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Association of *leptin receptor* gene polymorphisms with post-transplant diabetes mellitus: Short report and literature review

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Abstract

Background: Post-transplant diabetes mellitus (PTDM) is a common and important metabolic complication after renal transplantation. Although genetic variants of the leptin (*LEP*) and leptin receptor (*LEPR*) gene have been reported to be associated with insulin resistance and diabetes mellitus, few studies have examined these variants in patients with post-transplant diabetes mellitus (PTDM). In this study, we investigated the association between *LEP* and *LEPR* polymorphisms and PTDM in renal transplant recipients. We also reviewed the literature on the genetic variants associated with development of PTDM.

Methods: A total of 301 patients who received renal transplants and had no history of diabetes were included in this study. We analyzed the associations between development of PTDM and the five single nucleotide polymorphisms (SNPs) in *LEP* (rs1322837 and rs2167270) and *LEPR* (rs8179183, rs1137100, and rs1137101).

Results: PTDM developed in 48 of the 301 patients studied (15.9%). Patients with PTDM had significantly higher allele frequency of the *LEPR* rs1137100*G allele and rs1137101*G allele. After adjustment for age, gender, and tacrolimus usage, rs113700 and rs 1137101 in *LEPR* showed significant association with the development of PTDM.

Conclusions: *LEPR* polymorphisms were significantly associated with PTDM in renal transplant recipients. These data suggest that SNPs of *LEPR* may be associated with the pathogenesis of PTDM and may act as genetic markers for the development of PTDM.

Introduction

The development of post-transplant diabetes mellitus (PTDM) is a devastating metabolic complication after renal transplantation [1]. It affects 2–50% of renal transplant recipients and is associated with graft failure, cardiovascular complications, infection, and mortality [2,3]. As in type 2 diabetes mellitus (T2DM), decreased insulin secretion, increased insulin resistance, or a combination of both are believed to be involved in PTDM [3,4]. Although various risk factors such as older age, obesity, hepatitis C infection, and type of immunosuppressive regimen are well established, they do not fully account for the development of PTDM [3]. Recently, many studies have been conducted to analyze genetic polymorphisms as markers for PTDM [5,6]. These studies have suggested that the development of PTDM is related to the genotypes of several genes, such as adiponectin (*ADIPOQ*), transcription factor 7-like 2 (*TCF7L2*), potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*), and C-C motif ligand 5 (*CCL5*), which are involved in insulin resistance and sensitivity [7-10]. Leptin (*LEP*) and leptin receptor (*LEPR*) gene polymorphisms have been reported to be associated with insulin resistance, obesity, and diabetes mellitus [11,12]. However, only a few studies have evaluated the clinical impact of *LEP* and *LEPR* polymorphisms on the development of PTDM [13].

In this study, we ascertained whether *LEP* and *LEPR* polymorphisms are associated with PTDM in Korean patients who underwent renal transplantation. We also reviewed literature that investigated associations between gene polymorphisms and PTDM in renal transplant recipients.

Methods

A total of 301 renal transplant recipients were recruited at three transplant centers in the Republic of Korea (Kyung Hee University Medical Center, Kyung Hee University Hospital at Gangdong, and Inje University Busan Paik Hospital) from 2000 to 2009. Patients were excluded when they had a history of diabetes or impaired fasting glucose (fasting glucose level 100-125 mg/dL) before transplantation. All study procedures complied with the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2000. This study was approved by the ethics review committees of all three transplant centers and written informed consent was obtained from each subject.

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PTDM was diagnosed based on American Diabetes Association guidelines [14]. SNPs were selected in *LEP* and *LEPR* using the NCBI dsSNP database, version 131 (http:// www.ncbi.nlm.nih.gov/SNP) and the database of the International Hapmap Project (http://www.hapmap.org/index.html). Two *LEP* (rs1322837 and rs2167270) and three *LEPR* SNPs (rs8179183, rs1137100, and rs1137101) were ultimately selected and used to genotype the patients. Blood samples were collected from each subject and then stored at -20℃. Genomic DNA was isolated from blood samples with a commercially available Qiagen DNA extraction kit (Qiagen, Tokyo,Japan). SNP genotyping was conducted by direct sequencing. Genomic DNA was amplified with specific primers for two *LEP* and three *LEPR* SNPs (Table 1). The amplified products were sequenced with an ABI PRISM 3730XL analyzer (PE Applied Biosystems, Foster City, Calif, USA), and sequence data were analyzed with SeqManII software (DNASTAR Inc., Madison, Wisc., USA).

