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<td>山川, 賢二; 龜田, 新二; 中島, 理子; 岩崎, 久代; 平田, 未優; 川口, 他</td>
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<tr>
<td>引用</td>
<td>Therapeutic Drug Monitoring, 33(2): 244-250</td>
</tr>
<tr>
<td>発行日</td>
<td>2011-04-01</td>
</tr>
<tr>
<td>タイプ</td>
<td>論文</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/2298/24701">http://hdl.handle.net/2298/24701</a></td>
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<tr>
<td>著作権</td>
<td>© 2011 by Lippincott Williams &amp; Wilkins</td>
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Association of genetic polymorphisms in the influx transporter \textit{SLCO1B3} and the efflux transporter \textit{ABCB1} with imatinib pharmacokinetics in patients with chronic myeloid leukemia

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Acknowledgments

This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS) to Akinobu Hamada (KAKENHI 19590149) and Hideyuki Saito (KAKENHI 21390048).

Disclosure statement

The authors have no conflict of interest.
Abstract

This study explored the association of 14 single nucleotide polymorphisms (SNPs) in 3 genes coding for influx transporters (SLC22A1, SLCO1B1, and SLCO1B3), 2 genes coding for efflux transporters (ABCB1 and ABCG2), and 4 genes coding for enzymes (CYP2C9, CYP2C19, CYP2D6, and CYP3A5) with the pharmacokinetics of imatinib in Japanese patients with chronic myeloid leukemia (CML). Pharmacokinetic parameters were estimated by a population pharmacokinetic analysis based on 622 plasma samples from 34 patients at steady-state. Approximately 4.6-fold variability in individual clearance was observed (range, 3.4-15.5 L/hr). The individual estimated clearance was significantly increased in patients with SLCO1B3 334GG genotype (median value ± SD, 9.5 ± 3.1 L/hr; n = 19) compared with SLCO1B3 334TT and TG genotypes (7.0 ± 3.1 L/hr; n = 15) (P = 0.019). Patients with ABCB1 3435CC genotype had significantly higher imatinib clearance (12.7 ± 3.0 L/hr; n = 7) compared with patients with ABCB1 3435CT and TT genotypes (7.9 ± 2.7 L/hr; n = 27) (P = 0.035). In conclusion, the present study suggests that SNPs of the influx transporter SLCO1B3 and the efflux transporter ABCB1 were functionally associated with individual variability of imatinib pharmacokinetics in Japanese
patients with CML.

Key Words

imatinib, pharmacogenetics, pharmacokinetics, chronic myeloid leukemia
Introduction

Imatinib was approved as a molecular target drug that selectively inhibits Bcr-Abl tyrosine kinase which causes Philadelphia-positive chronic myeloid leukemia (CML) and KIT tyrosine kinase which causes KIT-positive gastrointestinal stromal tumors (GIST).\(^1\)\(^2\) The standard dosage of imatinib worldwide is 400 mg/day and is based on a fixed-dosing strategy derived from pharmacokinetic analyses in early clinical studies.\(^3\) However, considerable interindividual differences in imatinib pharmacokinetics have been observed. For example, Judson \textit{et al.} suggested that variability in clearance of imatinib was about 73% among 42 patients with GIST.\(^4\) Individual variability in imatinib pharmacokinetics sometimes leads to an insufficient clinical outcome among patients with CML.\(^5\)

