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ASSOCIATIONS OF *ABCB1* AND *IL-10* GENETIC POLYMORPHISMS WITH SIROLIMUS-INDUCED DYSLIPIDEMIA IN RENAL TRANSPLANT RECIPIENTS

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Abstract

Backgrounds—Hyperlipidemia is a common adverse effect of sirolimus (SRL). We previously showed significant associations of *ABCB1* 3435C>T and *IL-10* -1082G>A with log-transformed SRL dose-adjusted, weighted-normalized trough. We further examined to see whether these polymorphisms were also associated with SRL-induced dyslipidemia.

Methods—Genotyping was performed for *ABCB1* 1236C>T, 2677 G>T/A, and 3435C>T, *CYP3A4* -392A>G, *CYP3A5* 6986A>G and 14690G>A, *IL-10* -1082G>A, *TNF* -308G>A, and *ApoE* *e2*, *e3*, and *e4* alleles. The longitudinal changes of total cholesterol (TC), low-density lipoprotein (LDL)-C, and triglyceride (TG) levels after SRL treatment prior to statin therapy were analyzed by a linear mixed-effects model, with adjustments for selected covariates for each lipid.

Results—Under the dominant genetic model, *ABCB1* 3435C>T was associated with TC (p=0.0001) and LDL-C (p<0.0001) values after SRL administration. Mean TC and LDL-C levels were 26.9 and 24.9 mg/dL higher, respectively, in *ABCB1* 3435T carriers than 3435CC homozygotes at an average SRL trough concentration of 4 ng/mL without concomitant medication. *ABCB1* 1236C>T under the recessive model and *IL-10* -1082G>A under the dominant model were associated with log-transformed TG values (p=0.0051 and 0.0436, respectively). Mean TG value was 25.1% higher in *ABCB1* 1236TT homozygotes compared to *ABCB1* 1236C carriers and was 12.4% higher in *IL-10* -1082AA homozygotes than -1082G carriers.

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Conclusions—*ABCB1* polymorphisms were found to be associated with lipid responses to SRL treatment, confirming the role of *ABCB1* gene in SRL pharmacokinetics and pharmacodynamics. Further studies are necessary to define the role of *ABCB1* and *IL-10* polymorphisms on SRL-induced dyslipidemia in renal transplantation.

Keywords

Sirolimus; *ABCB1*; total and LDL cholesterol; triglyceride; pharmacogenetics

Introduction

Sirolimus (SRL) (Rapamune®, Wyeth Pharmaceuticals Inc., Philadelphia, PA) is a potent immunosuppressant that is used for the prevention of renal transplant rejection. One of the common adverse effects of SRL is hyperlipidemia. In the pivotal registration trials of SRL, hypercholesterolemia occurred in 46 – 80% and hypertriglyceridemia in 43 – 78% of renal transplant recipients receiving SRL in addition to maintenance cyclosporine with or without prednisone during the first 6 months after transplantation (1). The levels of total cholesterol (TC) and triglyceride (TG) were significantly increased compared with baseline at 1 to 3 months after transplantation, and these elevations were sustained beyond the third to fourth year post-transplantation while some patients were on lipid lowering therapy (1). Low-density lipoprotein (LDL)-C was increased in a time course resembling the elevation of TC (2), and increased levels of apolipoprotein B100, C2, and C3 were observed (2–5). SRL had no effects on high-density lipoprotein (HDL)-C levels (2,3,6). The mechanisms of SRL-induced hyperlipidemia are not well understood. It has been shown that SRL modified cholesterol homeostasis by reducing LDL receptors in hepatic cells, which could result in a delay in LDL-C clearance from circulation causing an increase in plasma TC concentration (7). Additionally, mRNA expression of several genes that are involved in lipid uptake and storage was down regulated in adipose tissue of rats receiving chronic SRL treatment (8).

