Influence of Cytochrome P450 (CYP) 3A4*1G Polymorphism on the Pharmacokinetics of Tacrolimus, Probability of Acute Cellular Rejection, and mRNA Expression Level of CYP3A5 Rather than CYP3A4 in Living-Donor Liver Transplant Patients

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Association between cytochrome P450 (CYP) 3A4*1G genotype of donors (n=410) and/or recipients (n=410), and the pharmacokinetics of tacrolimus and the risk of acute cellular rejection was examined in Japanese living-donor liver transplant patients between 2004 and 2011. The concentration/dose (C/D) ratio of tacrolimus in patients carrying graft liver with CYP3A4*1/*1 was significantly higher during 7d after surgery than in that with CYP3A4*/1/*1G (214 vs. 157 [μg/mL]/[mg/kg/day], p<0.01). After postoperative day 8, no significant difference was observed among CYP3A4*1G genotypes in the graft liver. However, the C/D ratio in CYP3A4*1/*1 of the intestine was significantly higher than that in CYP3A4*1/*1G for 5 weeks after surgery (postoperative days 1–14; p<0.001, postoperative days 15–35; p<0.01). During postoperative days 14 and 26, acute cellular rejection incidences tended to be lower in the patients with graft liver carrying the CYP3A4*1/*1 allele than in the patients carrying CYP3A4*1G allele (8.7% vs. 14.6%, p=0.0973). However, CYP3A4*1G in the intestine had almost no effect on the incidence of rejection (9.9% in CYP3A4*/1/*1 vs. 12.5% in CYP3A4/1/*1G allele, p=0.4824). CYP3A4*1G was significantly related to mRNA expression of CYP3A4 rather than of CYP3A4 in the graft liver and intestine and was strongly linked with the CYP3A5*1. Thus, we elucidated that CYP3A4*1G genotype in the intestine was an important indicator of the pharmacokinetics of tacrolimus, whereas this genotype in the graft liver tended to influence the frequency of acute cellular rejection after transplantation.

Key words  cytochrome P450 3A4*1G; tacrolimus; acute cellular rejection; liver transplantation

The immunosuppressive regimen with tacrolimus, a primary immunosuppressive agent, is essential for patients after liver transplantation. Because tacrolimus has a narrow therapeutic range and large intra- and inter-individual variability, therapeutic drug monitoring is required to maintain appropriate blood concentrations and to determine optimal daily dose.1,2) The pharmacokinetics of tacrolimus is affected by single nucleotide polymorphisms (SNPs) in the genes encoding the drug metabolizing enzymes. Previously, we showed that the cytochrome P450 (CYP) CYP3A4*1 allele not only in the liver (donor genotype) but also in the small intestine (recipient genotype) achieved lower concentration/dose (C/D) ratio of tacrolimus than that with CYP3A5*3 (rs776746)*3 homozygotes in living-donor liver transplant patients.3–6) Recently, a new SNP in the CYP3A4 gene, CYP3A4*1G in intron 10, has been found in human lymphoblastoid cell lines from different ethnic groups and is the most common SNP in Japanese patients.7,8) Miura et al.9) reported that dose-adjusted area under the concentration–time curve and trough level of tacrolimus in renal transplant patients with CYP3A4*1G/*1G was lower than those in patients with CYP3A4*/1/*1. However, to date, no studies on this SNP have been performed in liver transplant patients in whom the genotype of the graft liver is different from that of the recipients. Moreover, it is unclear whether CYP3A4*1G genotype is relevant to clinical outcomes such as the incidence of acute cellular rejection. Adequate immunosuppression with tacrolimus in transplant patients is required to prevent the occurrence of acute cellular rejection and severe adverse effects, including infectious complications, hypertension and nephrotoxicity. On the basis of these backgrounds, we examined the association between CYP3A4*1G genotype and the pharmacokinetics of tacrolimus, and the probability of acute cellular rejection in living-donor liver transplant patients. In addition, we examined the influence of CYP3A4*1G genotype on the mRNA expression level of CYP3A4 or CYP3A5 in the graft liver or native intestine.

MATERIALS AND METHODS

Patients, Clinical Samples, and Criteria for Acute Cellular Rejection

Between July 2004 and June 2011, we enrolled 410 Japanese living-donor liver transplant patients who received with tacrolimus as a primary immunosuppressant at Kyoto University Hospital and 412 donors in this study after obtaining their written informed consent. Two to 410 recipients were underwent retransplantation during this period. After liver transplantation, patients received tacrolimus-based immunosuppressive therapy combined with corticosteroids and with or without mycophenolate mofetil. Methylprednisol-
lone (10 mg/kg) was intravenously administered at graft reperfusion, and the dosage was gradually reduced, and the patients were switched to oral prednisolone 1 week after surgery. The dosage was tapered off and discontinued between 3 and 6 months after the transplantation. We excluded the patients receiving ABO blood type incompatible transplant or retransplantation in retrospective observational analyses of acute cellular rejection. This study was performed in accordance with the Declaration of Helsinki and its amendments, and was approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee.

