Search for novel biomarkers indicating cytochrome P450 3A5 activity using untargeted metabolomics

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Background: Cytochrome P450(CYP)3A5 activity varies widely among individuals. As genetic factor, individuals homozygous for the *CYP3A5*3* (rs776746, 6986 A>G) allele exhibit reduced CYP3A5 activity compared to carriers of at least one *CYP3A5*1* (wild type) allele. The use of endogenous biomarkers in biological samples to quantitatively assess drug-metabolizing enzyme activities in individuals has attracted attention, but no useful biomarkers that specifically indicate CYP3A5 activity have been reported. In this study, we searched for novel biomarkers for CYP3A5 activity using CYP3A5 gene polymorphism data combined with the results of untargeted metabolome analysis.
Methods: 432 general adults who participated in the Japan Multi-Institutional Collaborative Cohort Study and fulfilled selection criteria were studied. Plasma samples were pretreated by solid-phase extraction or liquid-liquid extraction, and untargeted metabolite analysis was performed using ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry. Hydrophobic and hydrophilic chromatography columns were used for analyses in positive and negative ion modes. Based on data of CYP3A5 gene polymorphisms, the subjects were classified into high-activity group (*CYP3A5*1/*1* or *CYP3A5*1/*3*) and low-activity group (*CYP3A5*3/*3*). Metabolic profiles in the two groups were constructed based on the measurement results. Compounds that showed significant differences between the two groups using ANOVA were further subjected to orthogonal partial least squares–discriminant analysis to search for novel biomarkers indicating CYP3A5 activity.
Results: In positive ion mode analysis using hydrophobic column, 13 compounds specific to the high- or low-activity group were detected as biomarker candidates indicating CYP3A5 activity. In negative ion mode analysis using hydrophobic column, 7 compounds specific to the high- or low-activity group were detected. In positive ion mode analysis using hydrophilic column, 7 compounds specific to the high- or low-activity group were detected. In negative ion mode analysis using hydrophilic column, 13 compounds specific to the high- or low-activity group were detected.
Conclusions: In this study, we searched for novel biomarkers indicating CYP3A5 activity using untargeted metabolomic approach and detected a total of 40 compounds as biomarker candidates. Further studies are required to evaluate the usefulness of the biomarker candidate compounds detected in this study.
Key Words: biomarker, cytochrome P450 3A5, gene polymorphism, untargeted metabolomics, UPLC-QTOF/MS