Previously, we investigated the influence of genetic polymorphisms of drug metabolizing enzymes, transporter proteins, and cytokines on SRL long-term dose requirements. The adenosine triphosphate-binding cassette, subfamily B, member 1 (*ABCB1*) 3435C>T under the dominant genetic model and interleukin (*IL*)-10-1082G>A under the recessive genetic model were found to be significantly associated with log-transformed SRL dose-adjusted, weighted-normalized trough concentration (C/D) (9). Mean SRL C/D was 48% higher in patients with *ABCB1* 3435CT/TT genotype than that with 3435CC genotype. Using the same statistical techniques, we further examined whether these single nucleotide polymorphisms (SNPs) were also associated SRL pharmacodynamic response, focusing on the changes in lipid values after SRL initiation prior to lipid-lowering therapy. Since TC, LDL-C, and TG levels post SRL treatment were affected by apolipoprotein E (*ApoE*) alleles (10,11), genotyping was also performed for *ApoE* in addition to the previously studied genes i.e. *ABCB1*, cytochrome P450, family 3, subfamily A, polypeptide 4 (*CYP3A4*), cytochrome P450, family 3, subfamily A, polypeptide 5 (*CYP3A5*), *IL-10*, and tumor necrosis factor (*TNF*). *ApoEε4* carriers have been shown to have higher circulating lipid levels than their common *ε2* and *ε3* counterparts (12,13), and were at increased risk for coronary artery disease (12,14).

Results

Ninety-three renal transplant patients were enrolled in this study; a complete genotype set was obtained in 83 subjects. The variant allele frequencies for the *ABCB1* 1236C>T, 2677 G>T/A, and 3435C>T, *CYP3A4*-392A>G, *CYP3A5* 6986A>G and 14690G>A, *IL-10* -1082G>A, and *TNF*-308G>A polymorphisms were summarized in a previous report (9).

The frequencies for *ApoEε2*, *ε3*, and *ε4* alleles were 0.119, 0.75, and 0.131, respectively. The *ApoE* alleles were in Hardy Weinberg equilibrium ($\chi^2_3 = 5.59$, $p = 0.133$).

TC, LDL-C, and TG concentrations after SRL treatment were collected longitudinally from the time of SRL initiation to the time of statin therapy up to a maximum of one year post SRL administration. Ten patients were excluded from data analysis because of incomplete genetic information and one is known to be noncompliant with medications. Eleven subjects were excluded because they received statin therapy prior to SRL initiation and 16 subjects had no lipid values during SRL administration prior to statin initiation. Table 1 summarizes the demographics and lipid values for the 55 patients included in the data analysis.

Using a linear mixed-effects model, screening of different variables revealed that baseline TC, duration of SRL therapy, SRL trough concentration, weight-normalized clotrimazole daily dose, and the presence of concomitant prednisone were significant confounding factors for TC. Similarly, LDL-C was found to be affected by baseline LDL-C level, duration of SRL therapy, SRL trough concentration, and weight-normalized clotrimazole daily dose. The variables that significantly affected TG included patient's age, baseline TG, duration of SRL therapy, SRL trough concentration, and weight-adjusted prednisone dose.

With adjustments for the selected covariates as described above for each lipid, the univariate effects of *ABCB1*, *CYP3A4*, *CYP3A5*, *TNF*, and *IL-10* polymorphisms under the dominant and recessive genetic models on TC, LDL-C, and TG are summarized in Tables 2, 3, and 4, respectively. The effects of *ApoEε2* and *ε4* status on these lipid values are also included in Tables 2 – 4. It is observed that *ABCB1* 1236C>T and 2677G>T/A under the recessive model and *ABCB1* 3435C>T and *CYP3A5* 6986A>G under the dominant model were significantly associated with both TC and LDL-C values. *ABCB1* 1236C>T, 2677G>T/A, and 3435C>T under the recessive model and *CYP3A5* 6986A>G and *IL-10-1082G>A* under the dominant model were significantly associated with log-transformed TG values after SRL administration. No associations were found between *ApoE* genotypes and these lipid values.

