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ORIGINAL ARTICLE

A single-nucleotide polymorphism in a gene modulating glucocorticoid sensitivity is associated with the decline in total lung capacity after lung transplantation

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Abstract

Purpose Glucocorticoids are used to prevent chronic lung allograft dysfunction (CLAD) after lung transplantation (LT). Our study was aimed at assessing the association between the glucocorticoid-induced transcript 1 gene (GLCCI1) variant, which modulates glucocorticoid sensitivity, and the postoperative lung function and development of CLAD after LT.

Methods A total of 71 recipients of LT were genotyped for the GLCCI1 variant (rs37972) and divided into three groups: the homozygous mutant allele (TT) group, the heterozygous mutant allele (CT) group, and the wild-type allele (CC) group. The results of pulmonary function tests were compared with the postoperative baseline values.

Results The total lung capacity (TLC) in the TT group was significantly lower than that in the CC group at 3 years after LT ($P=0.029$). In the recipients of cadaveric LT, the TLC and forced expiratory volume in 1 s in the TT group were significantly lower than those in the CC groups, resulting in a significant worse CLAD-free survival at 3 years after LT ($P=0.016$).

Conclusion The GLCCI1 variant was associated with a significant decrease of the TLC at 3 years after LT and the development of CLAD at 3 years, especially in patients undergoing cadaveric LT.

Keywords Lung transplantation · Glucocorticoid · Single-nucleotide polymorphism · Total lung capacity · Chronic lung allograft dysfunction

Introduction

The long-term survival after lung transplantation (LT) remains worse than that after other solid organ transplantations [1–3], and chronic lung allograft dysfunction (CLAD) is a major obstacle to the long-term survival after LT. To prevent CLAD after LT, adequate immunosuppression is key [4, 5]. At present, the most commonly used maintenance immunosuppression regimen after LT is a triple regimen consisting of a calcineurin inhibitor, mycophenolate mofetil, and a glucocorticoid [3]. Of these, the doses of the calcineurin inhibitor and mycophenolate mofetil are currently adjusted by monitoring the trough blood levels of the drug in each patient, whereas the dose of the glucocorticoid is uniformly tapered to 5–10 mg per day for maintenance therapy, according to the body weight or body surface area of the patients. Because individual glucocorticoid sensitivity is known to be influenced by various factors [6–11], monitoring the therapeutic levels of glucocorticoids is not a realistic option. Nonetheless, recipients of LT generally require glucocorticoids over their lifetimes, although the successful withdrawal of glucocorticoids after LT has previously been reported in a few patients after LT [12, 13]. Given the difficulty in monitoring the therapeutic levels of glucocorticoids, the routinely used maintenance dose of glucocorticoids might be insufficient for patients with poor

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glucocorticoid sensitivity, which may influence the risk of the onset of CLAD after LT.

Recently, a screening analysis of more than 530,000 SNPs revealed that the functional single-nucleotide polymorphism (SNP) rs37972, which maps to the glucocorticoid-induced transcript 1 gene (GLCCI1) and modulates glucocorticoid sensitivity, is associated with a decreased efficiency of glucocorticoid inhalation therapy in patients with asthma and chronic obstructive pulmonary disease (COPD) [14, 15]. Because the GLCCI1 gene is strongly expressed in the lung and lymphoid tissues, including T and B lymphocytes, the pharmacologic response to glucocorticoids and the postoperative lung graft function in recipients of LT might also be influenced by the presence of this functional GLCCI1 variant, similar to the patients with asthma and COPD described above [14, 15]. However, the association between the presence of the functional GLCCI1 variant and the postoperative lung graft function in recipients of LT remains to be clarified.

In this study, we investigated the association between the functional GLCCI1 gene polymorphism-modulating glucocorticoid sensitivity and the postoperative lung graft function, including the risk of development of CLAD after LT.

Methods

Patients

This was a single-center retrospective cohort study conducted in a cohort of 71 patients who underwent LT, including 33 cases of cadaveric LT (CLT) and 38 cases of living-donor lobar lung transplantation (LDLLT), at Okayama University Hospital between October 1998 and June 2014. Blood samples were collected from all 71 patients between September 2016 and August 2017. The maximum total number of human leukocyte antigen (HLA) mismatches could equal 12 in bilateral LDLLT involving 2 different donors and 6 in single LDLLT and CLT involving only 1 donor.

