RAPID GENOTYPING OF CYP2A6 ALLELES BY FLUORESCENCE RESONANCE ENERGY TRANSFER
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Cytochrome P450 2A6 (CYP2A6) is involved in the metabolism of coumarin, nicotine, tegafur and fadrozole. Since genetic polymorphism of CYP2A6 is one of the important factors altering the catalytic properties of CYP2A6, it is important to develop rapid and easier methods to determine CYP2A6 genotypes. The purpose of this study was to develop novel genotyping methods for the major variant alleles of the CYP2A6 gene in Oriental population, including 32-kb deletion polymorphism (CYP2A6*4A), 59-bp conversion polymorphism (CYP2A6*1B) and single nucleotide polymorphisms (CYP2A6*7 and CYP2A6*9). Genotyping for CYP2A6*1A, CYP2A6*1B, CYP2A6*4A, CYP2A6*7 and CYP2A6*9 was performed by rapid-cycle polymerase chain reaction (PCR) and fluorescence resonance energy transfer (FRET) analysis. This method was validated with Japanese, Caucasian and African individuals previously genotyped by PCR-restriction enzyme fragment polymorphism (RFLP), allele-specific PCR and direct sequencing methods. The genotypes determined by this method proved 100% accurate in these samples. Thus, we developed a rapid-cycle two-step genotyping method for the CYP2A6*1A, CYP2A6*1B, CYP2A6*4A, CYP2A6*7 and CYP2A6*9: the first step is genotyping for CYP2A6*1A, CYP2A6*1B and CYP2A6*4A alleles in a single capillary by the dual-color hybridization; the second step is the genotyping for CYP2A6*7 and CYP2A6*9 alleles in two separated capillaries at the same thermal cycling. This method enables to determine four alleles described above within ~1.5 hours, which may be easily implemented as a high-throughput genotyping method into clinical practice.

VISUALIZATION OF PATTERN OF CYP-METABOLISMS OF DRUGS USING A NOVEL HIERARCHICAL DATA VISUALIZATION TECHNIQUE
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It has been difficult to clarify the quantitative structure/activity relationship of CYP-mediated because the CYPs have a broad spectrum of substrate specificity. A novel hierarchical data visualization technique, named "HeiankyoView", helps us to understand large-scale multidimensional chemical information. HeiankyoView represents the hierarchical data effectively in the two-dimensional display space by mapping colored icons and rectangular borders. We applied HeiankyoView to visualize CYP metabolism data for 161 drugs collected from the published literature. First, to perform intuitively understandable classification of the drugs, a self-organizing map (SOM) was produced with vectors of metabolic susceptibility by 5 CYP isoforms (1A2, 2C9, 2C19, 2D6 and 3A4). Then, the best matching unit of the SOM was found for each drug. After determining the best number of clusters by k-means clustering of the SOM units, the drugs were classified into 6 categories. Moreover, to create the classification tree for predicting the patterns of CYP metabolisms as a function of molecular descriptors, the recursive partitioning analysis was performed using the information gain as a splitting index. The results of this analysis showed the sum of atomic Sanderson electronegativities (Se) was the most important descriptor to classify the patterns of CYP metabolisms. Large-scale visualization using HeiankyoView made it possible to understand trends of the CYP metabolism data much more easily.