Clinical samples were obtained from the upper jejunum using a part of the Roux-en-Y limb for biliary reconstruction between July 2004 and May 2010. Liver samples were obtained from biopsy specimens for pathological testing of the graft at surgery between July 2004 and June 2011 (zero biopsy).

Acute cellular rejection was defined on the basis of histological examination of liver biopsy specimens and/or biochemical abnormalities such as increase in the transaminase levels. Most patients with acute cellular rejection were treated with intravenous injection of high-dose steroid (10 mg/kg/day).

Measurement of Tacrolimus Concentrations Whole-blood trough concentrations of tacrolimus before oral administration in the morning were measured. We measured the blood concentration of tacrolimus using a microparticle enzyme-linked immunnoassay (IMx®, Abbott, Tokyo, Japan) between July 2004 and March 2009 and using a chemiluminescent enzyme immunoassay (ARCHITECT®, Abbott) after April 2009. We validated the equivalence of the data obtained using these 2 methods (data not shown). The daily oral dose of tacrolimus that was adjusted to achieve the target trough blood concentrations was 10–15 ng/mL during the first 2 weeks, approximately 10 ng/mL during the next 2 weeks, and 5–7 ng/mL from the second month after surgery.

Genotyping of CYP3A4*1G and CYP3A5*3 Genomic DNA was extracted from homogenate of liver biopsy specimens and intestinal mucosa with MagNAPure LC RNA Isolation kit II (Roche) or AllPrep DNA/RNA Mini kit (Qiagen, Hilden, Germany), and from peripheral blood with MagNAPure LC RNA Isolation kit I (Qiagen, Hilden, Germany), and from peripheral blood with MagNAPure LC DNA Isolation kit I (Qiagen, Hilden, Germany), or EZ1 DNA Blood Kit (Qiagen) according to the manufacturer’s instruction. The CYP3A5*3 was detected using the polymerase chain reaction (PCR)-restriction fragment length polymorphism method as described previously. We genotyped the CYP3A4*1G using Taqman® Drug Metabolism Assays (catalogue number: C_26201900_30, Applied Biosystems, Foster, California, U.S.A.). PCR was performed according to the manufacturer’s instructions using StepOnePlus Real-Time PCR System (Applied Biosystems).

Evaluation of Hepatic and Intestinal mRNA Expression Levels of CYP3A4 and CYP3A5 Total RNA was extracted using biopsy specimens from the graft liver and intestinal mucosa with MagNAPure LC RNA Isolation kit II (Roche) or AllPrep DNA/RNA Mini kit (Qiagen, Hilden, Germany). The mRNA expression levels of CYP3A4 and CYP3A5 in the graft liver and native intestine were measured using real-time PCR using an ABI prism 7700 sequence detector (Applied Biosystems). The primer/probe sets used for in this experiment were those reported by Koch et al. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal control as described previously. The mRNA expression data for each sample was corrected by the amount of GAPDH.

Classical Selection of Patients According to CYP3A4*1G Genotype in the Donor and Recipient We determined whether the CYP3A4*1G polymorphism

<table>
<thead>
<tr>
<th>Classification</th>
<th>Liver (donor) CYP3A4*1G genotype</th>
<th>Intestine (recipient) CYP3A4*1G genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver 3A4<em>1G/Intestine 3A4</em>1G</td>
<td>*1/G/*1G, *1/*1G</td>
<td>*1G/*1G, *1/*1G</td>
</tr>
<tr>
<td>Liver 3A4<em>1G/Intestine 3A4</em>1</td>
<td>*1/G/*1G, *1/*1G</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Liver 3A4<em>1/Intestine 3A4</em>1G</td>
<td>*1/*1</td>
<td>*1G/*1G, *1/*1G</td>
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<tr>
<td>Liver 3A4<em>1/Intestine 3A4</em>1</td>
<td>*1/*1</td>
<td>*1/*1</td>
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</table>

Table 1. Classification of Patients According to CYP3A4*1G Genotype in the Donor and Recipient