The study protocol (No. 1610-037) was approved by the institutional review board of Okayama University Hospital. Written informed consent for the study was obtained from each of the patients. All of the methods were performed in accordance with the relevant guidelines and regulations.

SNP genotyping

A genotype analysis for the functional polymorphism of the GLCCI1 gene (rs37972) was conducted in all 71 patients. Genomic DNA was isolated from whole blood with a TaqMan® Sample-to-SNP™ kit (Applied Biosystems, Foster City, CA, USA). Samples were analyzed by a TaqMan genotyping assay using the StepOne™ real-time polymerase chain reaction (PCR) system (Applied Biosystems) in a 96-well array plate that included 4 blank wells as negative controls. The polymerase chain reaction (PCR) profile consisted of an initial denaturation step at 95 °C for 20 s, 40 cycles at 95 °C for 3 s, and at 60 °C for 20 s. The PCR products were analyzed by the StepOne™ Software Ver 2.3 (Applied Biosystems). To assess the quality of the genotyping, repeat genotyping was conducted in a randomly selected 5% of the samples, and 100% agreement was confirmed. Based on the results of the genotyping, the patients were divided into three groups: the homozygous mutant T allele (TT) group, the heterogeneous mutant allele (CT) group, and the homozygous wild-type allele (CC) group.

The evaluation of the pulmonary function

To evaluate the postoperative changes in the pulmonary function parameters over time, the forced expiratory volume in 1 s (FEV1; an indicator for diagnosing obstructive CLAD [bronchiolitis obliterans syndrome, BOS]) [16], forced vital capacity (FVC; an indicator to diagnose restrictive CLAD [restrictive allograft syndrome, RAS]) [16], and total lung capacity (TLC; the indicator originally used to diagnose RAS) [17], were measured at 3, 6,12, 24, and 36 months after LT and compared with the postoperative stable baseline values among the three groups. The postoperative stable baseline values were calculated as the mean values between the two best points in postoperative pulmonary function tests. In addition, a subgroup analysis was performed based on the type of lung donor (cadaveric or living). CLAD was diagnosed using the classification system proposed by the International Society for Heart and Lung Transplantation (ISHLT) [16]. For the differential diagnosis of CLAD, a blood examination, chest X-ray, computed tomography of the chest, ventilation–perfusion scanning, the 6-min walk test, electrocardiogram, and echocardiogram were also performed at the same time as the pulmonary function testing.

Statistical analyses

All statistical analyses were performed using the GraphPad Prism 7.04 software program (San Diego, CA, USA). The postoperative changes in the pulmonary function parameters were expressed as the mean percentages ± standard errors of the baseline values. Difference in the baseline characteristics among the groups was tested by the Kruskal–Wallis test for continuous variables and Pearson's Chi-square test for categorical variables. Differences among the % baseline values of the individual measures in the different genotype groups were analyzed by a one-way analysis of variance followed by Tukey's test for individual between-group comparisons. The CLAD-free survival rate was analyzed using the Kaplan–Meier method, and the log-rank test was used

for the statistical comparison of the differences among the groups. Differences were considered significant at $P < 0.05$.

Results

The patient characteristics are shown in Table 1. The frequencies of the GLCCI1 gene polymorphism in our cohort were similar to those reported in a previous study [18]. The clinical characteristics of the patients were similar among the three groups. There were no significant differences in the