While *CYP3A5* 6986A>G was significant in the univariate analyses, it was not included in the multivariate analyses because it was not in Hardy-Weinberg equilibrium (9). Multivariate analyses showed that *ABCB1* 3435C>T under the dominant model was the only significant genetic factor associated with TC and LDL-C values after SRL administration ($p = 0.0001$ and <0.0001 , respectively, in the final model). Mean TC and LDL-C levels were 26.9 mg/dL and 24.9 mg/dL higher, respectively, in *ABCB1* 3435T carriers than 3435CC homozygotes at an average SRL trough concentration of 4 ng/mL in the absence of concomitant medication. There were significant interactions between *ABCB1* 3435C>T genotype and log SRL concentration ($p = 0.0001$) as well as concomitant prednisone administration ($p = 0.013$) for TC. A similar interaction was observed between *ABCB1* 3435C>T genotype and log SRL concentration for LDL-C ($p < 0.0001$). The effects of these interactions for TC and LDL-C are depicted in Figures 1A to 1C.

The *ABCB1* 1236C>T under the recessive model and *IL-10-1082G>A* under the dominant model were significantly associated with TG values after SRL administration ($p=0.0051$ and 0.0436 , respectively in the final model). Mean TG value was 25.1% higher in *ABCB1* 1236TT homozygotes compared to *ABCB1* 1236C carriers and was 12.4% higher in *IL-10-1082AA* homozygotes than -1082G carriers. There were interactions between age and concomitant prednisone ($p = 0.0005$) and between log SRL concentration and log baseline TG values ($p < 0.0001$). The final model equations for TC, LDL-C, and TG after SRL administration are described in the Supplemental Digital Content 1.

Discussion

This is a retrospective study examining the associations of genetic polymorphisms with SRL-induced dyslipidemia in renal transplantation. In addition to genetic factors, we found several covariates that were associated with the longitudinal changes of TC, LDL-C, and log-TG values post SRL administration. These factors included patient's age, baseline TC, LDL-C, or log-TG value, duration of SRL therapy, SRL trough concentration, and weight-adjusted daily clotrimazole and prednisone doses. Four out of six of these covariates were related to SRL administration and metabolism, indicating the major role of SRL in increasing TC, LDL-C, and TG values in patients receiving SRL-based maintenance therapy. Among all, the duration of SRL therapy contributed the most to the elevation in TC and LDL-C values. Mean TC and LDL-C were increased by 66 mg/dL and 40 mg/dL, respectively, up to 60 days after the start of SRL (Supplemental Digital Content 1), and these increases are similar to those lipid elevations as reported in previous studies (1,6,15,16). We also found that SRL trough concentration and concomitant prednisone administration interacted with *ABCB1* 3435C>T genotype to affect TC and LDL-C in a complex manner. TC were 11.7, 26.9 and 42.1 mg/dL higher and LDL-C were 12.4, 24.9 and 37.6 mg/dL higher in *ABCB1* 3435T carriers compared with wild type subjects at average SRL trough concentrations of 0.5, 4 and 30 ng/mL, respectively (Figures 1A and 1C). TC was further increased by 24.2 mg/dL at each specific SRL concentration when prednisone was co-administered in *ABCB1* 3435T carriers but not in wild type subjects (Figure 1B). Tacrolimus and mycophenolate mofetil were not found to be significant covariates (data not shown), suggesting minimal effects of these concomitant immunosuppressants on TC, LDL-C, and TG levels.