Results

The overall incidence of PTDM in the study population was 17.9% (54 of 301 patients). Table 1 shows the baseline characteristics of the study population according to the development of PTDM (PTDM *vs.* non-PTDM group). The mean follow-up duration for all 301 patients was 87.9 months. Patients in the PTDM group were significantly older than those in the non-PTDM group (45.17 ± 9.26 *vs.* 38.58 ± 11.20 years, respectively; p <0.001). Patients in the PTDM group used tacrolimus more frequently than did those in the non-PTDM group (p = 0.044).

Allele frequencies are shown in Table 2. The PTDM group had a significantly higher allele frequency compared to the non-PTDM group for the rs1137100*G allele (OR = 1.924; 95% CI: 1.024–1.192; p = 0.025) and the rs1137101*G allele (OR = 1.131; 95% CI: 1.045–1.1225; p = 0.019). The effect of genotype on development of PTDM remained significant even when adjusting for age, gender, and tacrolimus usage (Table 3). We nest, tested whether the LEPR haplotype was associated with PTDM. To demonstrate pair-wise linkage disequilibrium (LD), we analyzed three SNPs and found that they were in LD. The D' values between rs8179183 and rs1137100, and between rs8179183 and rs1137101, between rs1137100 and rs1137101 were 0.572, 0.655, and 0.876, respectively. The r^2 values between SNPs were also calculated.

Table 1. Clinical characteristics of the study population (PTDM vs. non-PTDM).

	PTDM (n=54)	non-PTDM (n=247)	p
Follow-up duration (months)	91.54 ± 85.36	76.85 ± 75.49	0.208
Age (years)	45.17 ± 9.26	38.58 ± 11.20	<0.001
Sex (male: female)	28:26	155:92	0.137
BMI (kg/m^2)	22.57 ± 3.39	22.47 ± 3.47	0.859
Dialysis duration (months)	33.20 ± 58.44	23.90 ± 34.09	0.336
HLA total mismatching (n)	3.10 ± 1.54	3.24 ± 1.53	0.512
HCV (+) (n, %)	0 (0%)	6 (2.36%)	0.244
Acute rejection (n, %)	13 (25.49%)	44 (17.32%)	0.197
Calcineurin inhibitor, n (%)			
Tacrolimus	24 (45.3%)	74 (30.8%)	0.044
Cyclosporine	29 (53.7%)	166 (67.2%)	0.098
Antimetabolite, n (%)			
Azathioprine	10 (18.5%)	72 (29.1%)	0.582
MMF	34 (62.9%)	165 (66.8%)	0.702
Serum creatinine (mg/dL)			
At 6 months after transplantation	1.27 ± 0.56	1.32 ± 0.49	0.529
At 12 months after transplantation	1.29 ± 0.36	1.37 ± 0.87	0.507

PTDM: post-transplantation diabetes mellitus; BMI: body mass index; HLA: human leukocyte antigen; HCV: hepatitis C virus; MMF: mycophenolate mofetil

Table 2. Allele frequencies for 5 SNPs in the *LEP* and *LEPR* genes in PTDM and non-PTDM subjects.

Gene	SNP	Allele	PTDM n (%)	Non-PTDM n (%)	OR (95% CI)	p
LEP	rs2167270	G	91 (84.2%)	388 (78.5%)	0.68(0.39 - 1.19)	0.182
.		A	17 (15.8%)	106 (21.5%)		
LEP	rs13228377	A	91 (84.2%)	380 (76.9%)	0.62(0.35 - 1.08)	0.094
.		G	17 (15.8%)	114 (23.1%)		
LEPR	rs8179183	G	97 (89.8%)	454 (91.9%)	1.28 (0.63- 2.59)	0.480
.		C	11 (10.2%)	40 (8.1%)		
LEPR	rs1137100	G	93 (86.1%)	377 (76.3%)	1.92 (1.02-1.19)	0.025
		A	15 (13.9%)	117 (23.7%)		
LEPR	rs1137101	G	101 (94%)	421 (85%)	1.13 (1.05-1.23)	0.019
		A	7 (6%)	73 (15%)		

SNPs: single nucleotide polymorphisms; PTDM: post-transplantation diabetes mellitus; LEP: leptin; LEPR: leptin receptor

The r^2 values between rs8179183 and rs1137100, and between rs8179183 and rs1137101, between rs1137100 and rs1137101 were 0.328, 0.509, and 0.647, respectively.

