Common mutant alleles of *CYP2D6* causing the defect of *CYP2D6* enzyme activity in a Japanese population

CYP2D6, an isoform of cytochrome P450 catalysing more than 50 clinically important drugs, is highly polymorphic. There are important interethnic differences in the frequencies of poor metabolizers (PM). In our previous study, we reported the frequencies of seven mutated alleles, *CYP2D6**1x2, *2, *2x2, *5, *10, *10x2 and *14 in 162 Japanese subjects [1, 2]. Based on the results of that study, the frequency of *CYP2D6* PM in the Japanese population was estimated to be 0.71% (95% confidence interval (CI) 0.56, 0.89). However, this frequency is not consistent with the frequency of this PM estimated to be 0.84% (95% CI 0.68, 1.04) by *in vivo* studies, suggesting that other mutations exist in the *CYP2D6* gene in the Japanese population [3].

Recently, it has been reported that *CYP2D6**21, in which one nucleotide (2573C) in exon 5 has been inserted, was responsible for the *CYP2D6* PM in the Japanese [4]. Furthermore, an individual heterozygous for *CYP2D6**36 has been reported to have a metabolic ratio that was just below the antinode for debrisoquine [5]. There is a possibility that *CYP2D6**21 or *36 may be included in our Japanese subjects. Therefore, we carried out additional analysis for the frequencies of *CYP2D6**21 and *36 variants in the 162 Japanese subjects.

Unrelated healthy Japanese ($n = 162$; 95 males and 67 females) were recruited for the genotyping study. All procedures were approved by the local Institutional Review Board, and all participants provided informed consent [1]. Genotyping for the *CYP2D6**21 allele was performed by allele-specific polymerase chain reaction

(PCR) as described by Chida *et al.* [4]. In order to detect *CYP2D6**36, assays for the mutations 100C/T and 4180G/C were performed by PCR-restriction fragment length polymorphism [1], and gene conversion in exon 9 derived from *CYP2D7* was confirmed by DNA sequencing [6].

In the present study, we detected *CYP2D6**21 (in one subject) and *CYP2D6**36 (in three subjects), and their frequencies were 0.3% and 0.9%, respectively (Table 1). To our knowledge, this is the first report on the frequency of *CYP2D6**36 in a Japanese population. The 17 different genotypes presented in our subjects (i.e. *CYP2D6**1/*1, *1/*2, *1x2/*2, *1/*2x2, *1/*5, *1/*10, *1/*10x2, *1/*14, *1/*36, *2/*5, *2/*10, *2/*14, *5/*10, *5/*21, *10/*10, *10/*10X2 and *10/*14) and the frequencies of all the genotypes observed in the present study were within the 95% CI estimated by the Hardy–Weinberg equation (data not shown).

Table 1 Frequencies of *CYP2D6* mutant alleles in 162 Japanese subjects.

Mutant allele	n	%	95% CI†
*1	129	39.8	34.6, 45.2
*1x2	1	0.3	0.1, 1.7
*2	40	12.3	9.2, 16.4
*2x2	1	0.3	0.1, 1.7
*5	20	6.2	4.0, 9.3
*10	120	37.0	32.0, 42.4
*10x2	2	0.6	0.2, 2.2
*14	7	2.2	1.1, 4.4
*21	1	0.3	0.1, 1.7
*36	3	0.9	0.3, 2.7

†95% confidence interval.

*CYP2D6**4 and *18, which create defective alleles, were found in a genotyping study on a Japanese population, while these two mutated alleles were not detected in our subjects [7]. We reported that the frequencies of *CYP2D6**5 and *14 could account for 83% of Japanese PM in our previous study. In the present study, frequency of PM in the Japanese, calculated by the frequencies of *CYP2D6**21 and *36 in addition to those of *5 and *14 in our subjects, was estimated to be 0.92% (95% CI 0.75, 1.13). This estimate is similar to those in previous Japanese population phenotyping studies. Therefore, we suggest that it could be possible to predict most of the *CYP2D6* PM phenotype by genotyping tests on six common defective mutated alleles, *CYP2D6**4, *5, *14, *18, *21 and *36, in the Japanese.

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