

# Impact of *CYP2D6\*10* on H1-antihistamine-induced hypersomnia

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## Abstract

**Objective** This study investigated the relevance of the cytochrome P450 (CYP) 2D6 genotype to the adverse drug reactions (ADRs) of H1-antihistamines and the level of sedation.

**Methods** Japanese participants in a health screening program were asked to describe any past history of ADRs. Any subjects reporting ADRs induced by H1-antihistamines were then individually interviewed and defined as cases. Excessive daytime sleepiness, which had occurred in the cases as an H1-antihistamine-induced ADR, was assessed by the Epworth sleepiness scale (ESS), and an ESS score  $\geq 12$  was considered hypersomnia. *CYP2D6\*4*, *\*5*, *\*14*, and *\*10* were genotyped by a panel of polymerase chain reaction techniques.

**Results** Out of 2,074 participants, 100 cases (M:F=37:63, mean age  $51.9 \pm 9.2$  years) were eligible for analysis. The most common etiological drug was chlorpheniramine, which is the most frequently used H1-antihistamine in Japan. *CYP2D6\*10* allele and genotypes were more frequently found in the cases than in the healthy Japanese population in a large study ( $P < 0.005$  and  $P = 0.039$ , respectively), but no difference was observed in the null alleles and genotypes. The ESS scores in 75 cases (M:F=25:50) who had experienced excessive daytime sleepiness were  $9.5 \pm 5.5$  in men and  $12.9 \pm 6.1$  in women ( $P < 0.001$ , cases vs. 34 subjects without symptoms;  $P = 0.001$  men vs. women). The occurrence of hypersomnia increased as the number of *CYP2D6* mutant alleles increased ( $P = 0.045$ ).

**Conclusion** The results suggest that the presence of the *CYP2D6\*10* allele is a risk factor for development of H1-antihistamine-induced ADRs in Japanese.

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## Introduction

Cytochrome P450 (CYP) 2D6 is involved in the metabolism of more than 50 clinically important drugs, including antidepressants, antipsychotics,  $\beta$ -blockers, and H1-antihistamines [1–3]. It is polymorphically expressed, thus causing marked interindividual and interethnic variations [1, 4]. Many case reports as well as retrospective and prospective studies have demonstrated that individuals exhibiting extremes in CYP2D6 activity tend to have significantly more problems when they receive medications metabolized by CYP2D6 [5–9].

The frequency of a poor metabolizer (PM) phenotype has been estimated to be 5–10% in Caucasians and less than 1% in Japanese [1, 2, 4]. In Caucasians, *CYP2D6*\*3, \*4, \*5, and \*6 alleles account for over 95% of PMs [4]. In Japanese PMs, the allele frequencies of *CYP2D6*\*3, \*4, \*5, \*6, and \*14 are 0.000, 0.002, 0.051, 0.000, and 0.014, respectively; these variants are too rare to be epidemiologically relevant in the Japanese population [4]. Approximately 10–15% of Caucasians and up to 50% of East Asians appeared to exhibit impaired *CYP2D6* activity [i.e., intermediate metabolizer (IM)] [1, 2, 4]. Several common IM alleles (e.g., *CYP2D6*\*9, \*10, \*17, and \*41) have been identified [1, 2, 4]. The most common allele in Asians (allele frequency in Chinese of >50%) and thus perhaps the most common *CYP2D6* allele in the world is *CYP2D6*\*10, with a frequency of about 40% in Japanese [2, 4]. *CYP2D6*\*10 has been shown to influence the pharmacokinetics of propranolol, codeine, haloperidol, and tramadol [10–13]. Although previous studies have reported that Japanese IMs were prone to antipsychotic-induced tardive dyskinesia [14, 15], the clinical relevance of the IM phenotype and/or the genotype to the *CYP2D6* substrate-induced adverse drug reactions (ADRs) remains to be elucidated.

H1-antihistamines are frequently used as over-the-counter (OTC) or prescribed drugs, and many of them are metabolized either mainly (e.g., promethazine, mequitazine) or partially (e.g., chlorpheniramine) by *CYP2D6* [3, 16]. The most common ADR of the first-generation H1-antihistamine is sedation, which is clearly governed by dose-response relationships [3, 16]. Therefore, individuals with a PM and/or IM phenotype of *CYP2D6* might be identified from a large population by their past history of H1-antihistamine-induced excessive daytime sleepiness, without the loading of a probe drug.

