

フェニトインは，治療域の範囲内で飽和による非線形的な体内動態を示すため，少量の投与量の増加が容易に中毒濃度に達する危険がある．この現象は*CYP2C9*多型により影響を受けることから，さらに注意を要する．

欧米人健康成人に対してフェニトイン100 mgを単回経口投与したところ，*CYP2C9*3/*3*を有する者（n=1）では血中濃度下面積が4.3倍に上昇し，半減期が3.3倍に延長，クリアランスは20%程度にまで低下している（Fig. 1-B）[19]．てんかん患者においても*CYP2C9*遺伝子多型の影響は認められ，Table 1には*CYP2C9*の遺伝子多型とフェニトインの投与量および血中濃度の報告をまとめて示した．日本人のてんかん患者におけるフェニトイン維持量は，**1/*3*では**1/*1*の60%程度である[20]．欧米人においても*CYP2C9*3*を有する患者のフェニトイン維持量は60～70%程度になっていた[21]．フェニトインの至適濃度は5～20 μg/mLであるが[22]，中毒濃度（30 μg/mL）を超えた患者の投与量を比較すると，*CYP2C9*1/*3*の患者では**1/*1*の患者の53～76%程度であった[23]．別のグループの報告でも，*CYP2C9*1/*3*の患者にフェニトイン4.2 mg/kg/day投与時の血中濃度は32.6 μg/mLに達していた[24]．標準投与量は5～8 mg/kg/dayとされている[22]ものの，フェニトインの投与量には乖離があり（Table 1），施設における治療法や併用薬などの違いが影響している可能性がある．しかし，遺伝子多型間の相対的な違いは明らかであり，欧米人でも同様のデータが得られていることからも，その妥当性が示唆

A：ワーファリン導入段階における遺伝子型別の投与量（イタリア人における検討）

（文献 6）より改変して引用）



B：フェニトイン 100 mg 単回経口投与時の血中濃度

（文献 19）より改変して引用）

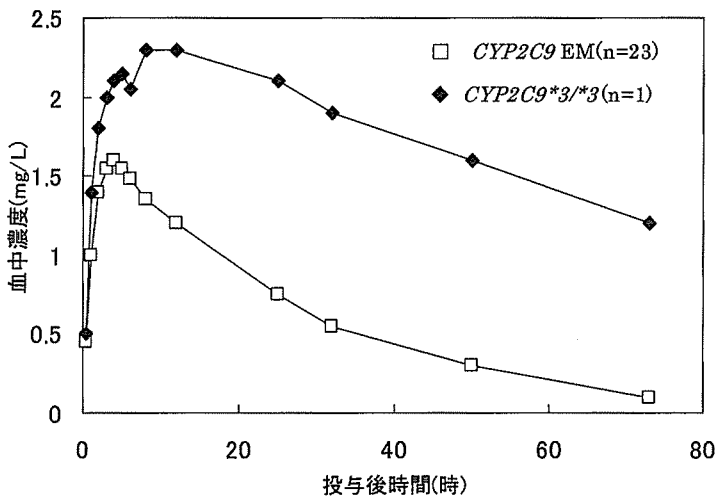


Fig. 1 *CYP2C9* 遺伝子多型による薬物への影響

Table 1　フェニトインの投与量-血中濃度関係に及ぼす *CYP2C9* 遺伝子多型の影響

	対象	年齢（歳）	CYP2C9	CYP2C19[c]	n	平均投与量（mg/kg/day）	血中濃度（μg/mL）	文献
	標準					5.0～8.0	5～20	22
日本人	てんかん患者[a]	18～76				Mean±SD	定常濃度	
			*1/*1	Wild	52	3.58±1.48	6.6±4.8	20
			*1/*3	—	3	2.09±0.17	4.7±2.0	
	てんかん患者（ケースレポート）	40	*1/*3	Hetero	1	4.17	32.6	24
	てんかん患者	1～33	全被験者		44	5.18		23
			*1/*1	Wild	1	8.6		
			*1/*1	Wild	1	7.1	>30	
			*1/*1	Homo	1	6.0	（中毒濃度）	
			*1/*3	Hetero	1	4.6		
欧米人	てんかん患者（オランダ人）[b]	16～74				(mg/day) [range]	定常濃度 [range]	
			*1/*1	—	37	287 [75～425]	15.8 [2.2～36.4]	21
			*1/*3	—	9	19 [150～275]	13.8 [5.1～18.2]	