Imatinib is mainly eliminated by hepatic metabolism and biliary excretion.\(^6\)\(^7\) Imatinib is metabolized by cytochrome P450 (CYP) CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5; CYP3A4/5 is the major enzyme responsible for hepatic metabolism.\(^6\) Given the important role of CYP activity in the regulation of imatinib metabolism, genetic differences in these metabolic enzymes may influence imatinib disposition.
Imatinib is transported by the drug efflux ATP-binding cassette (ABC) transporters, ABCB1 (P-glycoprotein) and ABCG2 (breast cancer resistance protein).8, 9 The organic cation transporters OCT1, encoded by SLC22A1, and OCTN2 as well as the organic anion transporting polypeptides OATP1A2 and OATP1B3 were suggested to mediate the uptake of imatinib into cells.10, 11 Previous pharmacogenetic studies of imatinib have mainly focused on efflux transporters.12-14 Gurney et al. reported that ABCB1 1236C>T, 2677G>T/A, and 3435C>T were associated with imatinib clearance.12 Recently, it was reported that the influx transporter OATP1B3, encoded by SLCO1B3, was responsible for the uptake of imatinib into hepatocytes.11, 15 It has been suggested that a mutation in SLCO1B3 334T>G polymorphism affects transport of endogenous and xenobiotic substances.16-18 However, it is not known whether polymorphism in the SLCO1B3 gene is associated with imatinib disposition.

In this study, we evaluated the influence of factors including 14 single-nucleotide polymorphisms (SNPs) in 3 genes coding for influx transporters (SLC22A1, SLCO1B1, and SLCO1B3), 2 genes coding for efflux transporters (ABCB1 and ABCG2), and 4 genes coding for enzymes (CYP2C9, CYP2C19, CYP2D6, and CYP3A5) on the pharmacokinetics of imatinib at
steady-state to identify covariates predicting variability in imatinib pharmacokinetics in Japanese patients with CML.
Material and Methods

Patients

Thirty-four Japanese patients with CML (32 with chronic-phase CML and 2 with accelerated-phase CML) who were receiving oral imatinib (Novartis, Basel, Switzerland) at daily doses ranging from 100 to 600 mg were eligible for enrollment. All patients were followed up at Kumamoto University Hospital, and blood samples were collected whenever patients were available for clinic visits. Since Gurney et al. showed that the mean estimated clearance of imatinib at steady-state was reduced by 26%, we collected blood samples at steady-state (on day 30 of imatinib treatment or later). The sampling frequency per patient was from 1 point to 41 points; 1-5 points at 3 patients, 6-10 points at 6 patients, 11-15 points at 7 patients, 16-20 points at 5 patients, 21-25 points at 4 patients, 26-30 points at 3 patients, and 31-points at 6 patients. Samples at 0-1 hr, 0-8 hr, 8-16 hr and 16-hr were obtained from 4 patients (4 samples), 21 patients (59 samples), 12 patients (97 samples) and 34 patients (466 samples). The detail of 466 samples at 16-hr was 4 samples at 16-18 hr, 5 samples at 18-20 hr, 20 samples at 20-22 hr, 51 samples at 22-24 hr, 230 samples at 24-26 hr, 146 samples at 26-28 hr, 9 samples at 28-30 hr, and 1 sample at 30.5 hr. The study
was approved by the ethics committee of Kumamoto University. All patients provided informed consent prior to participation in this study.

Patient demographic data and laboratory analyses when starting imatinib treatment included gender, age, height, weight, body surface area, ideal body weight, levels of aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine, and creatinine clearance. Concomitant medication was collected in this study to evaluate drug-drug interaction. We confirmed that concomitant medication including ketoconazole or acetaminophen which may affect the pharmacokinetics of imatinib was not administered.

Pharmacokinetic analysis

The concentration of imatinib was determined using high performance liquid chromatography (HPLC, model LC-6A; Shimadzu, Kyoto, Japan) as described previously. In brief, 100 μL of sample and 100 μL of methanol were mixed in a 0.5-mL tube, and tubes were centrifuged at 10,000 rpm for 5 min. The supernatant (50 μL) was injected into the HPLC column. Separation was performed on a reversed-phase column (LiChrospher 100 RP-18, 5-μm particle
size, 250 mm × 4 mm i.d., Merck KGaA, Darmstadt, Germany) at 40°C. The mobile phase was a 4:6:0.1 mixture of acetonitrile, water, and phosphoric acid, and the flow rate was 1.0 mL/min. Imatinib was detected by ultraviolet absorption at 267 nm.