In the present study, we investigated the impact of *CYP2D6* polymorphisms on the risk of ADRs induced by H1-antihistamines in a Japanese population, while paying special attention to the level of the sedating effect of H1-antihistamines.

## Methods

### Subjects

Approximately 3,300 participants in a health screening program at the Japanese Red Cross Kumamoto Health Care Center (Kumamoto, Japan) were asked by mail in 2003 about their past history of ADRs. Completed replies were available from 2,074 subjects (1,239 men and 835 women; mean age 52.0±10.2 years) for a response rate of 63.1%. The subjects who reported a past history of ADRs related to

H1-antihistamines were then individually interviewed by pharmacists. A semistructured questionnaire was used to record pertinent data, the name of the etiological drugs, the doses, the indications, concomitant diseases, comedications, adverse symptoms, and detailed relationships between the symptoms and the H1-antihistamine use. The records were reevaluated by investigators, consisting of two pharmacists and a physician. The decision regarding inclusion and exclusion was made before genotyping *CYP2D6*. The following criteria were used to define cases that were included: an association of adverse reactions with H1-antihistamine treatment at standard doses, the absence of potent inhibitors of *CYP2D6*, and the absence of renal and hepatic failure. The subjects were excluded if sedation was a possible reason for receiving promethazine or other antihistamines. The study protocol was approved by the ethical review boards of the Graduate School of Medical and Pharmaceutical Sciences of Kumamoto University, the Japanese Red Cross Kumamoto Health Care Center, and Hokkaido University. In addition, all subjects gave their written informed consent to participate in the study.

### Assessment of daytime sleepiness caused by H1-antihistamines

Excessive daytime sleepiness that had occurred in the cases as a symptom of the H1-antihistamine-induced ADR was assessed using the Epworth sleepiness scale (ESS) [17]. The ESS is a self-reported scale to measure sleep propensities in eight different real-life situations (range of an item score, 0–3). The ESS score is the sum of the eight item scores (range, 0–24); higher scores indicate being more sleepy. The ESS has a high sensitivity and high specificity, with a cut-off score ≥11 or 12 for daytime sleepiness [18]. In the present study, those who showed an ESS score ≥12 were diagnosed as having impairment in their daily activities due to their extraordinary sleepiness (hypersomnia). To determine the baseline ESS score, 34 age-matched controls without ADRs completed the ESS.

### Determination of *CYP2D6* genotype

Genomic DNA was isolated from peripheral blood samples obtained from the cases with the use of an extraction kit (Wako Pure Chemical Industries, Osaka, Japan). The null allele \*5, in which the *CYP2D6* gene is deleted, was identified by long-range allele-specific polymerase chain reaction (PCR) using the method of Steen et al. [19]. The genotyping of null alleles \*4 and \*14, as well as the reduced function allele \*10, was performed by a combined approach of PCR-restriction fragment length polymorphisms (RFLP) and allele-specific PCR. Briefly, the point mutation 188C>T that is associated with these alleles (i.e.,

\*4, \*10, and \*14) was detected by the PCR-RFLP method as described by Wang et al. [20]. Next, these three alleles were discriminated by identifying mutations 1934G>A and 1846G>A using the PCR-RFLP method of Wang et al. [20] and the allele-specific PCR method of Kubota et al. [21], respectively. When these variant alleles were absent, the allele was identified as wild type allele with a normal function (e.g., \*1 or \*2).

A large study on the genotype and allele frequencies of general Japanese populations was used to calculate the expected genotype frequencies [4].

### Data analysis

All data are given as the mean  $\pm$  standard deviation. The chi-square test was used to compare allele and genotype frequencies, along with other categorical tests. Two-way analyses of variance, the Mann-Whitney U-test, and Fisher's exact test were used to analyze any differences in the ESS scores. These statistical analyses were done using the SPSS software package (version 12.0, SPSS, Chicago, USA). A score of  $P < 0.05$  was defined as statistically significant.