Discussion

This is the first study to evaluate the genetic association of *LEPR* and PTDM in renal transplant recipients. Our study demonstrated that two SNPs in *LEPR* (rs1137100 and rs1137101) were significantly associated with the development of PTDM in Korean renal transplant patients. LEP is a hormone which is synthesized and secreted by adipose tissue, and is known to be important in regulating several neuropeptides and energy homeostasis. It has been reported to play an important role in regulation of body weight, fat metabolism, and glucose uptake [11,15]. Patients with T2DM showed decreased LEP expression in adipose tissue, and had lower serum LEP levels [16]. LEP modulates insulin secretion and action via LEPRs present in the hypothalamus, pancreatic cells, adipose tissue, and muscles [17]. In previous studies, *LEPR* polymorphisms were reported to be associated with diabetes, insulin resistance, metabolic syndrome, and obesity [18-20]. A hypothetical explanation for these results is that polymorphisms of the *LEPR* result in dysfunction of the LEP-associated signaling pathway and inhibition of the favorable effects of LEP [21].

In addition to the present study, our group previously reported that polymorphisms in *AGT*, *CCL5*, *IL17E*, *IL17RA*, *IL17RB*, *IL1B*, *IL2*, *IL4*, *IL7R*, *MMP2*, *TLR4*, and *TLR6* were significantly associated with the development of PTDM in Korean renal transplant recipients [10,22-25]. Considering the clinical impact of each gene, our previous data suggests that impaired insulin secretion, decreased insulin sensitivity, inflammation of islet β-cells, and activation of the innate immune system may play essential roles in the pathogenesis of PTDM.

In the last decade, numerous other genetic studies for PTDM have been conducted in renal transplant recipients, and nearly 50 loci have been established as suspected loci (Table 4) [7-10,13,22-41]. Polymorphisms in *AIPOQ*, *CAPN10*, *CDKAL1*, *CDKN2A/B*, *HHEX*, *KCN11*, *KCNQ1*, *SLC30A8*, and *TCFL2* are known to be associated with T2DM. Yang *et al.* [32] reported that polymorphisms in *IRS1* and *HNF4* increased the risk of PTDM in a Hispanic population. Elens *et al.* [37] showed that *PPARα* and *POR* polymorphisms are significantly associated with PTDM in renal transplant patients treated with tacrolimus. The *CYP4F2* gene, which is known to be the main gene involved in creation of 20-hydroxyeicosatetraenoic acid, was also reported as an independent risk factor for PTDM [30]. These genes are associated with decreased insulin secretion through β-cell impairment

Table 3. Logistic regression analysis of *LEP* and *LEPR* polymorphisms in PTDM and non-PTDM subjects adjusted for age, sex, and tacrolimus usage.

Gene	SNP	Model	Type	PTDM, n (%)	Non-PTDM, n (%)	OR (95% CI)	p
LEP	**rs2167270**	Codominant	G/G	39 (72.2%)	147 (59.8%)	0.55 (0.27-1.11)	0.200
			A/G	13 (24.1%)	92 (37.4%)		
			A/A	2 (3.7%)	7 (2.8%)		
		Dominant	G/G	39 (72.2%)	147 (59.8%)	0.60 (0.31-1.16)	0.12
			A/G + A/A	15 (27.8%)	99 (40.2%)		
		Recessive	G/G+A/G	52 (96.3%)	239(97.2%)	1.58 (0.30-8.24)	0.60
			A/A	2 (3.7%)	7 (2.8%)		
	rs13228377	Codominant	A/A	39 (72.2%)	142 (57.7%)	0.54 (0.27-1.08)	0.19
			A/G	13 (24.1%)	94 (38.2%)		
			G/G	2 (3.7%)	10 (4.1%)		
		Dominant	A/A	39 (72.2%)	142 (57.7%)	0.55 (0.28-1.07)	0.073
			A/G+G/G	15 (27.8%)	104 (42.3%)		
		Recessive	A/A+G/G	52 (96.3%)	236 (95.9%)	0.83 (0.17-4.09)	0.81
			A/G	2 (3.7%)	10 (4.1%)		
LEPR	**rs8179183**	Codominant	G/G	43 (79.6%)	207 (84.2%)	1.37 (0.63-2.97)	0.55
			C/G	11 (20.4%)	38 (15.4%)		
			C/C	0 (0%)	1 (0.4%)		
		Dominant	G/G	43 (79.6%)	207 (84.2%)	1.32 (0.61-2.85)	0.44
			C/G + C/C	11(20.4%)	39 (15.8%)		
		Recessive	G/G + C/G	54(100%)	245 (99.6%)	1.09 (0.48-2.47)	0.840
			C/C	0 (0%)	1 (0.4%)		
	rs1137100	Codominant	G/G	40 (74.1%)	145 (58.9%)	0.55 (0.27-1.11)	0.09
			A/G	13 (24.1%)	87 (35.4%)		
			A/A	1 (1.8%)	14 (5.7%)		
		Dominant	G/G	40 (74.1%)	145 (58.9%)	2.00 (1.02-3.93)	0.037
			A/G+A/A	14 (25.9%)	101 (41.1%)		
		Recessive	G/G+A/G	53 (98.2%)	232 (94.3%)	1.61 (0.80-3.23)	0.17
			A/A	1 (1.8%)	14 (5.7%)		
	rs1137101	Codominant	G/G	47 (87%)	179 (72.8%)	2.48 (1.05-5.87)	0.029
			A/G	7 (13%)	62 (25.2%)		
			A/A	0 (0%)	5 (2%)		
		Dominant	G/G	47 (87%)	179 (72.8%)	2.69 (1.14-6.35)	0.014
			A/G+A/A	7 (13%)	37 (27.2%)		
		Recessive	G/G+A/G	184 (74.8%)	47 (13%)	0.00 (0.00-NA)	0.17
			A/A	0 (0%)	5 (2%)		