For the population pharmacokinetic (PPK) analysis, NONMEM program (Version 6.2.0, GloboMax, ICON Development Solutions, Ellicott City, MD, USA) was used,24 and the first order conditional estimation method (FOCE) was used throughout the model building procedure. Because all 34 patients had taken imatinib for more than 1 month, all 622 imatinib concentrations were treated as steady-state levels. PPK analysis was performed using the plasma concentration data with the one-compartment with first-order absorption and elimination model because imatinib pharmacokinetics was best characterized by this model. The exponential error model, as shown below, was used to describe the interindividual variability on the pharmacokinetic parameters

\[ P_i = P \times \exp(\eta_i) \]

where \( P_i \) is the estimated parameter value in the \( i \)th individual, \( P \) is the typical population value (geometric mean) of the pharmacokinetic parameter \( P \), and \( \eta_i \) is the individual-specific interindividual random effect in the \( i \)th individual and
parameter $P$ and is assumed to be independently and normally distributed with a mean of zero and variance of $\omega^2$.

The additive error was used to describe the residual (intraindividual) variability

$$C_{pij} = \hat{C}_{pij} + \varepsilon_{ij}$$

where $C_{pij}$ is the observed plasma concentration for individual $i$ and measurement $j$, $\hat{C}_{pij}$ is the predicted plasma concentration for individual $i$ and measurement $j$, and $\varepsilon_{ij}$ is the additive residual random error for individual $i$ and measurement $j$ and is assumed to be independently and normally distributed with a mean of zero and variance of $\sigma^2$. The 95% two-tailed confident interval (standard bootstrap 95% C.I.) was calculated by the normal approximation method, as follows.

$$95\% \text{ C.I.} = (\text{mean} - 1.96 \times \text{S.E.}, \text{mean} + 1.96 \times \text{S.E.})$$

PPK parameters of the basic model were obtained by applying the fixed effects model, which does not include covariates or factors. As all doses were administered orally, the parameters clearance (CL) and volume of distribution (Vd) were interpreted as CL/F and Vd/F, respectively. The individual clearance of imatinib was calculated by the Bayesian method using FOCE in the Basic model.
Genotyping analysis

DNA was obtained from whole blood using MagNA Pure LC DNA Isolation Kit I TISSUE (Roche Diagnostics, Mannheim, Germany). Subsequently, genotyping assay was carried out using Applied Biosystems TaqMan SNP Genotyping Assays. Variant genotypes for 13 SNPs included SLC22A1 1022C>T (Assay ID C_15877554_40), SLCO1B1 521T>C (SLCO1B1*5, C_30633906_10), SLCO1B3 334T>G (SLCO1B3*2, C_25639181_40), ABCB1 1236C>T (ABCB1*8, C_75866662_10), ABCB1 3435C>T (ABCB1*6, C_7586657_20), ABCG2 421C>A (C_15854163_70), CYP2C9 430C>T (CYP2C9*2, C_25625805_10), CYP2C9 1075A>C (CYP2C9*3, C_27104892_10), CYP2C19 636G>A (CYP2C19*3, C_25986767_70), CYP2D6 100C>T (CYP2D6*10, C_11484460_40), CYP2D6 1846G>A (CYP2D6*4, C_27102431_D0), and CYP3A5 6986A>G (CYP3A5*3C, C_26201809_30) were determined using real-time quantitative reverse-transcriptase polymerase chain reaction (PCR) by ABI PRISM® 7900HT Sequence Detection Systems (Applied Biosystems, Tokyo, Japan). Because ABCB1 2677G>T/A (ABCB1*7,
C_11711720C_30) is a tri-allelic polymorphism, this genotype assay was performed by direct nucleotide sequencing. Primers were designed as follows: forward, 5’-TCTTAGCAATTGTACCCATCATTG-3’ and reverse, 5’-CAGGTTCTTGACCGAAACGA-3’. PCR reactions were performed in a final volume of 50 μL with 20 μM of each of the primers, 10× PCR buffer, 2 mM dNTPs, 50 mM MgCl₂, and 5 U/μL Taq DNA polymerase (Invitrogen, Tokyo, Japan). PCR amplification consisted of an initial denaturation for 5 min at 94°C followed by 40 cycles of denaturation at 94°C for 30 s, annealing at 62°C for 30 s, and extension at 72°C for 30 s. After cleanup using Microcon-100 (Millipore, Bedford, MA, USA), direct nucleotide sequencing was performed. These 14 SNPs were selected on the basis of a known or a potential functional consequence.

