Substantially Increased Plasma Coproporphyrin-I Concentrations Associated With OATP1B1*15 Allele in Japanese General Population

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Coproporphyrin-I (CP-I) in plasma is a sensitive and specific endogenous probe for phenotyping organic anion transporting polypeptides 1B (OATP1B, encoded by SLC01B). A few small-scale studies suggested that plasma CP-I concentration is affected by OATP1B1 polymorphism, but detailed studies are lacking. In this large-scale study, we measured plasma CP-I concentrations in 391 subjects from the Japanese general population, and evaluated the relationship between plasma CP-I concentrations and OATP1B1 polymorphisms to further assess the utility of plasma CP-I concentrations as an endogenous OATP1B probe. Plasma CP-I concentrations were 0.45 ± 0.12, 0.47 ± 0.16, 0.47 ± 0.20, 0.50 ± 0.15, 0.54 ± 0.14, and 0.74 ± 0.31 ng/mL in participants with OATP1B1*1b/*1b (n = 103), *1a/*1b (n = 122), *1a/*1a (n = 40), *1b/*15 (n = 74), *1a/*15 (n = 41), and *15/*15 (n = 11), respectively, showing an ascending rank order with significant difference (P < 0.0001). Post hoc analysis revealed significant increases in plasma CP-I concentration in OATP1B1*1b/*15 (P = 0.036), *1a/*15 (P = 0.0005), and *15/*15 (P = 0.0003) groups compared with the OATP1B1*1b/*1b group. There was no significant difference among OATP1B genotypes in plasma concentration of 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, a uremic toxin reported to decrease OATP1B activity in vivo. These findings confirm the utility of plasma CP-I concentrations as an endogenous biomarker for phenotyping of OATP1B activity. Plasma CP-I concentration is potentially useful for the study of drug-drug interactions via OATP1B or individual dose adjustment of OATP1B substrates.

Drug transporters are localized at cell membranes and involved in drug transport in various tissues such as the liver, kidneys, gastrointestinal tract, and brain endothelium. Organic anion transporting polypeptides 1B (OATP1B, encoded by SLC01B) is a hepatic uptake transporter that substantially affect pharmacokinetics of some drugs, such as hydroxymethylglutaryl (HMG)-CoA reductase inhibitors and some anti-hepatitis C virus drugs.1–6 In vivo OATP1B activity has large interindividual variability and is affected by environmental, physiologic, and genetic factors. For example, OATP inhibitors, such as rifampicin and cyclosporin A, inhibit OATP1B activity and increase plasma concentrations

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of OATP1B substrates. Chronic kidney failure has been reported to decrease OATP1B activity, and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) is suggested as a causative substance. As genetic factors, SLCO1B1 exhibits two major single nucleotide polymorphisms: A388G and T521C. These polymorphisms form four haplotypes: OATP1B1*1a (c.388A-c.521T), OATP1B1*1b (c.388G-c.521T), OATP1B1*15 (c.388A-c.521C), and OATP1B1*15 (c.388G-c.521C). Several studies have revealed that OATP1B1*15 and OATP1B1*15 are associated with decreased transport activities of OATP1B1. In the Japanese population, c.521C shows strong linkage disequilibrium with c.388G (r² = 0.0708, D' = 0.9999). Thus, OATP1B1*15 is an important polymorphism that affects individual OATP1B activity in vivo.

Phenotyping of OATP1B seems to be a useful tool for quantitative assessment of in vivo OATP1B activity. Several probes for phenotyping of OATP1B have been reported, such as probe drugs, including HMGC-CoA reductase inhibitors, and endogenous probes, including total and direct bilirubin, chenodeoxycholate 24-glucuronide, glyccholodeoxycholate 3-sulfate, and coproporphyrins. Especially coproporphyrin-I (CP-I) and CP-III in plasma are sensitive and specific endogenous probes for phenotyping OATP1B.

Rifampicin increases plasma CP-I and CP-III concentrations to a greater extent than other endogenous compounds and rosuvastatin. CP-I has been reported to be superior to CP-II as an endogenous OATP1B probe, because CP-I is a selective substrate for OATP1B1 and OATP1B3, whereas CP-III is also a substrate for OATP2B1. Thus, quantification of plasma CP-I concentration is a potentially useful tool for dose individualization of OATP1B substrates and assessment of OATP1B-mediated drug–drug interactions.

