Substantially increased plasma coproporphyrin-I concentrations associated with OATP1B1*15 allele in Japanese general population

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【Background】

- Coproporphyrin-I (CP-I) in plasma is a sensitive and specific endogenous probe for phenotyping organic anion transporting polypeptides 1B (OATP1B, encoded by SLCO1B).
- Quantification of plasma CP-I concentration is a potentially useful tool for dose individualization of OATP1B substrates and assessment of OATP1B-mediated drug-drug interaction.
- 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.

【Methods】

- We analyzed the data of 500 randomly selected subjects who received health check in Kyoto Prefectural University of Medicine, and selected 391 participants who met the following inclusion criteria: body mass index (BMI) lower than 30 kg/m^2, estimated glomerular filtration rate (eGFR) higher than 60 mL/min/1.73 m^2, total bilirubin lower than 1.5 mg/dL, and alanine aminotransaminase (ALT) lower than 100 IU/L.
- We identified rs2306283 (c.A388G, p.N130D, exon 5) and rs4149056 (c.T521C, p.V174A, exon 5) from genome-wide association study data, and formed four haplotypes: *OATP1B1*1a* (c.388A-c.521T), *OATP1B1*1b* (c.388G-c.521T), *OATP1B1*5* (c.388A-c.521C) and *OATP1B1*15* (c.388G-c.521C).
- Finally, the participants were stratified into six polymorphism groups: *OATP1B1*1b/*1b*, *OATP1B1*1a/*1b*, *OATP1B1*1a/*1a*, *OATP1B1*1b/*15*, *OATP1B1*1a/*15* and *OATP1B1*15/*15.*
- Furthermore, we evaluated the association of plasma CP-1 concentration with the following SNPs: rs717620 (ABCC2 variant; c.C-24T, 5'UTR), rs12422149 (SLCO2B1 variant; c.G935A, p.R312Q, exon 7), rs4149117 (SLCO1B3 variant; c.T334G, p.S112A, exon 33) and rs7311358 (SLCO1B3 variant; c.G699A, p.M233I, exon 6).
- Plasma CP-I concentrations were measured using an ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS).
- The UHPLC-MS/MS method was fully validated according to the recommendations published by the US Food and Drug Administration (FDA).

【Results】

Table 1 Characteristics of participants divided into OATP1B1 genotypes.

Characteristic	*OATP1B1*1b/*1b*	*OATP1B1*1a/*1b*	*OATP1B1*1a/*1a*	*OATP1B1*1b/*15*	*OATP1B1*1a/*15*	*OATP1B1*15/*15*	*p* value
No. of participants	103	122	40	74	41	11	
Males / females	32/71	37/85	12/28	17/57	10/31	4/7	NS
Age (year)	55.9 ± 11.0 [40-74]	55.3 ± 10.0 [39-74]	56.9 ± 9.1 [39-72]	56.0 ± 9.3 [40-73]	58.2 ± 8.7 [39-74]	56.6 ± 10.2 [41-68]	NS
BMI (kg/m^2)	21.9 ± 2.8 [15.4-29.9]	22.3 ± 3.0 [14.5-29.8]	22.1 ± 2.9 [17.4-28.0]	21.7 ± 3.4 [15.8-29.7]	21.4 ± 2.4 [17.6-29.5]	21.9 ± 3.6 [16.2-27.1]	NS
eGFR (mL/min/1.73 m^2)	77.3 ± 8.4 [60.0-96.3]	78.6 ± 9.1 [60.7-94.9]	78.9 ± 8.4 [60.4-92.7]	79.9 ± 8.0 [60.5-94.7]	78.8 ± 7.6 [60.7-90.6]	80.1 ± 6.5 [74.0-94.2]	NS
Total bilirubin (mg/dL)	0.79 ± 0.24 [0.4-1.4]	0.81 ± 0.24 [0.4-1.4]	0.70 ± 0.19 [0.4-1.0]	0.74 ± 0.22 [0.3-1.3]	0.78 ± 0.22 [0.3-1.3]	0.77 ± 0.28 [0.4-1.2]	NS
ALT (IU/L)	17.5 ± 9.4 [5-59]	17.5 ± 9.7 [6-53]	20.5 ± 10.1 [10-53]	19.7 ± 12.4 [7-99]	16.0 ± 6.7 [8-49]	26.1 ± 18.3 [9-61]	NS
Plasma CP-I concentrations (ng/mL)	0.45 ± 0.12 [0.21-0.88]	0.47 ± 0.16 [0.13-1.22]	0.47 ± 0.20 [0.19-1.41]	0.50 ± 0.15 [0.21-0.95]	0.54 ± 0.14 [0.25-0.84]	0.74 ± 0.31 [0.44-1.37]	*p* < 0.0001