**Statistical analyses**

All data are presented as median values along with the ranges, unless indicated otherwise. The Hardy-Weinberg equilibrium of SNPs was tested with the $\chi^2$ test to compare the observed and expected genotype frequencies.

The relationship between variant genotypes and the individual clearance
of imatinib was analyzed by the Kruskal-Wallis test or the Mann-Whitney U test. Since it was not clear which combination of genotypes (homozygous reference sequence (WT) vs heterozygous variant (Het) vs homozygous variant (Var), WT + Het vs Var, and WT vs Het + Var) affects imatinib clearance, all of these combinations were conducted. Correction was not performed to evaluate the significant of the multiple comparisons because this study was an exploratory study to investigate covariates influencing imatinib pharmacokinetics. Two-tailed \( P \) values < 0.05 were considered statistically significant. Statistical analyses were performed using the R program v.2.7.1 (http://cran.r-project.org).
Results

Subject demographics

The median age of the patients was 51 years (range, 21-80 years).

Other patient demographic data and laboratory analyses when starting imatinib treatment are provided in Table 1.

Imatinib pharmacokinetics.

Sampling time after dose is described in Appendix. Sampling time after dose was relatively concentrated at 24 hr. Detailed clinical effects and observed side effects were described in a previous report. The pharmacokinetics of imatinib was well described by the one-compartment model. The parameter estimates of the PPK model including the population mean, magnitude of interindividual variability (\( \omega \)), and the residual error magnitude (\( \sigma \)) are shown in Table 2. CL, Vd, and absorption rate constant (KA) at steady-state were 8.7 L/hr, 430 L, and 2.06, respectively. The bootstrap method showed the robustness of each parameter. Approximately 4.6-fold variability in individual clearance was observed (range, 3.4-15.5 L/hr).
Genotype

Fourteen SNPs in 3 genes coding for influx transporters (SLC22A1, SLCO1B1, and SLCO1B3), 2 genes coding for efflux transporters (ABCB1 and ABCG2), and 4 genes coding for enzymes (CYP2C9, CYP2C19, CYP2D6, and CYP3A5) were analyzed (Table 3). No patients with homozygous variants of ABCG2 421C>A, CYP2C9 1075A>C or CYP2C19 636G>A were observed. Similarly, no patients with heterozygous or homozygous variants of CYP2C9 430C>T or CYP2D6 1846G>A were observed. All genotype frequencies were found to be in Hardy-Weinberg equilibrium.

Association of genotype with imatinib clearance

The relationship between studied genotypes and individual clearance is summarized in Fig. 1 and Table 3. The influx transporter SLCO1B3 334T>G genotype significantly influenced individual clearance of imatinib ($P = 0.046$). Patients with SLCO1B3 334GG genotype had higher imatinib clearance than those with TT and TG genotypes ($9.5 \pm 3.1$ vs $7.0 \pm 3.1$ L/hr, respectively; $P = 0.019$), so that imatinib clearance of patients carrying the SLCO1B3 334GG genotype was 36% higher compared with patients carrying the TT and TG
genotypes.

In addition to the influx transporter, patients with the efflux transporter $ABCB1$ 3435CC genotype had significantly higher imatinib clearance compared with patients who had the $ABCB1$ 3435CT and TT genotypes ($12.7 \pm 3.0$ vs $7.9 \pm 2.7$ L/hr, respectively; $P = 0.035$), so that imatinib clearance of patients with the 3435CC genotype was 61% higher compared with patients with at least one $ABCB1$ 3435T allele.
Discussion

The present study suggests that \textit{SLCO1B3} 334T>G and \textit{ABCB1} 3435C>T polymorphisms are genetic factors influencing imatinib clearance. This is the first report describing the influence of both \textit{SLCO1B3} and \textit{ABCB1} polymorphisms on imatinib disposition.