In the current study, the effects of SNPs under the co-dominant model were not analyzed as they were previously with the pharmacokinetic data. It was because we had a priori knowledge to believe that the dominant or the recessive model would be the significant genetic model, and the number of patients in each genotype group (a total of three) was small with only 55 subjects in our analysis. Our final models showed that *ABCB1* 3435C>T was the only SNP significantly associated with TC and LDL-C after SRL administration. Mean TC and LDL-C levels were 26.9 mg/dL and 24.9 mg/dL higher in *ABCB1* 3435T carriers than 3435CC homozygotes for an average SRL trough of 4 ng/mL with no concomitant medication. These results agree with the trends of higher basal TC and LDL-C levels in *ABCB1* 3435T carriers with hypercholesterolemia (17), and are consistent with our previous finding showing higher SRL log C/D in *ABCB1* 3435T carriers, further confirming the role of *ABCB1* gene in SRL pharmacokinetics (9) and pharmacodynamics. Presumably, the presence of the *ABCB1* 3435T allele leads to lower p-glycoprotein (P-gp) activity causing higher SRL trough concentration (9) and enhanced SRL toxicity. Aggravated lipid elevations may be resulted from reduced P-gp mediated transport of steroids as well (18). Contrarily, no association was observed between *ABCB1* 3435C>T (rs1045642) with baseline LDL-C/HDL-C or LDL-C/HDL-C changes in patients participated in the Assessment of LEsocol in Renal Transplantation (ALERT) trial (19). It is noted that patients in the ALERT trial received cyclosporine-based immunosuppressive therapy but not ours, and direct comparison between our study and the ALERT trial cannot be made.

While P-gp is well known to be involved in drug transport affecting pharmacokinetics, it has also been shown to play a role in cholesterol homeostasis *in vitro* (20–22) and lipid homeostasis *in vivo* (23). The *ABCB1* polymorphisms may well play a direct role in lipid homeostasis in humans. In a selected group of 371 individuals from the STANISLAS cohort, the *ABCB1* 3435C>T variants were associated with higher ApoA1 levels, which are the major protein component of HDL-C (24). Additionally, women carrying the *ABCB1* 2677G>T/A allele had significantly lower TC and LDL-C levels before atorvastatin

treatment (25). Our findings showing higher TC and LDL-C in *ABCB1* 3435T carriers and higher TG in *ABCB1* 1236TT homozygotes seem to be inconsistent with these previous results, raising the question of potential interaction between P-gp involvement in drug modulation and lipid homeostasis.

Despite successful transplantation and the use of immunosuppressive drugs, renal transplant recipients have an increased risk of premature cardiovascular disease, which is three to five times that of the general population (26). This cardiovascular risk after renal transplantation was consistently underestimated by the Framingham Risk Score (27–29), showing that in addition to the traditional cardiovascular risk factors (e.g. hypertension, dyslipidemia, and diabetes mellitus etc.), there are other unconventional risk factors such as anemia, renal allograft dysfunction, proteinuria, and left ventricular hypertrophy (30,31). Nevertheless, the ALERT extension study demonstrated that LDL-C reduction by fluvastatin was associated with reduced cardiac death or non-fatal myocardial infarction (32), reinforcing the importance of dyslipidemia as a cardiovascular risk factor and the benefits of lipid-lowering therapy in renal transplant patients. We found that TC and LDL-C after SRL treatment were higher in *ABCB1* 3435T carriers compared to 3435CC homozygotes. The implication of these findings in terms of cardiovascular risk and the effect on statin response in SRL-induced dyslipidemia is unknown; several studies have shown associations of different *ABCB1* SNPs with statin pharmacokinetics (33,34), lipid responses to statin therapy (25,35–41), and risk of myocardial infarction (42,43). Because our study is limited by the small number of subjects and the retrospective nature of the analysis, it is important to follow up on the current findings to further investigate the role of *ABCB1* polymorphisms on SRL-induced dyslipidemia and its associated cardiovascular risk.

