NEW CYP2D6*10 HAPLOTYPE FOUND IN JAPANESE CAUSES IMPAIRED O-DEMETHYLATION BUT 7-HYDROXYLATION OF DEXTROMETHORPHAN MEDIATED BY CYP2D6.10 WITH F120I

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Two novel CYP2D6*10 haplotypes were discovered in 349 unrelated healthy Japanese. One haplotype of the CYP2D6 gene, newly designated as the CYP2D6*10B(1611) allele (CYP2D6*49), had a novel single nucleotide polymorphism of 1611T>A causing a F120I substitution associated with the CYP2D6*10B allele. In addition, we discovered the other haplotype, newly designated as the CYP2D6*10B(3318) allele, which contains a 3318G>A mutation causing E383K substitution associated with the CYP2D6*10B allele. The frequencies of the CYP2D6*10B(1611) and CYP2D6*10B(3318) alleles were 0.4% and 0.1% in Japanese, respectively. To investigate the effects of these two novel haplotypes on the CYP2D6 activities, the dextromethorphan O-demethylase activities of CYP2D6 enzymes encoded by these alleles were measured using genetically engineered E. coli membranes. The results indicated that the CYP2D6*10B(1611) enzyme was the most impaired, exhibiting an estimated enzyme efficiency (as $V_{\text{max}}/K_m$) 4.7-fold lower, compared with that of the CYP2D6*10B enzyme. Interestingly, it was found that the liver microsomes with the CYP2D6*10B/*10B(1611) genotype formed 7-hydroxy dextromethorphan. These results suggest that the 1611T>A mutation causes impaired O-demethylation, but the 7-hydroxylation of dextromethorphan is mediated by CYP2D6.10 with additional F120I substitution.