a：1カ月間投与量が安定している患者
b：6カ月以上フェニトインを服用し，維持量が安定している患者
c：(—)：non-determined（検討されていない）

Table 2 CYP2C9 基質薬物への多型の影響

薬物		対象（人種）	*1/*1 と比較したときの影響		備考
			薬物動態学的作用	薬力学的作用	
スルホニル尿素	Tolbutamide	健康成人（韓国人[27]）（欧米人[28~30]）	*1/*3 CL 48～75% AUC 約2倍[27~29] *3/*3 CL 16～21%[28,30]	血糖降下作用 ・*1/*3 作用増強※[27] ・差なし[28,29]	※100 g グルコース負荷時の血糖上昇作用 1/2
	Glibenclamide	健康成人（欧米人）	*3 保有者 AUC 2.8倍[31] *1/*3 CL 72%[32] *3/*3 CL 42%[32]	血糖降下作用 差なし[31,32]	
	Glimepiride	健康成人（欧米人）	*3 保有者 AUC 2.7倍[31]	血糖降下作用 差なし[31]	
サルタン系降圧薬	Losartan	健康成人（欧米人[33]）（日本人[26]）	Losartan → PK パラメータ差なし *1/*3 代謝物 C_{max} 40% 代謝比 1.7倍 *3/*3 代謝比 30倍[33]	降圧作用 ・*1/*3 で効果減弱 ・作用時間の短縮[26]	代謝物が活性体
	Candesartan	高齢患者（日本人1例）	*1/*3 CL 48% （ただし比較した対象は一般の高齢患者の平均[34]）	過度の降圧作用[34]	1例のみの症例報告
NSAIDs	Diclofenac	健康成人（日本人[35]）（欧米人[36]）	CL，AUC など差なし[35] *1/*3 尿中代謝比 1.3倍[36]	—	
	Ibuprofen	健康成人（欧米人）	*1/*3 CL 約70% AUC 1.8倍 *3/*3 CL 16～25% AUC 2.7倍[37]	—	*CYP2C8* 多型の影響も示唆される
	Flurbiprofen	健康成人（欧米人）	*1/*3 CL 56% AUC 1.7倍[38]	—	
	Tenoxicam	健康成人（ブラジル人）	*1/*3 CL 34% AUC 1.7倍[39]	—	
その他	Fluvastatin	健康成人（欧米人）	*1/*3 AUC 1.3倍 *3/*3 AUC 3倍[40]	コレステロール低下作用に差なし[40]	
	Torasemide	健康成人（欧米人）	*1/*3 AUC 1.5倍 *3/*3 AUC 2.8倍[41]	尿量に差なし Na^+ と Cl^- 排泄がわずかに増加[41]	
	Nateglinide	健康成人（欧米人）	*1/*3 CL 87% AUC 1.7倍 *3/*3 CL 52% AUC 2.0倍[42]	血糖降下作用 差なし[42]	

—：記述がない
CL：クリアランス，clearance
AUC：血中濃度下面積，area under the curve

される．その他，フェニトインの標的分子であるナトリウムイオンチャネルの遺伝子多型がフェニトイン量に関係していたとの報告[25]もあり，同一の *CYP2C9* 遺伝子型での個人差の解明が進むと期待される．

3）その他

スルホニル尿素系経口血糖降下薬，サルタン系降圧薬，NSAIDs などと *CYP2C9* 遺伝子多型との関係について報告されているものを Table 2 にまとめた．サルタン系降圧薬のうちロサルタンは，CYP2C9 により代謝活性化されるため，*CYP2C9* 多型保有者で降圧作用が弱くなることに注意が必要である[26]．これらの薬物では，対象が健康成人にほぼ限定されている