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Role of *CYP2E1* (PstI/RsaI) gene polymorphisms on the tacrolimus drug toxicity of kidney transplantations among South Indians

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Abstract

Introduction: *CYP2E1* is a member of P450 super family and cytochrome P450 (CYP) enzymes metabolize the immunosuppressive drugs, which are commonly used for renal transplantation patients. Studies have shown that single-nucleotide polymorphisms of *CYP2E1* are associated with higher-transcription, increased enzyme activity and with allograft rejection in kidney transplantation recipients.
Objectives: The aim of the current study is to evaluate the possible association between single nucleotide polymorphisms (SNPs) of the *CYP2E1* gene, and tacrolimus toxicity among renal transplant patients in a South Indian population.
Patients and Methods: The hypothesis was investigated by including 50 kidney transplantation patient recipients with tacrolimus based immunosuppressive treatment and 50 healthy volunteers as control subjects of the South Indian population. The *CYP2E*1 gene (PstI/RsaI) polymorphisms were genotyped using PCR-RFLP method. Genotypes were compared between renal transplantation and controls using the Fisher exact test. The SPSS v. 16.0 software were used to analyze the data.
Results: No significant association was observed between the renal transplantation patients and controls (genetic model $P=0.055$ and allelic model $P=0.06$) groups. The variant c1 vs. c2 (OR: 0.13; 95% CI: 0.02-0.89 and $P=0.018$) of the CYP2E1 PstI/RsaI polymorphism was found to be significantly associated with drug toxicity among the patients.
Conclusion: This study suggests that the *CYP2E1* polymorphism may be related to the development of drug toxicity in South Indian renal transplantation patients treated with tacrolimus.

Introduction

The *CYP2E1* gene, the key regulator of P450 super family is actively involved in the metabolism of many xenobiotics and bioactivation of many compounds with low molecular weight (1). *CYP2E1* is expressed in liver, kidney, nasal mucosa, brain, lung, and other tissues (2). *CYP2E1* gene located on chromosome 10q26.3 contains 9 exons which include 493 amino acid residues with a molecular weight of ~ 57 kDa (3). Several important polymorphisms have been identified near 5'-flanking and 3'-untranslated region which is known to alter the transcriptional activity of the gene (4). Among them the PstI and RsaI, the two point mutations located in the 5'-flanking region were found to be associated with higher-transcription and increased enzyme activity (5). Studies have reported that these mutations to be in complete linkage disequilibrium and they generate *CYP2E1* wild (c1) allele and the less common (c2) allele, which have been reported to confer a higher risk for cancer (6), schizophrenia (7), gastric cancer (8), head

Key point
In a study, *CYP2E1* gene (PstI/RsaI) polymorphisms were investigated in kidney transplantation patient recipients with tacrolimus and healthy volunteers. No significant association was observed between the renal transplantation patients and controls. However, it was found that the homozygote variant of the *CYP2E1* PstI/RsaI polymorphism was significantly associated with drug toxicity. These results imply that the c1 allele of *CYP2E1* gene is more susceptible to toxicity among the renal transplantation patients.

and neck cancer (9), gastrointestinal cancer (10), Hodgkin and non-Hodgkin lymphoma (11), oxidative injury (12) and ethanol metabolism (13).

Several lines of evidences have been reported that the oxidative stress plays an important role in adverse outcomes of renal transplantation (14,15) and it may cause vascular reactions and acute immune responses (16). Furthermore, stressed endothelium may promote adhesion and interaction with leukocytes (17). These findings suggest that the oxidative stress may lead to pathophysiologic process of renal transplantation, including acute rejection. The allele frequencies of *CYP2E1* gene polymorphisms differ remarkably among different human populations (18). So far, there was no study available in Indian population with regard to *CYP2E1* gene polymorphisms and renal transplantation.

Objectives

The present study was aimed to investigate the association between two important *CYP2E1*gene polymorphisms (-1295G>C and -1055C>T) and renal transplantation patients receiving tacrolimus and to further investigate the tacrolimus drug toxicity among renal transplantation patients of in South Indian population.