The influx transporter OATP1B3, encoded by \textit{SLCO1B3}, is highly expressed in the liver and considered to be involved in the regulation of hepatic elimination of several drugs\textsuperscript{26}. It has been recognized that the \textit{SLCO1B3} 334GG genotype was associated with impaired testosterone uptake and better survival of patients with prostate cancer\textsuperscript{17}. In contrast, it has been reported that patients with \textit{SLCO1B3} 334GG and TG genotypes had a higher value of the erythromycin breath test $1/T_{\text{max}}$, implying that the hepatic uptake in these genotypes was more than in the \textit{SLCO1B3} 334TT genotype\textsuperscript{18}. Similarly, it was shown that \textit{SLCO1B3} 334GG genotype increased transport activities for dehydroepiandrosterone-3-sulfate, cholytaurine, and cholecystokinin-8 in stably transfected MDCK II cells\textsuperscript{16}. The present findings showed that patients with \textit{SLCO1B3} 334GG genotype had higher imatinib clearance than those with TT and TG genotypes, and that the hepatic uptake of imatinib in patients with
SLCO1B3 334GG genotype might be much greater than that in patients with SLCO1B3 334TT and TG genotypes.

A significant association between imatinib clearance and ABCB1 3435C>T polymorphism, encoding the drug efflux transporters ABCB1 (P-glycoprotein), was observed in our study. In previous reports, the influence of polymorphisms in the efflux transporters on pharmacokinetics and response of imatinib had been suggested.12-14 Gardner et al. and Dulucq et al. suggested that pharmacokinetics of imatinib was not related to ABCB1 3435C>T polymorphism13, 14; however, Gurney et al. suggested that ABCB1 1236T-2677T-3435T diplotype was associated with imatinib clearance.12 The number of patients with TT genotypes at each of ABCB1 1236C>T, 2677G>T/A and 3435C>T was only 4 in this study, however, individual clearance was not significantly influenced by this diplotype (P = 0.699). A larger number of subjects needs to be evaluated to characterize the relationship between these polymorphisms and the pharmacokinetics of imatinib. It was also shown that ABCG2 421C>A polymorphism affects imatinib disposition in vitro but not in patients.14 Similarly, the present data demonstrated that the ABCG2 polymorphism did not affect imatinib disposition. There may be differences
between in vitro and patients’ results due to the existence of several covariates likely to influence imatinib pharmacokinetics simultaneously in patients.

A previous study showed that clearance of imatinib was not significantly affected by SNPs in the genes encoding metabolic enzymes including CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 6986A>G, even though clearance of imatinib was slightly reduced in patients with heterozygous or homozygous variant at the CYP2D6 1846G>A polymorphism compared with patients with wild type genotype.\textsuperscript{14} Similarly, we analyzed genotypes of the metabolic enzymes, and no significant differences were observed. In spite of the important role of CYP activity in the regulation of imatinib metabolism,\textsuperscript{6} genetic polymorphisms in CYP isoforms were not correlated with individual clearance.

We evaluated the influence of polymorphisms in the influx transporters OCT1 and OATP1B1, encoded by SLC22A1 and SLCO1B1, respectively, and results showed that SLC22A1 1022C>T and SLCO1B1 521T>C were not significantly correlated with individual clearance. SLC22A1 1022C>T was reported to be associated with decreased transport activity.\textsuperscript{27} Though OCT1 activity is suggested to be important for the efficacy of imatinib therapy,\textsuperscript{28} no SNPs in SLC22A1 influencing imatinib pharmacokinetics have been detected as
OATP1B1 has been identified as a liver-specific transporter that transports endogenous and exogenous compounds. \(^{30}\) \(SLCO1B1\ 521T>C\) genotype has been reported to be associated with reduced activity of OATP1B1 in vitro. \(^{31, 32}\) OATP1B1 was not found to transport imatinib in vitro, \(^{11}\) with similar results likely to apply to humans.