Table 1 Patient characteristics

	CC ($N=33$)	CT ($N=28$)	TT ($N=10$)	P value
Preoperative variables				
Age, years, median (range)	29 (7–55)	38 (10–61)	36.5 (13–57)	0.33
Gender				
Male	11 (33%)	10 (36%)	3 (30%)	0.94
Female	22 (66%)	18 (64%)	7 (70%)	
Body mass index, median (range)	16.7 (12.4–25.9)	17.7 (10.8–28.8)	18.8 (13.7–23.1)	0.26
Diagnoses				
Interstitial lung disease	7 (21%)	10 (36%)	2 (20%)	0.61
Pulmonary hypertension	7 (21%)	8 (29%)	2 (20%)	
Pulmonary graft-versus-host disease	6 (18%)	2 (7%)	1 (10%)	
Emphysema	2 (6%)	3 (11%)	0 (0%)	
Bronchiectasis	2 (6%)	2 (7%)	1 (10%)	
Other diseases	9 (27%)	3 (11%)	4 (40%)	
Preoperative use of glucocorticoids, yes	7 (21%)	10 (36%)	5 (50%)	0.18
Preoperative diabetes mellitus, yes	1 (3%)	3 (11%)	0 (0%)	0.30
Lung allocation score, median (range)	38.1 (32.9–86.0)	40.7 (32.9–58.5)	39.0 (33.5–45.8)	0.73
CMV mismatch (recipient negative/donor positive), yes	5 (15%)	6 (21%)	1 (10%)	0.66
Lung donor				
Living donor	17 (52%)	15 (54%)	6 (60%)	0.89
Deceased donor	16 (48%)	13 (46%)	4 (40%)	
Total number of HLA-A, HLA-B, and HLA-DR mismatches, median (range)	5 (2–10)	5 (3–9)	5 (3–7)	0.69
Intraoperative variables				
Lung transplant procedure				
Single	4 (12%)	6 (21%)	1 (10%)	0.53
Double	29 (88%)	22 (79%)	9 (90%)	
Operative time (min), median (range)	466 (238–682)	493 (247–690)	514 (352–785)	0.39
Ischemic time (min), median (range)	209 (74–701)	193 (89–665)	217 (136–787)	0.47
Cardiopulmonary bypass use, yes	30 (91%)	25 (89%)	9 (90%)	0.98
Postoperative variables				
Maximum grade of PGD (0–72 h), median (range)	2 (0–3)	0 (0–3)	1 (0–3)	0.31
Acute rejection, yes	12 (36%)	15 (54%)	3 (30%)	0.28
Antibody-mediated rejection, yes	3 (9%)	2 (7%)	0 (0%)	0.62
Postoperative GERD, yes	1 (3%)	1 (4%)	0 (0%)	0.84
Total amount of glucocorticoids within 90 days after transplant (mg), median (range)	2817 (960–9750)	2199 (1571–15,541)	2327 (2014–7093)	0.91
Maintenance dose of glucocorticoids (mg/day), median (range)	5 (2.5–7.5)	5 (3.75–8)	5 (5–7)	0.63
Time since transplant to follow-up (day), median (range)	2113 (950–6298)	2608 (796–5931)	1797 (889–5293)	0.27

Data are presented as *n*, median (range), or *n* (%)

CMV cytomegalovirus, *GERD* gastroesophageal reflux disease, *HLA* human leukocyte antigen, *PGD* primary graft dysfunction

previously described risk factors for CLAD, including HLA mismatches, cytomegalovirus mismatches, primary graft dysfunction, acute rejection, and gastroesophageal reflux disease [19]. The total amount of glucocorticoids administered during the first 90 days after LT and the maintenance dose of glucocorticoids did not differ significantly among the three groups. CLAD developed in nine patients during the first 3 years after LT.

As shown in Fig. 1, the percent baseline value of the TLC at 3 years after LT was significantly lower in the TT group than in the CC group ($P=0.029$) (Fig. 1a). In contrast, there were no significant differences in the percent baseline values of the FEV1 or FVC at 3 years after LT among the three genotype groups (Fig. 1b, c). Of note, in the recipients of CLT (Table 2), the percent baseline value of TLC as well as that of FEV1 at 3 years after LT was significantly lower in the TT group than in the CC group (TLC, $P=0.031$; FEV1, $P=0.0074$) (Fig. 2a, b).

The CLAD-free survival rates at 3 years after LT were similar among the three groups (Fig. 3a). However, in the recipients of CLT, the CLAD-free survival rate at 3 years after LT was significantly worse in the TT group than in the CC group (Fig. 3b, $P=0.016$), whereas no significant differences in the CLAD-free survival rates at 3 years after LT were noted among the three groups ($P=0.82$) in the recipients of LDLLT.

Discussion

In this study, we found that the presence of the GLCCI1 gene polymorphism rs37972, which modulates glucocorticoid sensitivity, was associated with a significant decrease in the TLC at 3 years after LT (both CLT and LDLLT). In the recipients of CLT, the functional GLCCI1 variant was associated with a significant decrease in not only the TLC but also of the FEV1 and also a significantly worse CLAD-free survival rate at 3 years after CLT. These results suggest that this SNP might be a risk factor for a decline in the TLC after LT as well as for a decline in the FEV1 and the development of CLAD after CLT.