A few previous small-scale studies suggested that plasma CP-I concentration is affected by OATP1B polymorphism, but detailed studies are lacking. Shen et al. reported a significant decrease in plasma CP-I concentration in healthy volunteers with SLCO1B1 c.388AG compared with SLCO1B1 c.388AA, but there were no data on haplotypes of SLCO1B1 T521C. Yee et al. measured plasma CP-I concentrations in 16 healthy volunteers and found significant differences among 3 groups: SLCO1B1 c.521TT (n = 8), c.521TC (n = 6), and c.521CC (n = 2), but the number of participants was inadequate and data on haplotypes of SLCO1B1 A388G were unknown. The report by Mori et al. showed that plasma CP-I concentrations increased in Japanese participants with OATP1B1*15/*15 compared with those with OATP1B1*1b/*1b or OATP1B1*1b/*15, but only 2 participants with OATP1B1*15/*15 were included in the study and statistical analysis was not performed. In the present large-scale study, we measured plasma CP-I concentrations in 391 subjects from the Japanese general population, and evaluated the relationship between plasma CP-I concentrations and OATP1B1 polymorphisms to further assess the utility of plasma CP-I concentration as an endogenous OATP1B probe.

METHODS

Study participants
We analyzed the data of participants recruited in the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study. The J-MICC study recruited subjects from the general Japanese population, and detected and confirmed gene–environment interactions related to lifestyle-associated diseases using genetic and clinical data. All participants in the J-MICC study gave written informed consent, and the study protocol was approved by the ethics committees at institutions participating in the J-MICC study. We analyzed the data of 500 randomly selected subjects who received a health check in Kyoto Prefectural University of Medicine, and selected 391 participants who met the following inclusion criteria: body mass index lower than 30 kg/m², estimated glomerular filtration rate (eGFR) higher than 60 mL/min/1.73 m², total bilirubin lower than 1.5 mg/dL, and alanine aminotransaminase lower than 100 IU/L. The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for Japanese. All plasma samples for quantification of CP-I and CMPF were stored in deep freeze (~80°C) and light-resistant condition. This study was approved by the ethics committees of Kyoto Prefectural University of Medicine (approval number: ERB-C-1384) and Meiji Pharmaceutical University (approval number: 3206).

Genotyping
The 14,539 study participants in the J-MICC study from 12 areas of Japan were genotyped at RIKEN Center for Integrative Medicine using a Human OmniExpressExome-8 version 1.2 BeadChip array (Illumina, San Diego, CA, USA). Quality control filtering of samples and single nucleotide polymorphisms (SNPs) have been reported previously. Briefly, for quality control filtering, samples with inconsistent sex information, one of each pair of samples found to be closely related by descent, and samples with ancestry estimated to be outside the Japanese population were excluded. SNPs with a call rate < 0.98 or a Hardy Weinberg equilibrium P value < 1 × 10⁻⁶ were also filtered out. Such quality control filtering resulted in the selection of 14,091 subjects and 873,254 SNPs, from whom we selected the above-mentioned 391 participants and their data. Among the SNPs that passed quality control, we identified rs2306283 (c.A388G, p.N130D, and exon 5) and rs4149056 (c.T521C, p.V174A, and exon 5) from genomewide association study data, and formed four haplotypes: OATP1B1*1a (c.388A-c.521T), OATP1B1*1b (c.388G-c.521T), OATP1B1*15 (c.388A-c.521C), and OATP1B1*15 (c.388G-c.521C). Finally, the participants were stratified into six polymorphism groups: OATP1B1*1a/*1b, OATP1B1*1a/*1b, OATP1B1*1a/*1a, OATP1B1*1b/*15, OATP1B1*1a/*15, and OATP1B1*15/*15 (Table 1). CP-I may also be transported by other OATPs, such as OATP2B1 (encoded by SLCO2B1) and OATP1B3 (encoded by SLCO1B3), and also by other types of transporters, such as MRP2 (encoded by ABCC2) and MRP3 (encoded by ABCC3). We therefore evaluated the association of plasma CP-I concentration with the following SNPs: rs717620 (ABCC2 variant; c.-24T and 5’UTR), rs12422149 (SLCO2B1 variant; c.G935A, p.R312Q, and exon 7), rs4149117 (SLCO1B3 variant; c.T334G, p.S112A, and exon 5), and rs37311358 (SLCO1B3 variant; c.G699A, p.M233I, and exon 6).
Measurement of plasma concentrations of CP-I and CMPF

Plasma concentrations of CP-I and CMPF were measured simultaneously using an ultra-high performance liquid chromatography coupled to tandem mass spectrometry according to the procedures that we reported previously. Inter-assay and intra-assay accuracy and precision were < 7.6% for CP-I and < 4.1% for CMPF.

Data analysis and statistics

Data are expressed as mean ± SD. The genotype distributions were tested for Hardy–Weinberg equilibrium by χ² test. Data were tested for normal distribution using Shapiro–Wilk test. Values in some genotype groups were found to be not normally distributed. Clinical characteristics of participants and plasma CMPF concentrations among groups were compared by Kruskal–Wallis test or χ² test. Plasma CP-I concentrations between groups were compared using Kruskal–Wallis test with Dunn's post hoc test. Correlation between plasma CP-I and CMPF concentrations was assessed by Spearman's rank correlation coefficient. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using Graph Pad Prism 7 (GraphPad Software, La Jolla, CA, USA).