The present result showed that imatinib clearance in Japanese patients is 8.7 L/hr. On the other hand, different population means of clearance in Westerners calculated with NONMEM have been reported. \(^{4, 33-37}\) Judson et al., Schmidli et al., and Widmer et al. reported that clearance of imatinib was 14.74 L/hr (extension phase), \(^4\) 14 L/hr, \(^{34}\) and 14.3 L/hr, \(^{35}\) respectively. Because Menon et al. and Petain et al. described exposure in a population including children and young adults, clearance in their studies would be low (6.81 and 7.29 L/hr, respectively). \(^{33, 37}\) However, the reason for low clearance in the report of Delbaldo et al. remains unknown (8.13 L/hr). \(^{36}\) It has been assumed that imatinib clearance of Japanese people is relatively low compared with that of Westerners. Kanda et al. suggested that the small body size of Japanese patients resulted in imatinib levels exceeding the toxic threshold. \(^{38}\)

In conclusion, individual clearance of imatinib appears to be associated
with genetic polymorphisms in the influx transporter \textit{SLCO1B3} 334T>G and efflux transporter \textit{ABCB1} 3435C>T. These results raise the possibility that \textit{SLCO1B3} may be a covariate for the administration of imatinib. As the individual variability of imatinib pharmacokinetics was affected by the transporter SNPs, genotypic characterization may be a useful guide for imatinib therapy in CML. Further studies with larger sample sizes are required to confirm these new observations.
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suboptimal response to imatinib have low OCT-1 activity: higher doses of imatinib may overcome the negative impact of low OCT-1 activity. *Blood.* 2007;110:4064-72.


Appendices

Appendix 1. Distribution of plasma concentrations of imatinib.

Figure Legends

Figure 1. Association of individual clearance with targeted genotypes. Each symbol represents an individual patient, and horizontal lines represent median values.
### TABLE 1. Patient characteristics

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<th>Median (Range)</th>
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<td>Gender (n)</td>
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<tr>
<td>Male</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (21-80)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (147-188)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62 (40-83)</td>
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<tr>
<td>Body surface area (m²)</td>
<td>1.7 (1.3-2.0)</td>
</tr>
<tr>
<td>Ideal body weight (kg)</td>
<td>60 (45-82)</td>
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<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>22 (9-61)</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>18 (7-220)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>13 (8-24)</td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.8 (0.5-1.5)</td>
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<tr>
<td>Creatinine clearance (mL/min)</td>
<td>83 (24-133)</td>
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TABLE 2. Summary of imatinib pharmacokinetic parameters in CML patients