PTDM: post-transplantation diabetes mellitus; SNPs: single nucleotide polymorphisms

(*CCL2*, *CCL5*, *CDKAL1*, *CDKN2A/B*, *HNF4A*, *KCNJ11*, *KCNQ1*, *MMPs*, *NFATc4*, *SLC30A8*, and *TCF7L2*), increased peripheral insulin resistance (*ADIPOQ*, *AGT*, *IRS1*, and *LEP*), inflammation (*ILs*, *TLR4*, and *TLR6*), and oxidative stress (*GPX1*). In light of these results, PTDM is caused by an imbalance between insulin secretion and resistance, and β-cell dysfunction may be a dominant mechanism.

However, most of these studies are underpowered and were conducted in relatively small populations. To overcome these limitations, alternative approaches such as genome-wide association studies (GWAS) and meta-analyses are performed. McCaughan *et al.* [2] performed GWAS with secondary validation. They reported 26 SNPs that were associated with PTDM, and the association was validated for 8 SNPs. These SNPs were associated with apoptosis of beta cells, and the authors suggested that beta cell dysfunction and death play a crucial role in the pathogenesis of PTDM. Benson *et al.* [6] conducted a comprehensive meta-analysis of 18 polymorphisms in 12 genes which were reported to be genetic markers of PTDM. Of these various polymorphisms, *CDKAL1* rs10946398, *KCNQ1* rs2237892, and *TCF7L2* rs7903146 were significantly associated with PTDM ($p < 0.05$).

In conclusion, we demonstrated a significant association between *LEPR* polymorphisms and the development of PTDM in Korean renal transplant patients. Considering our present results and the above

Table 4. Previous candidate gene studies evaluating genetic susceptibility to PTDM in renal transplant recipients.