Patients and methods

Patients

A case-control study in 50 (74% males and 24% females; mean age 34.4 ± 12.28 years) tacrolimus-treated renal transplant recipients and 50 (86% males and 14% females; mean age 52.4 ± 14.50 years) unrelated, healthy volunteers of South Indian origin, were included. After transplantation, the tacrolimus levels in blood were measured as part of their routine care using the chemiluminescent microparticle immunoassay (CMIA) method. The trough C_0 (ng/mL) concentrations, corrected by dose and patient body weight were obtained. Further, all renal transplantation subjects treated with tacrolimus were divided into two groups based on the toxicity of the drug such as toxicity (18%) and non-toxicity group (82%).

Genotyping

Genomic DNA was extracted from human peripheral blood samples by phenol chloroform extraction and ethanol precipitation protocol (19). The total concentration of isolated genomic DNA was determined by UV/VIS spectrophotometer Nano-Drop ND-1000. The *CYP2E1*5B* gene (rs2031920; -1295G>C and rs3813867; -1055C>T) polymorphisms were genotyped using PCR-RFLP method. The forward 5'-ccagtcgagtctacattgtca-3' and reverse 5'-ttcattctgtcttctaactgg-3' primers were used to amplify 413bp product. Further, the 10 µl of PCR product was digested separately with 10 U of RsaI and PstI in restriction enzyme at 37°C for 18 hours, and visualized on 2.5% agarose gel (20).

Ethical issues

The study protocol was approved by the Institutional Ethics Committee of the Sri Ramachandra University, Chennai, India (CSP/14/JUN/35/73), and written informed consent was obtained from all study participants.

Statistical analysis

Allele frequencies were calculated by the direct gene-counting method. The genotype distribution was evaluated for Hardy–Weinberg equilibrium (HWE). A Fisher's exact test was carried out to check the association between case and control. Odds ratios (ORs) and 95% CIs were calculated. SPSS (version 16.0; SPSS, Chicago, IL) was used to assess the relationship between the genetic variants and *P* values <0.05 were considered to be statistically significant.

Results

PstI/RsaI gene polymorphisms and renal transplantation patients

A total of 50 renal transplantation patients treated with tacrolimus and 50 unrelated control subjects were genotyped in this study. The genotypes of -1295G>C (rs3813867) and -1055C>T (rs2031920) single nucleotide polymorphisms (SNPs) in 5'-flanking regions were designated as c1/c1 for wild type homozygous, c1/c2 for heterozygous and c2/c2 for mutant homozygous individuals. The genotype and allele frequencies of all the studied polymorphisms are shown in Table 1. The genotype frequencies of the renal transplantation patients treated with tacrolimus and control group were in accordance with the HWE. The genotype frequencies of *CYP2E1*5B* polymorphism were found to be 98% for c1/c1 and 2% for c1/c2 in controls, and 88% for c1/c1 and 12% for c1/c2 in renal transplant cases. Allele frequencies of *CYP2E1*5B* were 99% for c1 and 1% for c2 in controls and 88% for c1 and 12% for c2 in renal transplant cases. No mutant homozygote (c2/c2) was

Table 1. Genotype and allele frequencies of *CYP2E1* gene polymorphisms between the control and case subjects

SNP	Genotypes	Control (n = 50)	Case (n = 50)	OR (95% CI)	*P* value
C-1055T;G-1293C	c1/c1	49 (98)	44 (88.0)	Reference	
	c1/c2	1(2)	6 (12.0)	6.68 (0.77-57.7)	0.050
	c2/c2	0	0		
	c1/c2+ c2/c2	1(2)	6 (12.0)		
	c1	99 (99.0)	94 (94.0)	Reference	
	c2	1 (1.0)	6 (6.0)	6.31 (0.74-53.48)	0.054
	MAF	1.0	5.1		
	HWE-p	0.943	0.651		

Abbreviations: OR, Odds ratio; P value, degrees of freedom 2; HWE, Hardy-Weinberg equilibrium; SNP, single nucleotide polymorphism.

observed in the studied population (Table 1). The results were confirmed with digestion with PstI, since this polymorphic site is located on the same fragment and complete linkage disequilibrium was observed between RsaI and PstI positions. There were no significant differences in the genotype distribution between the control and renal transplantation patients treated with tacrolimus ($P=0.050$) in genetic and allelic model ($P=0.054$; Table 1).