RESULTS

Patients, Frequency of CYP3A4*1G Genotype and Its Association with mRNA Levels of CYP3A4 The demographics of recipients and donors in this study, including their age, sex, graft-to-recipient body weight ratio, and primary diseases, are shown in Table 2. The allele frequencies of CYP3A4*1G in the graft livers and native intestines were 0.22 and 0.24, respectively. The median expression levels of CYP3A4 mRNA in the graft liver and native intestine with CYP3A4*1G were 60.3, 52.5 and 55.2 amol/µg total RNA, and 5.44, 4.22 and 4.70 amol/µg total RNA, respectively; these values were not significantly different (Figs. 1A, B).
influenced the C/D ratio of tacrolimus \((n=407)\). The steroid was intravenously administered at a high dose to treat acute cellular rejection. The trough concentrations of tacrolimus during and for 4 d after this treatment were excluded because high-dose steroid therapy caused an increase in the intestinal CYP3A4 mRNA levels. The C/D ratio of tacrolimus in the patients with graft liver carrying CYP3A4*1/*1 genotype was significantly higher during the immediate 7 d after surgery than that with CYP3A4*1/*G (median, 214 vs. 157 \([\text{ng/mL}] / \left[ \text{mg/kg/day} \right]\); \(p<0.01\) by Kruskal–Wallis test) (Fig. 2A). However, after postoperative day 8, no significant difference was observed in the C/D ratio of tacrolimus on the basis of the genotypes of the graft liver (Figs. 2B–E). Recipients with CYP3A4*1/*1 had a statistically significant higher C/D ratio than those with CYP3A4*1/*G for all periods (postoperative days, 1–14; \(p<0.001\) and postoperative days, 15–35; \(p<0.01\), Kruskal–Wallis test).

**Influence of Combination of CYP3A4*1G Genotype in the Donor and Recipient on the C/D Ratio of Tacrolimus for 5 Weeks after Transplantation**

In the patients

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**Table 2. Recipient and Donor Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Total patients</th>
<th>Adult recipients</th>
<th>Pediatric patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>410</td>
<td>286</td>
<td>124</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>46 (0.1–69)</td>
<td>54 (15–69)</td>
<td>1.0 (0.1–14)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>185/225</td>
<td>137/149</td>
<td>48/76</td>
</tr>
<tr>
<td>Body weight (kg)*</td>
<td>52 (3.1–106)</td>
<td>59 (32–106)</td>
<td>8.7 (3.1–46)</td>
</tr>
<tr>
<td>GRWR (^\dagger) (%)</td>
<td>1.1 (0.5–5.3)</td>
<td>1.0 (0.5–2.1)</td>
<td>2.7 (0.7–5.3)</td>
</tr>
<tr>
<td>ABO blood group match (identical/compatible)</td>
<td>231/78/103</td>
<td>164/49/75</td>
<td>67/29/28</td>
</tr>
<tr>
<td><strong>Primary disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>225</td>
<td>224</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis C virus infection (^\dagger)</td>
<td>106</td>
<td>106</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis B virus infection (^\dagger)</td>
<td>57</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>35</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>alcoholic cirrhosis</td>
<td>11</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Other cirrhosis</td>
<td>16</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>100</td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>After liver transplantation</td>
<td>24</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Others (^\dagger)</td>
<td>43</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td><strong>Donor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>412</td>
<td>288</td>
<td>124</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>39 (20–66)</td>
<td>45 (20–66)</td>
<td>34 (21–64)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>213/199</td>
<td>138/150</td>
<td>61/63</td>
</tr>
</tbody>
</table>

\(^\dagger\)Data are expressed as medians with ranges in parenthesis. \(^\ddagger\)GRWR: graft-to-recipient body weight ratio \(^\dagger\)Two patients with hepatitis C were complicated with hepatitis B virus, and two were complicated with alcoholic cirrhosis. The condition of 1 patient with hepatitis B was complicated with alcoholic cirrhosis. \(^\dagger\)The primary diseases with case numbers in parentheses (adults, pediatrics) were autoimmune hepatitis (5, 0), Byler disease (0, 2), Budd–Chiari syndrome (4, 0), Caroli (1, 0) or Wilson (3, 0) disease, non-alcoholic steatohepatitis (4, 0), biliary dilation (0, 2), hyperoxaluria (1, 1), hypothyroidism (1, 0), polycystic liver disease (2, 0), Alagille syndrome (0, 3), ornithine carbamyl-transferase deficiency disease (1, 0), glycogenosis (2, 0), Jeune’s syndrome (0, 1), congenital extrahepatic portosystemic shunt (0, 1), carbamyl phosphate synthetase deficiency (0, 1), somatostatinoma (1, 0), argininosuccinate lyase deficiency (0, 1), amyloidosis (1, 0), hemangioendothelioma (0, 1), and portal vein deficiency (0, 4).