Gene	SNPs	Ethnicity	PTDM Case	Control	References
ADIPOQ	rs1501299	Asian (Korean)	154	421	Kang et al. [7]
	rs1501299	Caucasian	83	187	Nicoletto et al. [26]
AGT	rs4762	Asian (Korean)	49	253	Lee et al. [22]
CAPN10	rs5030952	Caucasian	56	158	Kurzawski et al. [27]
CCL2	rs1024611	Caucasian	43	272	Dabrowska-Zamojcin et al. [28]
CCL5	rs2107538	Asian (Korean)	56	255	Jeong et al. [10]
	rs2280789	Asian (Korean)	56	255	Jeong et al. [10]
	rs3817655	Asian (Korean)	56	255	Jeong et al. [10]
CDKAL1	rs10946398	Asian (Korean)	145	444	Kang et al. [29]
CDKN2A/B	rs10811661	Asian (Korean)	145	444	Kang et al. [29]
CYP4F2	rs2108622	Caucasian	34	130	Gervasini et al. [30]
GPX1	rs1050450	Caucasian	21	138	Dutkiewicz et al. [31]
HHEX	rs1111875	Asian (Korean)	145	444	Kang et al. [29]
	rs5015480	Asian (Korean)	145	444	Kang et al. [29]
	rs7923837	Asian (Korean)	145	444	Kang et al. [29]
HNF4A	rs1884614	Hispanic	133	170	Yang et al. [32]
	rs2144908	Hispanic	133	170	Yang et al. [32]
IL17E	rs1124053	Asian (Korean)	53	253	Kim et al. [23]
IL17F	rs763780	Caucasian	23	146	Romanowski et al. [33]
IL17RA	rs2229151	Asian (Korean)	53	253	Kim et al. [23]
	rs4819554	Asian (Korean)	53	253	Kim et al. [23]
IL17RB	rs1025689	Asian (Korean)	53	253	Kim et al. [23]
	rs1043261	Asian (Korean)	53	253	Kim et al. [23]
IL1B	rs3136558	Asian (Korean)	53	253	Kim et al. [23]
IL2	rs2069762	Asian (Korean)	53	253	Kim et al. [23]
	rs2069763	Asian (Korean)	53	253	Kim et al. [23]
IL4	rs2070874	Asian (Korean)	53	253	Kim et al. [23]
	rs2243250	Asian (Korean)	53	253	Kim et al. [23]
IL6	rs1800795	Caucasian	59	302	Bamoulid et al. [41]
IL7R	rs1494558	Asian (Korean)	53	253	Kim et al. [23]
	rs2172749	Asian (Korean)	53	253	Kim et al. [22]
IRS1	rs1801278	Hispanic	133	170	Yang et al. [32]
KCNJ11	rs5219	Caucasian	115	205	Tavira et al. [34]
	rs5210	Asian (Indian)	140	500	Khan et al. [9]
KCNQ1	rs2237892	Asian (Korean)	145	444	Kang et al. [29]
	rs2237895	Caucasian	145	260	Tavira et al. [35]
	rs2283228	Asian (Indian)	140	500	Khan et al. [9]
LEP	re2167270	Caucasian	43	280	Romanowski et al. [30]
MMP2	rs1132896	Asian (Korean)	52	257	Ong et al. [24]
	rs243849	Asian (Korean)	52	257	Ong et al. [24]
NFATc4	rs10141896	Hispanic	162	157	Chen et al. [36]
POR	rs1057868	Caucasian	9	76	Elens et al. [37]
PPARα	rs4253728	Caucasian	9	76	Elens et al. [37]
SLC30A8	rs13266634	Asian (Korean)	174	450	Kang et al. [38]
	rs13266634	Asian (Indian)	42	98	Khan et al. [39]
TCF7L2	rs7903146	Asian (Korean)	119	392	Kang et al. [40]
	rs7903146	Caucasian	114	958	Ghisdal et al. [8]
	rs7903146	Asian (Indian)	42	98	Khan et al. [39]
TLR4	rs1927914	Asian (Korean)	51	254	Kim et al. [25]
TLR6	rs1039559	Asian (Korean)	51	254	Kim et al. [25]

PTDM: post-transplantation diabetes mellitus; SNPs: single nucleotide polymorphisms; ADIPOQ: adiponectin; AGT: angiotensinogen; CAPN10: calpain-10 gene; CCL2: C-C motif chemokine ligand 2; CCL5: C-C motif chemokine ligand 5; CDKAL1 cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1; CDKN2A/B: cyclin-dependent kinase inhibitor-2A/B; CYP4F2: cytochrome P450 family 4 subfamily F member 2; GPX1: glutathione peroxidase 1; HHEX: hematopoietically expressed homeobox; HNF4A: hepatocyte nuclear factor 4 alpha; IL: interleukin; IRS1: insulin receptor substrate 1; KCNJ11: potassium voltage-gated channel subfamily J member 11; KCNQ1: potassium voltage-gated channel subfamily Q member 1; LEP: leptin; MMP2: matrix metalloproteinase 2; NFATc4: nuclear factor of activated T cells: cytoplasmic: calcineurin dependent 4; POR. P450 oxidoreductase; PPAR α, p eroxisome proliferator-activated receptor α; SLC30A8: solute carrier member 3 zinc transporter member 8; TCF7L2: transcription factor 7 like 2; TLR; toll-like receptor

mentioned studies, genetic susceptibility plays an essential role in the pathogenesis of PTDM. Discovery of precise genetic polymorphisms that impact the development of PTDM is important to understanding its mechanisms and contributing to early diagnosis and proper management of the condition. Prospective, large-scale investigations that include assessment of the biological effects of gene polymorphisms are needed.

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