PstI/RsaI gene polymorphisms and drug toxicity among the renal transplantation patients

The clinical characteristics between the toxicity and non-toxicity groups are documented in Table 2. Among different characteristics studied, the tacrolimus dose mg/kg/day ($P=0.002$) and concentration/dose ratio ($P=0.004$) show a significant difference between toxicity and non-toxicity groups (Table 2). The genotype distribution of *CYP2E1* gene between the non-toxicity and toxicity groups are documented in Table 3. No significant difference was observed between the groups in genetic and dominant model. But the allelic models c1 vs. c2 (OR: 0.13; 95% CI: 0.02-0.89 and $P=0.018$) showed a significant difference between the groups (Table 3). These results suggest that the c1 allele of *CYP2E1*5B* polymorphisms are more susceptible to toxicity among the renal transplantation patients treated with tacrolimus.

Discussion

In the present study, the association between *CYP2E1* gene polymorphisms (-1295G>C, rs3813867; -1055C>T, rs2031920) and kidney transplant patients treated with tacrolimus was examined. The homozygote variant of the *CYP2E1* PstI/RsaI polymorphism was found to be significantly associated with drug toxicity among the patients.

In Europe, the United States and Japan, studies are investigated the use of tacrolimus as primary immunosuppressive therapy in kidney transplantation and few studies focused on the efficacy on standard cyclosporine based immunosuppressive regimens (21-23). However, few studies have found that the reduced doses of cyclosporine improved renal function, and low-dose of tacrolimus based regimen showed better renal function when compared with standard-dose of cyclosporine (24-26). Recent comparative studies conducted between tacrolimus and cyclosporine in terms of renal graft survival, rejection rates and preservation of glomerular filtration rate (GFR) revealed that the tacrolimus to be superior to cyclosporine (27-30) and some centers reported the rejection rate to be 10%-15% and one-year graft survival to be 90%-95% for tacrolimus based immunosuppression (31,32). Recent data on discharge summary showed that 72% of renal transplant recipients were prescribed tacrolimus, 81% were prescribed Mycophenolate mofetil (MMF), 21% were advised cyclosporine and 12% were prescribed sirolimus (33,34). In vitro study by Lecointre et al, in 2002 observed that the tacrolimus had no effect on any CYP at concentrations below 1 mM, but for *CYP3A4* and *3A5* had shown mild inhibitory effect at higher concentration (35). In contradictory to this a very recent study conducted on Mexican renal transplantation patients, proved the usefulness of tacrolimus therapeutic range (36).

CYP2E1 is a phase I enzyme, which plays an important

Table 2. Clinical characteristics of the study participants between the non-toxicity and toxicity groups

Characteristics	No Toxicity (n = 41) Mean ± SD	Toxicity (n = 9) Mean ± SD	P value[a]
Age	35.0 ± 13.23	31.5 ± 4.9	0.465
HB	12.25 ± 1.67	12.85 ± 2.31	0.345
Creatinine	1.32 ± 0.40	1.31 ± 0.31	0.927
BUN	12.34 ± 3.35	13.12 ± 3.6	0.553
Sodium	133.6 ± 6.7	134 ± 7.08	0.808
Potassium	3.68 ± 0.88	3.58 ± 0.45	0.773
SBP	130 ± 13.5	121 ± 8.34	0.077
DBP	78 ± 10.77	70 ± 14.1	0.073
Tacrolimus dose mg/kg/day	0.048 ± 0.019	0.026 ± 0.012	0.002
Concentration/dose ratio	197.26 ± 128.88	349 ± 172.0	0.004