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<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Estimate (S.E.)</th>
<th>Bootstrap 95% C.I.(^a)</th>
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<tr>
<td>CL (L/hr)</td>
<td>8.7 (5.3)</td>
<td>(8.6, 8.7)</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>430 (9.9)</td>
<td>(428, 439)</td>
</tr>
<tr>
<td>KA</td>
<td>2.06 (3.0)</td>
<td>(2.05, 2.14)</td>
</tr>
<tr>
<td>(\omega_{CL})</td>
<td>0.363 (24.2)</td>
<td>(0.360, 0.366)</td>
</tr>
<tr>
<td>(\omega_{Vd})</td>
<td>0.457 (29.6)</td>
<td>(0.415, 0.463)</td>
</tr>
<tr>
<td>(\omega_{KA})</td>
<td>0.747 (119.2)</td>
<td>(0.681, 0.832)</td>
</tr>
<tr>
<td>(\sigma)</td>
<td>0.400 (14.8)</td>
<td>(0.399, 0.403)</td>
</tr>
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S.E., standard error of the estimates; C.I., confidence interval; \(^a\)obtained from successful NONMEM runs using 879 bootstrap data sets.
<table>
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<tr>
<th>Allele</th>
<th>Region</th>
<th>Effect$^a$</th>
<th>Number of patients (n)</th>
<th>Allele frequency$^b$</th>
<th>Clearance ± SD (L/hr)</th>
<th>P-value</th>
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<tr>
<td>SLC22A1</td>
<td>Exon6</td>
<td>P341L</td>
<td>24</td>
<td>0.82 0.18</td>
<td>8.8 ± 2.9 8.2 ± 3.5 8.3 ± 3.5</td>
<td>0.973 0.913 0.926</td>
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<tr>
<td>SLC22A1</td>
<td>Exon6</td>
<td>V174A</td>
<td>26</td>
<td>0.87 0.13</td>
<td>8.7 ± 3.1 8.3 ± 2.0 5.5</td>
<td>0.304 0.235 0.288</td>
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<td>SLC22A1</td>
<td>Exon3</td>
<td>S112A</td>
<td>5</td>
<td>0.29 0.71</td>
<td>5.7 ± 2.3 7.4 ± 2.4 9.5 ± 3.1</td>
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<tr>
<td>ABCB1</td>
<td>Exon12</td>
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<td>5</td>
<td>0.43 0.57</td>
<td>11.7 ± 3.1 8.1 ± 2.7 8.2 ± 3.2</td>
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<td>ABCB1</td>
<td>Exon21</td>
<td>A893S/T</td>
<td>10</td>
<td>0.50 0.50</td>
<td>9.8 ± 3.2 8.1 ± 2.5 8.0 ± 3.3</td>
<td>0.494 0.445 0.270</td>
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<tr>
<td>ABCB1</td>
<td>Exon26</td>
<td>I1145I</td>
<td>7</td>
<td>0.51 0.49</td>
<td>12.7 ± 3.0 7.9 ± 2.4 9.2 ± 3.5</td>
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<tr>
<td>ABCG2</td>
<td>Exon5</td>
<td>Q141K</td>
<td>21</td>
<td>0.81 0.19</td>
<td>7.9 ± 3.1 9.5 ± 2.8 N/A</td>
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<td>34</td>
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<td>8.3 ± 3.0 N/A N/A</td>
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<td>33</td>
<td>0.99 0.01</td>
<td>8.6 ± 3.0 10.0 N/A</td>
<td>0.508 N/A 0.647</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Exon5</td>
<td>W212X</td>
<td>27</td>
<td>0.90 0.10</td>
<td>8.1 ± 2.8 9.7 ± 3.3 N/A</td>
<td>0.242 N/A 0.257</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Exon4</td>
<td>Splice defect</td>
<td>16</td>
<td>0.66 0.34</td>
<td>8.6 ± 3.6 9.5 ± 2.6 7.0 ± 1.1</td>
<td>0.473 0.252 0.852</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Exon1</td>
<td>P34S</td>
<td>13</td>
<td>0.62 0.38</td>
<td>7.3 ± 3.2 8.2 ± 2.4 12.7 ± 3.3</td>
<td>0.190 0.089 0.276</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Exon4</td>
<td>Splice defect</td>
<td>34</td>
<td>1.00 0.00</td>
<td>8.3 ± 3.0 N/A N/A</td>
<td>N/A N/A N/A</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Intron3</td>
<td>Splice defect</td>
<td>2</td>
<td>0.24 0.76</td>
<td>6.3 ± 1.0 7.9 ± 3.4 9.4 ± 2.8</td>
<td>0.285 0.323 0.175</td>
</tr>
</tbody>
</table>

WT, homozygous reference sequence; Het, heterozygous variant; Var, homozygous variant; p, frequency for reference allele; q, frequency for variant allele; N/A, not available; $^a$Number represents amino acid codon; $^b$Hardy-Weinberg notation for allele frequencies. $P$-values were obtained from a Kruskal-Wallis test or a Mann-Whitney U-test.
FIGURE 1 Yamakawa Y et al.
Association of individual clearance with targeted genotypes.
Appendix 1
Yamakawa Y et al.
Distribution of plasma concentrations of imatinib.