ALT, alanine aminotransaminase; BMI, body mass index; eGFR, estimated glomerular filtration rate; OATP1B1, organic anion transporting polypeptides 1B1

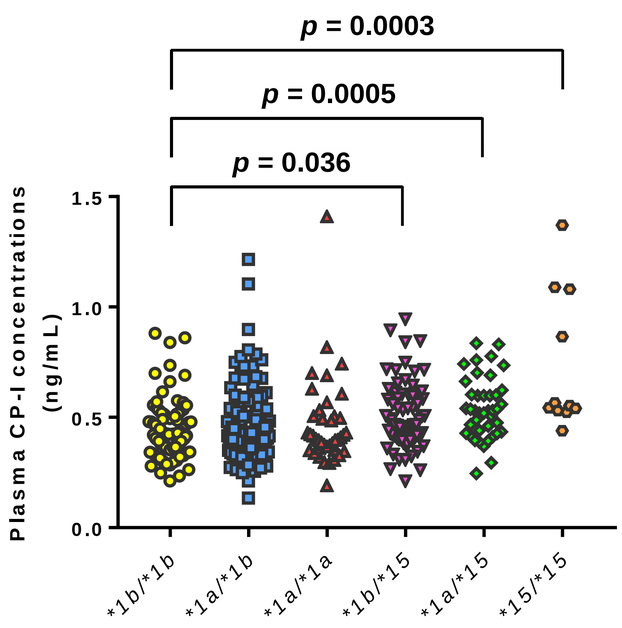

Fig. 1 Plasma coproporphyrin-I (CP-I) concentrations in participants with *OATP1B1*1b/*1b*, **1a/*1b*, **1a/*1a*, **1b/*15*, **1a/*15* and **15/*15*.
Data were analyzed by Kruskal-Wallis test ($p < 0.0001$) followed by Dunn's post hoc test.