RESULTS

Participants background

Table 2 shows the laboratory data of the 391 study participants. The genotype distributions of these 2 SNPs conformed to Hardy–Weinberg equilibrium with P values > 0.05 (rs2306283: χ² = 0.281 and rs4149056: χ² = 0.123). The participants were divided according to OATP1B1 polymorphism into OATP1B1*1b/*1b (n = 103), *1a/*1b (n = 122), *1a/*1a (n = 40), *1b/*15 (n = 74), *1a/*15 (n = 41), and *15/*15 (n = 11). There were no significant differences in demographic and laboratory variables among genotypes. The eGFR was within the normal range in all groups, with no significant difference among groups.

Plasma CP-I concentrations in six OATP1B1 genotypes

Plasma CP-I concentration (mean ± SD) in all participants was 0.48 ± 0.17 (range 0.13–1.41) ng/mL, showing large individual variability. When stratified by OATP1B1 genotype, plasma CP-I concentrations were 0.45 ± 0.12, 0.47 ± 0.16, 0.47 ± 0.20, 0.50 ± 0.15, 0.54 ± 0.14, and 0.74 ± 0.31 ng/mL in participants with OATP1B1*1b/*1b, *1a/*1b, *1a/*1a, *1b/*15, *1a/*15, and *15/*15, respectively, showing an ascending rank order with a significant difference detected...
by Kruskal–Wallis test ($P < 0.0001$; Figure 1). Post hoc analysis revealed significant increases in plasma CP-I concentrations in OATP1B1*1b/*1b, *1a/*1b, *1a/*1a, *1b/*15, *1a/*15, and *15/*15 groups compared with OATP1B1*1b/*1b group (Figure 1).

Plasma CP-I concentrations and OATP1B1*15

Suzuki et al.

Figure 2 shows the association of plasma CP-I concentrations with genotypes of four additional transporter genes. There was no significant difference among three genotypes in rs717620 (MRP2), rs12422149 (OATP2B1), rs4149117 (OATP1B3), and rs7311358 (OATP1B3).

Relationship between plasma CP-I and CMPF concentrations

Plasma CMPF concentrations were 2,739 ± 1,591, 2,583 ± 1,384, 2,684 ± 1,582, 2,508 ± 1,210, 2,445 ± 1,745, and 2,660 ± 1,461 ng/mL in participants with OATP1B1*1b/*1b, *1a/*1b, *1a/*1a, *1b/*15, *1a/*15, and *15/*15, respectively, with no significant difference (Figure 3). Figure 4 shows the relationship between plasma CP-I and CMPF concentrations for each OATP1B1 genotype. No significant correlation was observed for all genotypes.

DISCUSSION

In 2016, CP-I was reported for the first time as a useful endogenous biomarker for phenotyping of OATP1B activity.19–21 Currently, CP-I is assumed to be the most sensitive and specific biomarker for phenotyping of OATP1B activity compared with the other endogenous biomarkers and probe drugs, such as HMG-CoA reductase inhibitors.22 In fact, CP-I was used for OATP1B activity phenotyping in clinical drug-drug interaction studies24,37–39 and in model-based analysis of drug-drug interactions.23,40–42 Three previous studies reported the relationship between plasma CP-I concentrations and OATP1B1 polymorphism, but the
numbers of participants in all studies were insufficient to detect significant differences among the genotypes. In the present study of a large sample from the Japanese general population, we evaluated the differences in plasma CP-I concentrations in participants with OATP1B1*1b/*1b, *1a/*1b, *1a/*1a, *1b/*15, *1a/*15, or *15/*15 to evaluate the utility of plasma CP-I concentrations.

Hepatic failure decreased mRNA levels of OATPs in liver biopsy specimens in a previous study. Chronic kidney disease was also reported to decrease OATP1B activity in patients. Furthermore, polycystic kidney disease decreased the protein expression of OATPs in rats. In our study, all of the 391 participants had normal values of eGFR, total bilirubin, and alanine aminotransaminase, suggesting that plasma CP-I concentrations in this study were not affected by disease states, such as hepatic and renal failure, but were influenced mainly by OATP1B1 polymorphisms. We evaluated four haplotypes: OATP1B1*1a, OATP1B1*1b, OATP1B1*15, and OATP1B1*15. SLCO1B1 c.521C shows strong linkage disequilibrium with SLCO1B1 c.388G in the Japanese population ($r^2 = 0.0708, D' = 0.9999$). Therefore, we evaluated the influence of 6 types of polymorphism; OATP1B1*1b/*1b, *1a/*1b, *1a/*1a, *1b/*15, *1a/*15, and *15/*15, on plasma CP-I concentrations. The allele frequency of OATP1B1*15 in the Japanese population was reported to be 0.11–0.16, which is consistent with the finding in this study. Our study population included 11 participants with OATP1B1*15/*15, and this is the largest number.