Although glucocorticoid sensitivity in LT recipients has received a little attention to date, the recipients with the TT genotype of GLCCI1 showed a lower TLC at 3 years after LT than other genotypes in this study. This result indicates that, for patients with a decreased glucocorticoid sensitivity, the routinely used maintenance dose of glucocorticoid might not be sufficient to prevent a decline in the TLC after LT. Individual glucocorticoid sensitivities can be influenced by various factors, including genetic factors, the number of cellular glucocorticoid receptors, and the availability of glucocorticoids [6–11]. The GLCCI1 genotype may influence dexamethasone-induced apoptosis of immune cells [14, 20]. In addition, different foci of lymphoid neogenesis in different anatomical compartments of the lung, such as small airways and many anatomical compartments of the lung, may contribute to different phenotypes of CLAD (e.g., BOS and RAS) [21]. We, therefore, speculated that, in LT recipients with decreased glucocorticoid sensitivity, the decreased induction of apoptosis of lymphocytes might trigger lymphoid neogenesis, predominantly in the anatomical compartments of the lung, causing a decline in the TLC after LT. In addition, our study focused on the GLCCI1 variant in the recipients and not the donors. This is because lymphoid neogenesis in the transplanted lung has been shown to be derived from the recipient's bone marrow [22], which is closely involved in the development of allograft rejection after LT. Further examinations will be required to clarify the mechanism underlying the decline in the TLC in LT recipients with decreased glucocorticoid sensitivity.

Regarding the pulmonary function markers of CLAD, the GLCCI1 variant was associated with a significant

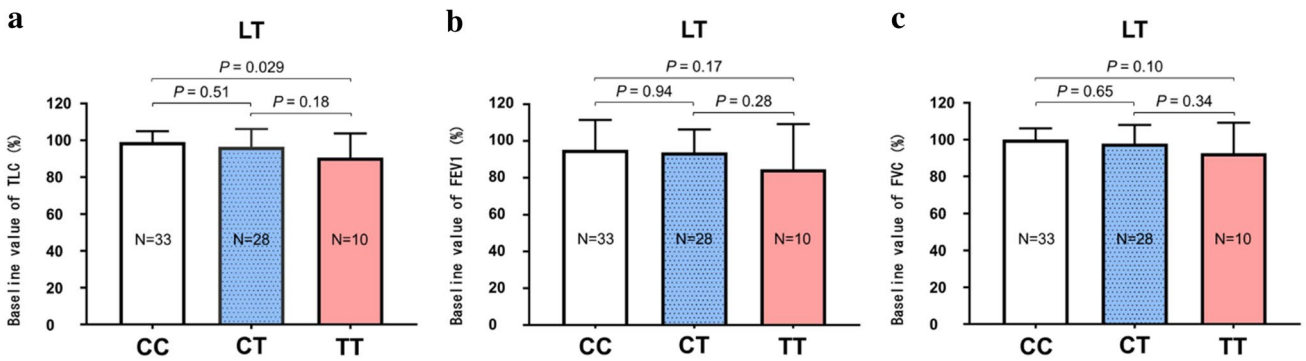

Fig. 1 Postoperative changes in the pulmonary function at 3 years after lung transplantation (LT) in the recipients according to the GLCCI1 genotype. **a** Total lung capacity (TLC), **b** forced expiratory volume in 1 s (FEV1), and **c** forced vital capacity (FVC) in all the recipients of LT. The percent baseline values of TLC in all of the recipients of LT (**a**) in the homozygous mutant T allele (TT) group were significantly lower than those in the homozygous wild-type allele (CC) group