### Results

One hundred cases (37 men and 63 women; mean age  $51.9 \pm 9.2$  years) were thus eligible for analysis. All cases were judged to be healthy based on physical examination and blood chemistry and urinalysis data. The etiological drugs were chlorpheniramine ( $n=20$ ), promethazine ( $n=16$ ), clemastine ( $n=5$ ), and mequitazine ( $n=2$ ). Five cases had had repeated ADRs caused by the different H1-antihistamines, and 62 cases could not specify the drug name(s) of the etiological H1-antihistamine(s). Indications for the H1-antihistamines were upper respiratory tract infection (common cold) in 56 cases, allergic rhinitis in 36 cases, and urticaria in eight cases. These cases had had no concomitant diseases or comedications that might have interacted with the H1-antihistamines. They had had one or more adverse symptoms. The most prevalent was excessive daytime sleepiness (75/100), followed by fatigue (18/100), mouth dryness (15/100), gastrointestinal symptoms (12/100), and others (18/100).

The frequencies of alleles and genotypes in the present study and in a referential study of healthy Japanese populations [4] are shown in Table 1. The observed genotype frequency distribution was consistent with Hardy-Weinberg equilibrium. The genotype and allele frequencies in the cases significantly differed from those in the healthy Japanese populations. The *CYP2D6*\*10 allele and its genotypes were observed significantly more frequently in these cases than in

**Table 1** Genotype and allele frequencies in the cases and references

|                                   | Cases <sup>a</sup><br>( $n=100$ )<br>[ $n$ (%)] | References <sup>b</sup><br>[%] | Cases vs.<br>references <sup>c</sup> |
|-----------------------------------|-------------------------------------------------|--------------------------------|--------------------------------------|
| <i>CYP2D6</i> genotype            |                                                 |                                |                                      |
| *Wild/*wild                       | 22 (22.0)                                       | 29.7                           | $P=0.039$                            |
| *Wild/*10                         | 41 (41.0)                                       | 42.3                           | $\chi^2=10.101$                      |
| *Wild/*0                          | 6 (6.0)                                         | 7.3                            |                                      |
| *10/*10                           | 26 (26.0)                                       | 15.1                           |                                      |
| *10/*0                            | 5 (5.0)                                         | 5.2                            |                                      |
| *0/*0                             | 0                                               | 0.4                            |                                      |
| <i>CYP2D6</i> allele <sup>d</sup> |                                                 |                                |                                      |
| *Wild                             | 91 (45.5)                                       | 54.5                           | $P=0.013$                            |
| *10                               | 98 (49.0)                                       | 38.8                           | $\chi^2=8.765$                       |
| *0                                | 11 (5.5)                                        | 6.7                            |                                      |
| <i>CYP2D6</i> *10 allele          |                                                 |                                |                                      |
| Noncarriers                       | 28 (28.0)                                       | 37.5                           | $P=0.005$                            |
| Heterozygous carriers             | 46 (46.0)                                       | 47.5                           | $\chi^2=10.399$                      |
| Homozygous carriers               | 26 (26.0)                                       | 15.1                           |                                      |

<sup>a</sup> Cases: subjects with a past history of H1-antihistamine-induced adverse drug reactions

<sup>b</sup> References: healthy Japanese populations from a large study [4]

<sup>c</sup> The chi-square goodness of fit test and test of homogeneity were used to assess the genotype and allele frequencies of healthy Japanese. [4]

<sup>d</sup> Total allele number =200

the healthy Japanese, but those of the null alleles (\*0: i.e., \*4, \*5, and \*14) or genotypes containing null alleles did not differ between the groups.