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**Fig. 1. Effect of Cytochrome P450 (CYP) 3A4*1G Polymorphism on the mRNA Expression Levels of CYP3A4 in the Graft Liver and Small Intestine**

The mRNA expression levels of CYP3A4 were determined using real-time polymerase chain reaction method in the graft liver (donors, A) and intestinal mucosa (recipients, B).
Fig. 2. The Influence of Cytochrome P450 (CYP) 3A4 Polymorphism in the Graft Liver or Recipient Intestine on the Concentration/Dose (C/D) Ratio of Tacrolimus in Living-Donor Liver Transplant Recipients over 5 Weeks

The mean tacrolimus C/D ratio for the period 1–7 (A, F), 8–14 (B, G), 15–21 (C, H), 22–28 (D, I), and 29–35 (E, J) days after transplantation was compared on the basis of the CYP3A4 genotype. The bar shows the median of the tacrolimus C/D ratio in each group. *p < 0.05, **p < 0.01, ***p < 0.001, significant difference between groups. POD; postoperative days.

Fig. 3. The Influence of Combinations of Graft Liver and Native Intestinal Cytochrome P450 (CYP) 3A4 Genotype on the Concentration/Dose (C/D) Ratio of Tacrolimus for 1–35 Days after Living-Donor Liver Transplantation

The patients in whom the CYP3A4 genotype was determined in both donors and recipients were categorized into 4 groups on the basis of graft genotype and intestinal genotype, respectively. (*1G; CYP3A4*1G*/1G and CYP3A4*1/*1G, *1; CYP3A4*1/*1). The C/D ratio of tacrolimus is compared in each group for 5 weeks, over the period 1–7 (A), 8–14 (B), 15–21 (C), 22–28 (D), and 29–35 (E) days after transplantation. *p < 0.05, **p < 0.01, ***p < 0.001, significant difference between groups. POD; postoperative days.
receiving living-donor liver transplantation, the difference of \( \text{CYP3A4}^*1G \) SNPs should be considered in the graft liver (donor) and in the native intestine (recipient). To examine the influence of genotype matching, we classified patients into 4 groups according to each genotype of the donor and recipient, including \( \text{CYP3A4}^*1G^*/1G \) and \( \text{CYP3A4}^*1/1G \) in \( \text{CYP3A4} \) genotype (Table 2).

![Fig. 4. Effect of Hepatic or Intestinal Cytochrome P450 (CYP) 3A4*1G Polymorphism on the Frequency of Acute Cellular Rejection during Postoperative Days 14 and 26](image)

The Kaplan–Meier curve shows the association of occurrence of acute cellular rejection and \( \text{CYP3A4}^*1G \) genotype in liver (donors; A) or intestine (recipients; B), and in pediatric patients (C) or adult patients (D) that have the same \( \text{CYP3A4}^*1G \) genotype both in graft liver and native intestine (Liver 3A4*1G/Intestine 3A4*1G or Liver 3A4*1/Intestine 3A4*1).

![Fig. 5. Linkage between Cytochrome P450 (CYP) 3A4*1G and CYP3A5*3 Single Nucleotide Polymorphisms](image)

Both \( \text{CYP3A4}^*1G \) and \( \text{CYP3A5}^*3 \) genotype were determined in the donors and recipients (\( n=818 \)). Blue, green, and red columns indicate percentage of \( \text{CYP3A5}^*1/1^1 \), \( \text{CYP3A5}^*1/3^3 \) and \( \text{CYP3A5}^*3/3^3 \) genotype in each \( \text{CYP3A4}^*1G \) genotype, respectively.
The mRNA expression levels of CYP3A5 were determined using the real-time polymerase chain reaction method in the graft liver (donors, A) and intestinal mucosa (recipients, B). ***p<0.001, significant difference between groups.

**A)** donor’s genotype vs. CYP3A5 mRNA level in the liver

**B)** recipient’s genotype vs. CYP3A5 mRNA level in the intestine

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**Effect of CYP3A4*1G Allele on the Frequency of Acute Cellular Rejection during Postoperative Days 14 and 26 in Living-Donor Liver Transplant Patients**

To elucidate whether CYP3A4*1G polymorphisms in the graft liver and native intestine were associated with patient outcome, we retrospectively obtained data about events of acute cellular rejection during postoperative days 14 and 26 in living donor liver transplant patients from medical record. The mRNA expression level of multidrug resistance 1 (MDR1) in the native intestine has almost no effect on the clearance of tacrolimus after oral administration in liver transplant patients.