Table 2 Patient characteristics of cadaveric lung transplantation

	CC ($N=16$)	CT ($N=13$)	TT ($N=4$)	P value
Preoperative variables				
Preoperative use of glucocorticoids, yes	2 (13%)	5 (38%)	1 (25%)	0.27
Preoperative diabetes mellitus, yes	1 (6%)	2 (15%)	0 (0%)	0.55
Lung allocation score, median (range)	36.1 (32.9–51.0)	39.8 (32.9–48.3)	36.7 (33.5–42.2)	0.94
CMV mismatch (recipient negative/donor positive), yes	3 (19%)	3 (23%)	0 (0%)	0.58
Total number of HLA-A, HLA-B, and HLA-DR mismatches, median (range)	5 (3–6)	5 (3–6)	5 (4–6)	0.69
Intraoperative variables				
Lung transplant procedure				
Single	3 (19%)	5 (38%)	1 (25%)	0.49
Double	13 (81%)	8 (62%)	3 (75%)	
Operative time (min), median (range)	516 (238–682)	472 (247–690)	553 (352–654)	0.75
Ischemic time (min), median (range)	540 (286–701)	462 (92–665)	596 (460–787)	0.20
Cardiopulmonary bypass use, yes	13 (81%)	10 (77%)	3 (75%)	0.94
Postoperative variables				
Maximum grade of PGD (0–72 h), median (range)	2 (0–3)	1 (0–3)	1.5 (1–3)	0.36
Acute rejection, yes	3 (19%)	5 (38%)	0 (0%)	0.23
Antibody-mediated rejection, yes	0 (0%)	1 (8%)	0 (0%)	0.45
Postoperative GERD, yes	0 (0%)	0 (0%)	0 (0%)	–
Total amount of glucocorticoids within 90 days after transplant (mg), median (range)	2261 (1800–5464)	2251 (1879–4578)	2223 (2014–2304)	0.88
Maintenance dose of glucocorticoids (mg/day), median (range)	5 (5–7.5)	5 (4–5)	5 (5–5)	0.20
Time since transplant to follow-up (day), median (range)	1637 (950–4628)	1898 (796–4184)	1519 (889–1916)	0.59

Data are presented as *n*, median (range), or *n* (%)

CMV cytomegalovirus, *GERD* gastroesophageal reflux disease, *HLA* human leukocyte antigen, *PGD* primary graft dysfunction

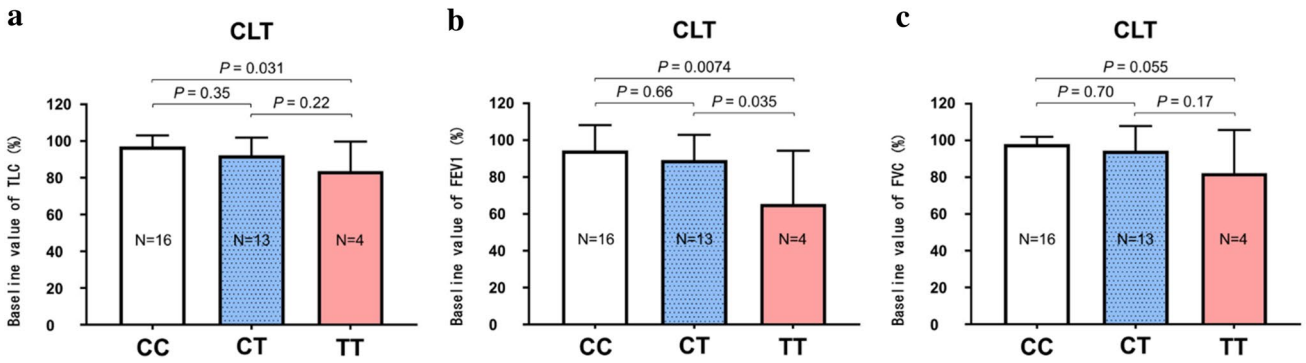

Fig. 2 Postoperative changes in the pulmonary function at 3 years after cadaveric lung transplantation (CLT) in the recipients according to the GLCCI1 genotype. **a** Total lung capacity (TLC), **b** forced expiratory volume in 1 s (FEV1), and **c** forced vital capacity (FVC) in the recipients of CLT. The percent baseline values of TLC **a** and FEV1 **b** in the recipients of CLT in the homozygous mutant T allele (TT) group were significantly lower than those in the homozygous wild-type allele (CC) group

difference only in the TLC, but not in the FEV1 or FVC after LT, although in the subgroup analysis, there was a significant difference in the TLC and FEV1 in the TT group compared with the CC group in the recipients of CLT. Originally, RAS was characterized by upper lobe-predominant fibrotic changes and a restrictive pulmonary function test profile, defined as FEV1 ≤ 80% of the baseline FEV1, and TLC ≤ 90% of the baseline TLC for ≥ 3 weeks [17]. FVC has since been proposed as a more practically measured marker for diagnosing RAS [16], as TLC is not routinely measured at LT centers worldwide. However, our results suggest that TLC might be a more sensitive