The distribution of the ESS scores in the 75 cases (25 men and 50 women; mean age  $51.3 \pm 9.2$  years) who had experienced excessive daytime sleepiness and the baseline scores in 34 subjects (21 men and 13 women; mean age  $49.4 \pm 6.9$  years) without ADRs are shown in Fig. 1. The mean ESS scores of the female and male cases were  $12.9 \pm 6.1$  and  $9.5 \pm 5.5$ , respectively, and the female and male baseline scores were  $6.5 \pm 4.1$  and  $4.0 \pm 2.3$ , respectively. The mean ESS score of the cases was significantly higher than the baseline and was higher in women than in men. We assessed the effect of the *CYP2D6* genotypes among three groups of the homozygotes for wild type alleles (\*wild/\*wild), heterozygotes for a wild type allele and a variant allele (\*wild/\*0 or \*10), and heterozygotes or homozygotes for variant alleles (\*0 or \*10/\*0 or \*10), because the frequencies of the null alleles were low. The ratio of cases with hypersomnia, as diagnosed by an ESS score  $\geq 12$ , increased as the number of variant alleles increased ( $P=0.045$ ; Fig. 2). The mutant allele frequency in cases with hypersomnia (0.65) was also higher than that of controls (0.44;  $P=0.015$ ). The mean ESS scores of the \*wild/\*wild, the \*wild/\*0 or \*10, and the \*0 or \*10/\*0 or \*10 were  $8.9 \pm 4.6$ ,  $11.9 \pm 6.2$ , and  $13.5 \pm 6.3$ , respectively ( $P=0.085$ , Kruskal-Wallis test), and that of mutant allele(s) carriers was  $12.5 \pm 6.2$  ( $P=0.045$  vs.

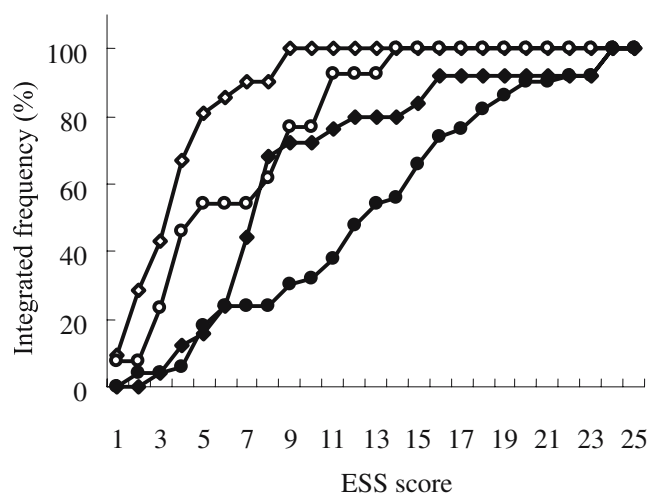


**Fig. 1** Distribution of the baseline Epworth sleepiness scale (ESS) scores in men (open square) and women (open circle), and those of the cases who experienced H1-antihistamine-induced excessive daytime sleepiness in men (closed square) and women (closed circle). The baseline refers to the subjects without H1-antihistamine-induced adverse drug reactions. The Mann-Whitney U-test was used to compare the ESS scores between the baseline and the cases for each gender ( $P<0.001$ ) and between men and women for baseline ( $P=0.068$ ) and for cases ( $P=0.018$ )

noncarriers, Mann-Whitney U-test). The gender distribution did not differ among the *CYP2D6* genotypes ( $P=0.285$ , Fisher's exact test). In addition, the mean ESS scores in the cases that specified etiological H1-antihistamines were  $12.2 \pm$