Figure 3 Plasma 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) concentrations in participants with organic anion transporting polypeptide (OATP)1B1*1b/*1b, *1a/*1b, *1a/*1a, *1b/*15, *1a/*15, and *15/*15. Data were analyzed by Kruskal-Wallis test.

Figure 4 Correlation between plasma coproporphyrin-I (CP-I) and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) concentrations for each organic anion transporting polypeptide (OATP)1B1 genotype.
compared with previous studies that evaluated OATP1B1 polymorphism and plasma CP-I concentrations.\textsuperscript{25,27,28} The Japanese population has higher allele frequency of OATP1B1*15 compared with white, African American, and other Asian populations.\textsuperscript{45,46} Thus, the Japanese population seems to be suitable for the purpose of this study.

We obtained several important findings in this study. First, significant increases in plasma CP-I concentration were observed in OATP1B1*1b/*15, *1a/*15, and *15/*15 groups compared with the OATP1B1*1b/*1b group. Especially, substantial increase was observed in OATP1B1*15/*15. These findings suggest that plasma CP-I concentrations reflect the individual variation of OATP1B activity caused by OATP1B1 polymorphism. Second, we observed an ascending rank order of plasma CP-I concentrations in subjects with OATP1B1*1b/*1b, *1a/*1b, *1a/*1a, *1b/*15, *1a/*15, and *15/*15. This trend is rational considering previous reports showing that the OATP1B1*1b allele increases the transportation function of OATP1B1,\textsuperscript{47} whereas the OATP1B1*15 allele decreases transportation function compared with wild type (OATP1B1*1a).\textsuperscript{12–16} On the other hand, Choi et al.\textsuperscript{48} studied the effect of OATP1B1 polymorphisms on rosuvastatin pharmacokinetics, and reported that mean areas under the curve of rosuvastatin in OATP1B1*1b/*1b, *1a/*1b, *1a/*1a, *1b/*15, *1a/*15, and *15/*15 were 116, 126, 87.4, 105, 167, and 191 ng h/mL, respectively, which showed no consistent pattern, unlike the ascending trend found in the present study. These results suggest that plasma CP-I concentrations may have better specificity than rosuvastatin as an OATP1B probe. Third, polymorphisms of MRP2, OATP2B1, and OATP1B3 were not associated with plasma CP-I concentrations in this study. This suggests that CP-I is a more sensitive endogenous probe for OATP1B1 than other transporters. Finally, there was no significant difference in plasma CMPF concentrations among the OATP1B1 genotypes, and no significant correlation between plasma CMPF and CP-I concentrations in all genotypes, suggesting that the variation in CP-I concentration was not due to recruitment of subjects with chronic kidney disease. CMPF has been reported to decrease OATP1B activity in a concentration–dependent manner, both in vitro\textsuperscript{9} and in clinical studies,\textsuperscript{10,36} which further support the absence of effect of CMPF in our study and that the effect of OATP1B1 polymorphism on plasma CP-I concentrations was evaluated appropriately. These findings further demonstrate the utility of plasma CP-I concentration as an endogenous biomarker for phenotyping of OATP1B activity. Plasma CP-I concentrations is useful for studies of drug–drug interaction via OATP1B1 and individual dose adjustment of OATP1B1 substrates.

In this large-scale study in the Japanese general population, the mean plasma CP-I concentration was 0.48 ng/mL. This value was slightly lower compared with previous studies in the white population (mean concentration: 0.60–0.71 ng/mL).\textsuperscript{49} The difference might be due to genetic differences, such as OATP1B1 polymorphism, but the detail mechanism is unknown. Further studies are needed to reveal the racial differences of plasma CP-I concentrations.

There was a limitation in this study. We measured plasma CP-I concentrations in this study, but did not measure other endogenous probes, such as direct bilirubin, chenodeoxycholate 24-glucuronide, and glycochenodeoxycholate-3-sulfate. Further studies are needed to evaluate the relationship of OATP1B1 genotypes with these probes.

In conclusion, significant differences in plasma CP-I concentrations were observed among OATP1B1 genotypes, and the concentrations were significantly increased in OATP1B1*1b/*15, *1a/*15 and *15/*15 compared with OATP1B1*1b/*1b. These findings further substantiate the utility of plasma CP-I concentrations as an endogenous biomarker for phenotyping of OATP1B activity.

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Plasma CP-I concentrations and OATP1B1*15
Suzuki et al.

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