We demonstrated in this study that higher TG values post SRL were associated with *IL-10* -1082AA homozygotes, which have the low *IL-10* production genotype (44). This finding may be independent of the *IL-10*-1082G>A effect on lowering SRL log C/D (9) and hence SRL toxicity, as low *IL-10* production capacity was associated with metabolic syndrome, dyslipidemia, and diabetes mellitus in the Leiden 85-Plus Study (45). Interestingly, this result appears to be in line with other studies showing associations of cardiovascular disease with *IL-10* genotype in renal transplant recipients. The *IL-10* high or intermediate-producer genotypes had a significantly lower risk of cardiovascular disease than the lower-producer genotype (46). Likewise, *IL-10*-1082GG homozygotes had low carotid artery intima media thickness compared with the *IL-10*-1082G carriers, although the difference was not statistically significant (47). Nonetheless, because of the marginal level of significance, the validity of the association between *IL-10*-1082G>A and TG values after SRL administration needs to be confirmed in larger replication study.

In conclusion, *ABCB1* 3435C>T was associated with TC and LDL-C levels and *ABCB1* 1236C>T and *IL-10*-1082G>A were associated with TG after SRL treatment. Further studies are necessary to define the role of *ABCB1* and *IL-10* polymorphisms on SRL-induced dyslipidemia in renal transplantation.

Materials and Methods

Patients and Data Collection

The study population consisted of renal transplant recipients who participated in one of the treatment protocols at the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Transplantation Branch between 1999 and 2006. Patients were enrolled if they received or switched to SRL as the maintenance immunosuppressive therapy. Informed consent was obtained from all patients in the screening protocol for genetic analysis. This study, as well as the screening and treatment

protocols, was approved by the NIDDK Institutional Review Board. SRL, and all other prescribed immunosuppressive medications, was provided for all patients free of charge to lessen the variability associated with limited access to drug.

Clinical data including patient demographics, type and date of transplantation, induction and maintenance immunosuppression therapies, time of statin initiation, and concomitant medications were collected for all patients from the NIDDK transplant database. TC, LDL-C, and TG concentrations after SRL treatment were collected longitudinally from the time of SRL initiation to the time of statin therapy up to a maximum of one year post SRL administration. Typically, lipid profile was obtained every month for the first 3 months post-transplant and then every 3 months thereafter. Patients were instructed to fast overnight the day before blood collection for lipid profile the next morning. On the days when lipid levels were available, whole blood SRL trough concentrations were collected. SRL whole blood concentrations were measured by a validated high-performance liquid chromatography tandem mass spectrometric assay with a quantification limit of 2 ng/mL.

Genotyping

Genotyping was performed using the Sequenom™ MassArray iPLEX™ platform (48) by Bioserve™ (Beltsville, MD) for the following SNPs: *ABCB1* 1236C>T (rs1128503), 2677G>T/A (rs2032582), and 3435C>T (rs1045642), *CYP3A4* -392A>G (rs2740574), *CYP3A5* 6986 A>G (rs776746) and 14690G>A (rs10264272), *IL-10* -1082G>A (rs1800896), *TNF* -308G>A (rs1800629), and *ApoE* rs429358 and rs7412. *ApoE* genotype is classified primarily by two SNPs (rs429358 and rs7412). *ApoEε3* is the most common allele and is represented by rs259358(T) and rs7412(C). *ApoEε2* is rs429358(T) with rs7412(T) and *ε4* is rs259358(C) with rs7412(C). For rs429358, the more common allele is the T allele and the less common allele is the C allele. For rs7412, the ancestral and variant alleles are the C allele and T allele, respectively.