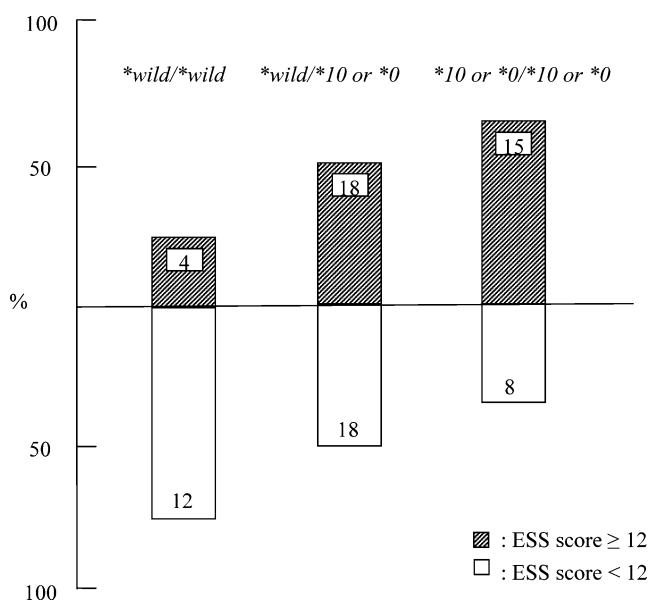


**Fig. 2** Genotype distribution in the cases who experienced H1-antagonist-induced excessive daytime sleepiness corresponding to an Epworth sleepiness scale (ESS) score  $\geq 12$  (hypersomnia) or  $< 12$ . A significant genotypic association between  $\geq 12$  and  $< 12$  of the total ESS score was identified ( $P=0.045$ , Fisher's exact test). A significant allelic association between  $\geq 12$  and  $< 12$  of the total ESS score was also identified ( $P=0.015$ , Fisher's exact test). The number of cases is shown in each bar

6.8 in men and  $17.0 \pm 4.5$  in women ( $n=19$ ), which were significantly higher than in those unspecified cases, namely  $7.7 \pm 3.8$  in men ( $n=15$ ) and  $10.4 \pm 5.6$  in women ( $n=31$ ; specified vs. unspecified for men  $P=0.046$  and for women  $P<0.001$ , Mann-Whitney U-test).

## Discussion

This study investigated the relationship between the *CYP2D6* genotype and the occurrence of H1-antihistamine-induced ADRs while using the ESS to assess the most common symptom, daytime sleepiness. The main results showed that the *CYP2D6*\*10 allele was the risk factor for the ADRs caused by H1-antihistamines and that the occurrence of hypersomnia increased as the number of *CYP2D6* mutant allele increased. In addition to the extremes of the *CYP2D6*, the impact of the IM genotype or phenotype on the pharmacokinetics of  $\beta$ -blockers, morphine, antipsychotics, and such has been principally demonstrated [10–13, 22, 23]. As for antidepressants, an attempt toward dose adjustment based on *CYP2D6* genotype, including IM, was reported by providing distinct dose recommendations [24]. Moreover, evidence is emerging that *CYP2D6* genotyping can predict not only the pharmacokinetics but also the risk of adverse effects and treatment outcome [5–9]. However, all of these studies indicated that the IM genotype was not overrepresented in patients with the ADRs [5–9]. The IM genotype *CYP2D6*\*10 has been reported to be significantly associated with the tardive dyskinesia occurrence in Japanese psychotic populations [14, 15], but a recent meta-analysis reported that the risk of tardive dyskinesia was inconclusive for the *CYP2D6*\*10 allele [25]. Taken together, the present study showed a significant impact of the *CYP2D6*\*10 allele and the IM genotype on the H1-antihistamine-induced ADRs, but these results need to be interpreted carefully.

In the present study, the distribution of *CYP2D6*\*10 polymorphism in the cases was significantly different from that in healthy Japanese populations [4] (Table 1). The cases had about a 2.0-fold higher likelihood of being homozygotes for *CYP2D6*\*10 than healthy Japanese populations [4, 21]. These results indicate that *CYP2D6*\*10 was associated with H1-antihistamine-induced ADRs in Japanese. On the other hand, the frequencies of null alleles did not differ from the others. Although more than 95% of PMs in Caucasians can be diagnosed by four mutant alleles, *CYP2D6*\*3–\*6, only 30% in Asian PMs have these mutant alleles [4]. We therefore determined the most common mutant alleles, *CYP2D6*\*4, \*5, and \*14, which account for 95% of the known Japanese null alleles [4]. However, only 60% of the Japanese PMs could be explained by these null alleles, as uninvestigated mutant alleles might also exist [4].

Further study to identify these alleles is currently in progress.