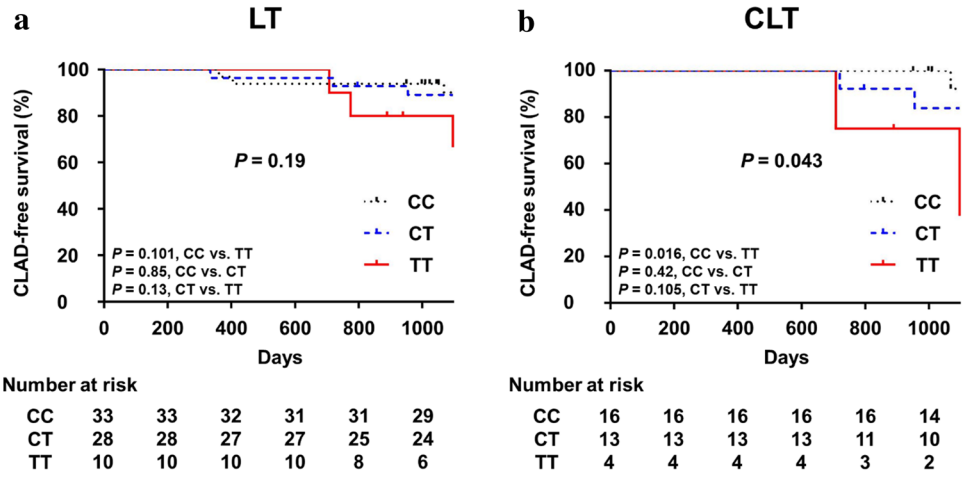

Fig. 3 Chronic lung allograft dysfunction (CLAD)-free survival after lung transplantation (LT) according to the rs37972 genotype. **a** There were no significant differences in the CLAD-free survival among the three groups after LT. **b** In the recipients of cadaveric lung transplantation (CLT), the CLAD-free survival in the homozygous mutant T allele (TT) group was significantly worse than that in the homozygous wild-type allele (CC) group ($P = 0.016$)

indicator for diagnosing RAS than FVC, as previously described [17].

The differences in the outcomes between CLT and LDLLT could reflect the postoperative expansion of the undersized lobar grafts after LDLLT. LDLLT is still a realistic option for resolving the severe donor shortage in Japan, and in LDLLT, the right and left lower lobes from two healthy donors are implanted in the recipient in place of the whole lungs. Because of the placement of undersized lobar grafts into the large chest cavity of the recipient, the FEV1 and FVC can increase up to 2 years after LDLLT [23]. Therefore, the expansion of the transplanted lobes during the first 2 years after LDLLT can be offset by a reduction in the TLC. Furthermore, because of the immunogenic heterogeneity of the transplanted lobes obtained from two different donors, CLAD develops unilaterally in most recipients after LDLLT, and the unaffected contralateral lobar lung acts as a reservoir [24]. These characteristics might enable the maintenance of the pulmonary function after LDLLT and lend support to our finding of the GLCCI1 variant being associated with a worse CLAD-free survival only after CLT. A better understanding of the effect of the GLCCI1 variant in LDLLT recipients might be obtained from the long-term follow-up of these patients.

Several limitations associated with the present study warrant mention. First, this was a retrospective study conducted at a single transplant center, and the number of patients was small. Second, the follow-up period was middling, and longer follow-up periods will be required for the further validation of the incidence of CLAD. Third, this study targeted only Japanese patients, thereby limiting the generalizability of the results.

In conclusion, the presence of a functional GLCCI1 gene polymorphism-modulating glucocorticoid sensitivity was associated with a decline in the TLC at 3 years after LT. Furthermore, in the recipients of CLT in particular, the GLCCI1 variant was associated with a decrease in the TLC and FEV1 and a worse CLAD-free survival at 3 years after CLT. Genotyping for this SNP might prove useful for adjusting the glucocorticoid dose to prevent a decline in the TLC after LT and reducing the risk of CLAD after CLT.

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Compliance with ethical standards

Conflict of interest Haruchika Yamamoto and his co-authors have no conflicts of interest.

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