Statistical analyses

The longitudinal changes of TC, LDL-C, and TG levels over time were analyzed by a linear mixed-effects model as previously described in detail (9). Data that exhibited high variability and were not normally distributed were logarithmic-transformed prior to data analysis. Each lipid was analyzed in the same manner but separately. Briefly, significant covariates were selected using backward elimination for each lipid initially. Univariate analysis was then performed to investigate the effects of *ABCB1*, *CYP3A4*, *CYP3A5*, *IL-10*, and *TNF* polymorphisms on each lipid under the dominant or recessive genetic model as described previously (9). The univariate effect of *ApoE* genotype was investigated with reference to the status of the *ε2* and *ε4* alleles. *ApoEε2* and *ε4* carriers (either as homozygotes or heterozygotes) were classified as two separate groups and compared with the *ApoEε3/ε3* homozygotes. A multivariate analysis was followed using the most significant genetic models from the univariate analysis, with adjustments for the covariates as previously determined. The final model equation was then obtained including all the significant SNPs and covariates. Statistical analysis was performed using the open source statistical software R (version 2.5.0). P-values <0.05 were considered statistically significant. Adjustments for multiple testing were not performed. As such, our results are considered exploratory and hypothesis generating.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ABCB1	Adenosine triphosphate-binding cassette, subfamily B, member 1
AIC	Akaike's information criterion
ApoE	apolipoprotein E
C/D	dose-adjusted, weighted-normalized trough concentration
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5
HDL-C	high-density lipoprotein cholesterol
IL-10	interleukin 10
LDL-C	low-density lipoprotein cholesterol
P-gp	p-glycoprotein
SNP	single nucleotide polymorphism
SRL	sirolimus
TC	total cholesterol
TG	triglyceride
TNF	tumor necrosis factor

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Figure 1.

Predicted total cholesterol (TC) levels up to 60 days after sirolimus (SRL) treatment in patients with different *ABCB1* 3435C>T genotypes receiving A) no prednisone (PRED) and B) concomitant PRED, illustrating the interactions of SRL concentration and concomitant prednisone with genotype. C) Predicted low-density lipoprotein cholesterol (LDL-C) levels up to 60 days after SRL treatment in patients with different *ABCB1* 3435C>T genotypes. Lipid concentrations were simulated using SRL troughs of 0.5, 4, and 30 ng/mL.

Table 1

Patient demographics and summary of lipid concentrations for 55 patients treated with sirolimus maintenance therapy

Gender (M/F)	32/23
Age (yr) ^a	43.3 (20.6 – 66.2)
Weight (kg)	75.3 ± 16.2
Body mass index (kg/m ²)	26.5 ± 7.27
Race	
White	43
Black	9
Asian	3
Type of transplantation	
Cadaveric	20
Living-related	16
Living-unrelated	19
Maintenance immunosuppressive therapy	
SRL/TAC ± MMF	14
SRL/TAC/PRED ± MMF	21
SRL/PRED ± MMF	14
SRL ± MMF	6
SRL trough concentration (ng/mL)	9.92 ± 7.94
Lipid values before SRL administration (mg/dL)	
Total cholesterol	170 ± 38.3
LDL cholesterol	98.0 ± 28.3
HDL cholesterol	47.5 ± 15.0
Triglycerides	192 ± 159
Lipid values after SRL administration prior to statin initiation (mg/dL)	
Total cholesterol	212 ± 56.1
LDL cholesterol	125 ± 39.0
HDL cholesterol	54.7 ± 15.0
Triglycerides	239 ± 180

^aData expressed as median (range). Other data are expressed as mean ± standard deviation.

HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMF, mycophenolate mofetil; PRED, prednisone; SRL, sirolimus; TAC, tacrolimus

Table 2

Univariate analysis of *ABCB1*, *CYP3A4*, *CYP3A5*, *IL-10*, *TNF*, and *ApoE* genetic polymorphisms with total cholesterol (TC) in renal transplant patients

Gene	Nucleotide	Model	Coefficient	Standard Error	P Value	AIC Value
<i>ABCB1</i>	1236C>T	Dominant	10.0	5.67	0.082	3491
		Recessive	23.1	6.51	0.0008	2483
<i>ABCB1</i>	2677G>T/A	Dominant	10.6	5.62	0.0578	2490
		Recessive	23.4	5.80	0.0002	2482
<i>ABCB1</i>	3435C>T	Dominant	21.0	5.10	0.0002	2480
		Recessive	22.4	6.59	0.0013	2485
<i>CYP3A4</i>	-392A>G	Dominant	-11.3	6.28	0.0784	2491
		Recessive	-1.92	10.5	0.856	2494
<i>CYP3A5</i>	6986A>G	Dominant	-17.8	5.74	0.0033	2485
		Recessive	-1.83	9.57	0.850	2494
<i>CYP3A5</i>	14690G>A	Dominant	-2.24	13.8	0.872	2494
<i>IL-10</i>	-1082G>A	Dominant	-1.91	6.49	0.770	2494
		Recessive	0.814	7.28	0.911	2494
<i>TNF</i>	-308G>A	Dominant	6.76	6.55	0.307	2493
<i>ApoE</i>		<i>e2/2, e3/2</i>	3.38	7.29	0.645	2496
		<i>e4/3, e4/4</i>	2.16	8.00	0.788	