The risks of H1-antihistamines demand particular attention because they are a top-selling class of drugs that are widely available over the counter [3, 26]. These drugs are indicated for allergic rhinitis, and approximately 20 million people use OTC antihistamines in the United States [27]. In Japan, the most frequently used antihistamine is chlorpheniramine, and 1,118 variations of chlorpheniramine are on the market as OTC drugs (Japan Pharmaceutical Information Center, <http://www.japic.or.jp/>). Clemastine follows chlorpheniramine. Promethazine is a component of a popular prescribed cold medicine in Japan, PL, which contains a four-times-daily dose of 13.5 mg of promethazine and was the etiological agent in all cases who complained of promethazine-induced adverse reaction in this study. The potentially dangerous sedating effect of first-generation H1-antihistamines (e.g., diphenhydramine, chlorpheniramine) among drivers has been documented [26, 28, 29]. Sedation, ranging from mild drowsiness to deep sleep, can occur even at the usual therapeutic doses in 25% of adults [26]. The first-generation H1-antihistamine-induced excess risk of injury is a potentially substantial public health problem because of the high frequency of injuries and their associated costs to patients, insurers, and society [26, 27]. A retrospective cohort study reported that the use of diphenhydramine contributes to 55% of the serious injuries in the patients taking the drug [27]. Our results suggest that the daytime sleepiness resulting from the first-generation H1-antihistamines may reach a level of hypersomnia at the usual therapeutic dose, and this therefore appears to be a substantial risk of serious injury, especially in females and/or in individuals with a reduced CYP2D6 activity.

The ESS, which we used to assess the level of H1-antihistamine-induced sedation, has been proposed as a simple method for measuring the general level of daytime sleepiness in adults [17, 18]. The mean ESS score of the cases was significantly higher than that of the baseline in both men and women. The occurrence of hypersomnia increased as the number of CYP2D6 mutant alleles increased, in a manner of consistent with a gene-dose effect (Fig. 2). The mean ESS score also increased in the same trend of manner, and the score in the carriers of mutant allele(s) was significantly higher than that in the non-carriers. We wondered whether the inhibitory effect of H1-antihistamines on the CYP2D6 activity might amplify the influence of the IM genotype [3, 30–32], but we could not find any supportive information [33, 34].

Another possible risk factor for the H1-antihistamine-induced ADRs is the female gender. The mean female ESS score was significantly higher than that for males, and it was over the level of hypersomnia (Fig. 1). Previous studies have produced conflicting results regarding the influence of

gender on the CYP2D6 activity: For some CYP2D6 substrates, such as propranolol and desipramine, the mean metabolism was lower in women than in men [35], whereas for dextromethorphan it was higher in women than in men [36], and for debrisoquine it was the same in both sexes [37]. In addition, gender-related differences also exist regarding other factors (e.g., transporters, receptors, sex hormones, body weight, history of drug use) [38]. Female gender has been shown to be a risk factor for ADRs, and women are also known to be more sensitive than men to the sedating effects of drugs [27, 39, 40]. Some studies have reported women to be more prone to an impairment of driving ability by H1-antihistamines than men are [27].

In general, the present study is limited by the self-reporting nature (potential participation bias) and the time delay (potential recall bias) between a history of adverse drug reaction and the time of survey. Specific limitations are as follows: First, we investigated only the cases. If we could choose a nested sample of H1-antihistamine users who did not report an ADR while taking the medication as the control group, it would be more informative. Second, the data were not controlled for H1-antihistamine exposure in this population. In this study, the incidence of ADRs induced by H1-antihistamines was significantly higher in women than in men, 63/835 (7.5%) and 37/1,239 (3.0%), respectively. The relative risk of women vs. men was 2.53 (95% CI, 1.70–3.76). However, we deleted the data from the results because we could not clarify the frequencies of the H1-antihistamine exposure in each sex. Third, we could not specify the etiological H1-antihistamines in 60% of the cases. The mean ESS score in the cases of the specified etiological drugs was 12.2 in men and 17.0 in women, which was 1.6 times higher than that in the unspecified cases in both genders. This suggests that some cases who complained of ADRs caused by drugs other than the classic H1-antihistamines might be included in the present study and that the impact of the classic H1-antihistamines might thus be underestimated. Consequently, a prospective study of a nested sample of H1-antihistamine users is further required.

In conclusion, we demonstrated the presence of the CYP2D6\*10 allele to be the risk factor of the ADRs caused by H1-antihistamines, and the occurrence of hypersomnia increased as the number of CYP2D6 mutant alleles increased in Japanese. However, we obviously need further study to elucidate the relevance of the CYP2D6 phenotype and genotype to H1-antihistamine-induced ADRs.

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