Thus, we set the term to examine the association between the genotype and clinical event for two weeks from the surgery.

The mRNA expression levels of CYP3A5 in the graft liver (donors, A) and intestinal mucosa (recipients, B) in living-donor liver transplantation. We showed that the C/D ratio of tacrolimus in living-donor liver transplant patients comparable with data reported in kidney transplantation.

In the present study, CYP3A4*1G genotype showed a significant association with the C/D ratio of tacrolimus in living-donor liver transplant patients comparable with data reported in kidney transplantation. We showed CYP3A4*1G genotype showed no correlation with the mRNA expression level of CYP3A4 both in graft liver and native intestine. Consistent with the finding by Fukushima-Uesaka et al., our results showed that the CYP3A4*1G genotype was strongly linked with the CYP3A5*3/*3 genotype (93.6%). Furthermore, CYP3A4*1G genotype showed a significant association with the mRNA expression level of CYP3A5 rather than CYP3A4 in the graft liver and native intestine. Taken together, our results suggested that the pharmacokinetic effect of CYP3A4*1G genotype mainly reflects the influence of CYP3A5*3 genotype in the liver and intestine.

The contributions of CYP3A4*1G genotype on the pharmacokinetics of tacrolimus between the liver and intestine could be compared in the liver transplant patients, because the genotype of the graft liver was basically different from that of the recipients. In the present study, we showed that the C/D ratio of tacrolimus in the patients with intestinal CYP3A4*1G allele was lesser than that with intestinal CYP3A4*1G/*1 during 3 weeks after surgery when they were engrafted with the liver carrying CYP3A4*1G. These results are similar to our previous results, which focused on the CYP3A5*3/*3 genotype. These results support the strong linkage between CYP3A4*1G genotype and CYP3A5*1G genotype in the pharmacokinetics of tacrolimus in liver transplant patients. To clarify the statistical significance of CYP3A4*1G genotype in tacrolimus pharmacokinetics, the multivariate analysis is needed. However, in the present study, the CYP3A4*1G genotype in only the 75 among 818 subjects including recipients and donors did not link with CYP3A5*3 genotype. Therefore, we could not carry out this analysis for the shortage of cases. In addition, influence of...
the probability of acute cellular rejection was analyzed for intestine tended to show a higher occurrence of acute cellular rejection than CYP3A4*1/*1. However, to date, no information is available about the molecular mechanism of the effect of CYP3A4*1G genotype on the activity of drug metabolism in the liver. Because the CYP3A4*1G genotype is an intronic SNP, molecular effect of the SNP might be on the expression level of matured CYP3A4 and/or CYP3A5. In the present study, the CYP3A4*1G genotype was clearly associated with the mRNA expression level of CYP3A5 rather than of CYP3A4. Although further molecular examination is required, the phenotype of CYP3A4*1G1 may be explained on the basis of the function of CYP3A5. The CYP3A4*1G genotype was strongly but not completely linked to the CYP3A5*1 genotype. Some patients without linkage between the 2 genotypes may be useful models to clarify the molecular mechanisms underlying the functional influence of CYP3A4*1G genotype. Moreover, to examine the influence by the age of recipients, patients were divided into two groups; that is, pediatric patients (less than 15 years) and adult patients (above 15 years). In groups with the same phenotype both in graft liver and intestine, pediatric patients have no difference in the probability of acute cellular rejection between CYP3A4*1G genotype. However, adult patients with CYP3A4*1G allele both in graft liver and intestine had higher probability of the acute cellular rejection than that with CYP3A4*1/*1 both in graft liver and intestine. Because graft liver size in adult recipients is larger than that in pediatric recipients, the effect of the CYP3A4*1G genotype in graft liver on the occurrence of acute cellular rejection in adult patients might be larger than that in pediatric patients, even though the cause of this difference was unclear. Taken together, we elucidated that CYP3A4*1G genotype in the small intestine of recipients was more important as an indicator of the systemic exposure of tacrolimus for 1 month after transplantation compared to that in graft liver, whereas patients with CYP3A4*1G allele in graft liver tended to have a higher frequency of acute cellular rejection after transplantation than those in patients with CYP3A4*1/*1. In addition, the molecular relation between CYP3A4*1G genotype and CYP3A5*3 genotype should be precisely elucidated in the future with several substrate drugs in addition to tacrolimus. Although CYP3A4*1G genotype in the graft liver might be a risk factor of occurrence of acute cellular rejection after postoperative day 14 in living-donor liver transplantation, especially in adult patients, further studies are required to elucidate the association between CYP3A4*1G genotype and the clinical outcome, acute cellular rejection, nephrotoxicity, etc., in these patients.

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