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Univariate analysis of *ABCB1*, *CYP3A4*, *CYP3A5*, *IL-10*, *TNF*, and *ApoE* genetic polymorphisms with low-density lipoprotein cholesterol (LDL-C) in renal transplant patients

Table 3

Gene	Nucleotide	Model	Coefficient	Standard Error	P Value	AIC Value
<i>ABCB1</i>	1236C>T	Dominant	4.81	4.02	0.236	2303
		Recessive	11.3	4.83	0.0228	2299
<i>ABCB1</i>	2677G>T/A	Dominant	4.32	3.97	0.282	2303
		Recessive	12.9	4.37	0.0046	2298
<i>ABCB1</i>	3435C>T	Dominant	13.3	3.72	0.0008	2293
		Recessive	14.0	4.86	0.0057	2298
<i>CYP3A4</i>	-392A>G	Dominant	-8.41	4.37	0.0598	2301
		Recessive	-0.482	7.34	0.948	2304
<i>CYP3A5</i>	6986A>G	Dominant	-8.92	4.21	0.0390	2300
		Recessive	-1.65	6.77	0.808	2304
<i>CYP3A5</i>	14690G>A	Dominant	2.46	9.59	0.798	2304
<i>IL-10</i>	-1082G>A	Dominant	0.752	4.52	0.869	2304
		Recessive	0.400	4.94	0.936	2304
<i>TNF</i>	-308G>A	Dominant	3.20	4.65	0.494	2304
<i>ApoE</i>	<i>e2/2, e3/2</i> <i>e4/3, e4/4</i>		-3.19	4.80	0.509	2306
			0.520	5.42	0.924	

Table 4

Univariate analysis of *ABCB1*, *CYP3A4*, *CYP3A5*, *IL-10*, *TNF*, and *ApoE* genetic polymorphisms with log-transformed triglyceride (TG) in renal transplant patients

Gene	Nucleotide	Model	Coefficient	Standard Error	P Value	AIC Value
<i>ABCB1</i>	1236C>T	Dominant	0.0432	0.0284	0.134	-174
		Recessive	0.111	0.0354	0.003	-180
<i>ABCB1</i>	2677G>T/A	Dominant	0.0341	0.0285	0.238	-173
		Recessive	0.0812	0.0330	0.0175	-177
<i>ABCB1</i>	3435C>T	Dominant	0.0512	0.0280	0.0737	-175
		Recessive	0.0924	0.0387	0.0207	-177
<i>CYP3A4</i>	-392A>G	Dominant	-0.0473	0.0310	0.133	-174
		Recessive	-0.0294	0.0504	0.562	-172
<i>CYP3A5</i>	6986A>G	Dominant	-0.0592	0.0289	0.0459	-175
		Recessive	-0.0495	0.0459	0.286	-173
<i>CYP3A5</i>	14690G>A	Dominant	-0.0730	0.0698	0.300	-173
<i>IL-10</i>	-1082G>A	Dominant	-0.0672	0.0316	0.0384	-176
		Recessive	-0.00701	0.0385	0.856	-172
<i>TNF</i>	-308G>A	Dominant	0.0364	0.0331	0.276	-173
<i>ApoE</i>	<i>e2/2, e3/2</i> <i>e4/3, e4/4</i>		-0.0158	0.0343	0.646	-172
			0.0438	0.0385	0.261	