Abbreviations: SD, standard deviation; HB, Hemoglobin; BUN, blood urea nitrogen; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a]t-test *P* value

Table 3. Association test for *CYP2E1* gene polymorphisms between the tacrolimus toxicity and non-toxicity among the kidney transplantation patients

SNP	Genotype	No Toxicity, n = 41(%)	Toxicity, n = 9 (%)	OR (95% CI)	P value[a]
C-1055T	c1/c1	37 (92.5)	7 (77.7)	Reference	
G-1293C	c1/c2	3 (7.5)	2 (22.2)	3.52 (0.49-25.09)	0.187
	c2/c2	0 (0)	0	-	
	c1	77 (96.3)	16 (88.9)	Reference	
	c2	3 (3.8)	2 (11.1)	0.13 (0.02-0.89)	0.018

Abbreviations: OR, Odds ratio; SNP, single nucleotide polymorphism.

[a]χ^2 *P* value.

role in the metabolic activation of low molecular compounds, pro-carcinogens (5) and its genetic determinants in the metabolism of drugs and endogenous compounds has long been suspected (37). Recently, in several studies, significant association has been found between *CYP2E1* polymorphisms and respiratory system cancer (6), schizophrenia in the Chinese Han population (7), gastric cancer in Chinese patients (8), head and neck cancer in Asians (9), Gastrointestinal cancer in Malaysians (10), Hodgkin and non-Hodgkin lymphoma (11). In contrary South Indians population are failed to conform significant association between *CYP2E1* and oral cancer (38).

Among the xenobiotic-metabolizing genes, the *CYP2E1* polymorphisms frequency differs distinctly among ethnic and racial groups (39). Although, the molecular basis of the human *CYP2E1* regulation largely remains to be unknown, previous studies have shown that the c2 mutant allele is related to an increase in *CYP2E1* expression, oxidative stress and inflammatory responses (40,41). Studies have reported that the oxidative stress and anti-oxidative mechanisms to be the important causes of allograft dysfunction after kidney transplantation (42).The *CYP2E1* gene c2 mutation showed 10 times better expression in HepG2 cells (5) and 1.7-fold higher mRNA content than the c1 allele carriers indicating that RsaI polymorphism affected the binding of a transcription factor and the transcriptional activation of *CYP2E1* gene (43). A very recent and first study conducted between the *CYP2E1* polymorphisms and acute rejection in kidney transplantation of Korean population found that the exonic SNP rs2515641 was significantly associated with development of acute rejection in kidney transplantation. But the other two SNPs of *CYP2E1* did not show a significant association with acute rejection in kidney transplantation (44). On the contradictory, the present study failed to find any significant association between the *CYP2E1* gene polymorphism and transplantation patients treated with tacrolimus. But a significant association between toxicity and non-toxicity groups was found among the patients treated with tacrolimus.

Conclusion

In conclusion, present study revealed that the *CYP2E1* gene polymorphisms are not associated with renal transplantation patients treated with tacrolimus but it was found that the homozygote variant of the *CYP2E1* PstI/RsaI polymorphism was significantly associated with drug toxicity among the patients.

Limitations of the study

Our study has several limitations; the small sample size and the retrospective nature of the study do not allow us to draw any conclusion about the effectiveness between the groups. Furthermore, the follow-up was limited. Larger series with long-term follow-up are needed to confirm the association between the genotypes and renal transplantation patients treated with tacrolimus. However our results are the first report from our population with regard to *CYP2E1* gene and renal transplantation.

Authors' contribution

GR and RE conceived the study and contributed reagents and tools. GR and PS performed the experiments. GR and RE analyzed the data and drafted the final manuscript; all authors read, revised, and approved the final manuscript.

Conflicts of interest

There is no conflict of interests. The results presented in this paper have not been published previously in whole or part.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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