Exploration of endogenous biomarker candidates for evaluating organic anion transporting polypeptide 1B3 (OATP1B3) activity in Japanese general adults using untargeted metabolomics analysis approach

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Background: Organic anion transporting polypeptide 1B3 (OATP1B3) transports organic anion substrate drugs from blood to hepatic cells. OATP1B3 activity is affected by various factors including coadministration of inhibitors, physiological factors, and single nucleotide polymorphisms in OATP1B3, such as rs11045585. It has been reported that rs11045585 increases adverse events of docetaxel, an OATP1B3 substrate drug. Recently, phenotyping of transporter activities using biomarkers has drawn attention as a potentially useful tool to individualize the dosage of substrate drugs. The present study explored suitable endogenous biomarkers for evaluation of OATP1B3 activity, using OATP1B3 gene data combined with untargeted metabolomics analysis approach.
Methods: A total of 432 Japanese general adults who participated in the Japan-Multi Institutional Collaborative Cohort study and met the selection criteria were studied. Plasma samples were pretreated by solid-phase extraction and 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. The participants were grouped into high OATP1B3 activity group and low OATP1B3 activity group, according to the absence and presence of rs11045585, respectively. For compounds showing significant differences between two groups by ANOVA, additional orthogonal partial least squares discriminant analysis was conducted to select biomarker candidates for the evaluation of OATP1B3 function.
Results: In positive ion mode analysis using hydrophobic column, 22 specific compounds in high or low activity group were detected as biomarker candidates indicating OATP1B3 activity. In negative ion mode analysis using hydrophobic column, 11 specific compounds in high or low activity group were detected. In positive ion mode analysis using hydrophilic column, 11 specific compounds in high or low activity group were detected. In negative ion mode analysis using hydrophilic column, 6 specific compounds in high or low activity group were detected.
Conclusions: We found 50 compounds as novel biomarker candidates for evaluation of OATP1B3 activity. Further analyses are warranted to determine the usefulness of the biomarker candidates detected in this study for evaluating OATP1B3 activity.
Keywords: biomarker, organic anion transporting polypeptide 1B3, OATP1B3 polymorphism, untargeted metabolomics analysis, UPLC-QTOF/MS