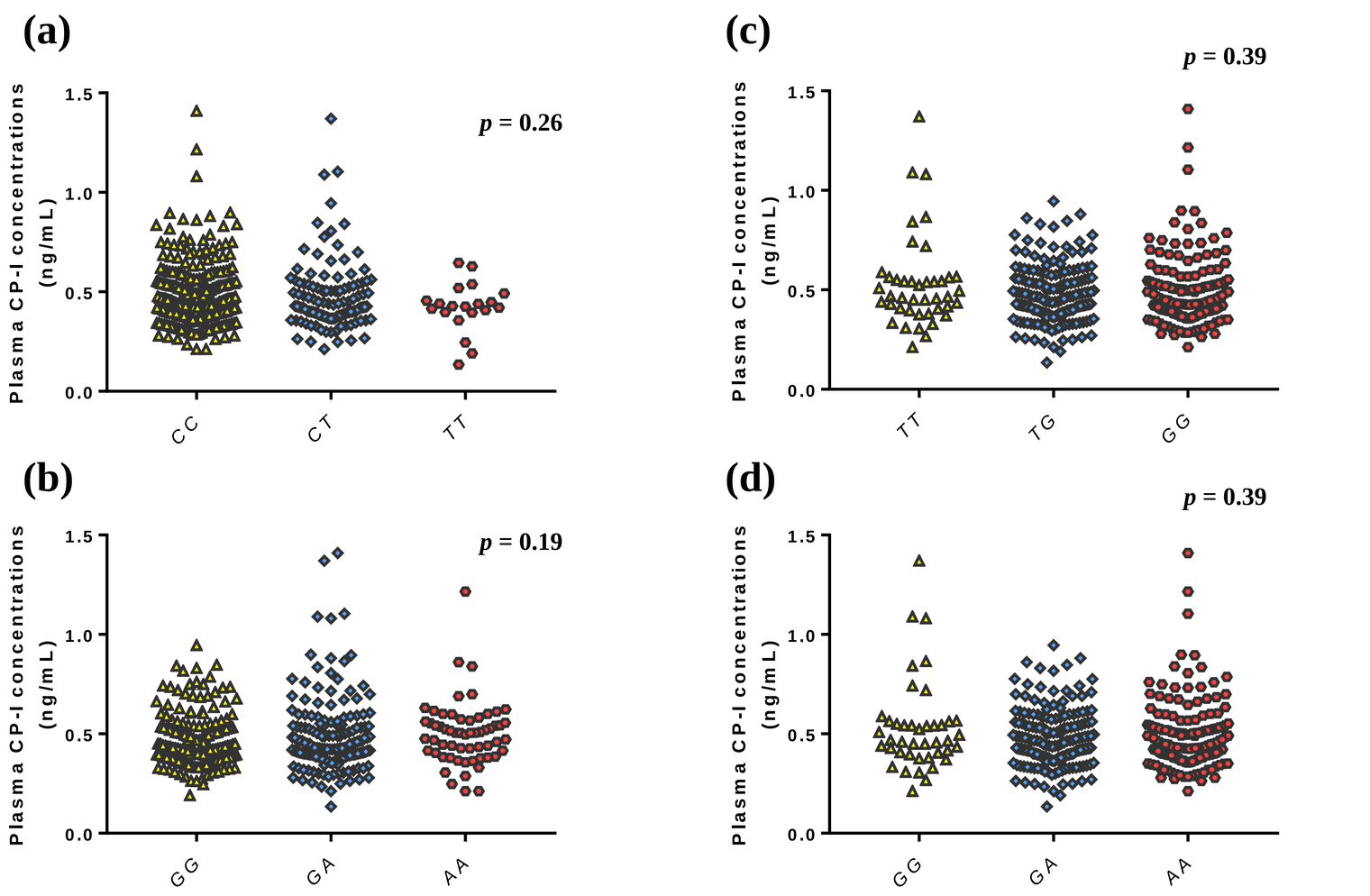

Fig. 2 Relationship between plasma coproporphyrin-I (CP-I) concentration and genotypes of rs717620 (a), rs12422149 (b), rs4149117 (c) and rs7311358 (d).
rs4149117 (c) and rs7311358 (d) demonstrate complete linkage disequilibrium.

- 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). **(Table 1)**
- There were no significant differences in demographic and laboratory variables among genotypes. **(Table 1)**
- 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 ($p < 0.0001$). **(Table 1 and Fig. 1)**
- Post-hoc analysis revealed significant increases in plasma CP-I concentrations in *OATP1B1*1b/*15*, **1a/*15*, **15/*15* groups compared to *OATP1B1*1b/*1b* group. **(Fig. 1)**
- There was no significant difference among three genotypes in rs717620 (MRP2), rs12422149 (OATP2B1), rs4149117 (OATP1B3) and rs7311358 (OATP1B3). **(Fig. 2)**

【Conclusion】

- Significant increases in plasma CP-I concentration were observed in *OATP1B1*1b/*15*, **1a/*15* and **15/*15* groups compared to *OATP1B1*1b/*1b* group, especially substantial increase in *OATP1B1*15/*15*.
- These findings confirm the utility of plasma CP-I concentrations as an endogenous biomarker for phenotyping of OATP1B activity.

【Conflict of interests】

- All authors have no conflict of interests to declare.