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 rs1137101 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 (KCQ1), 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 dbSNP 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°C. 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 rs131700*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 next, 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 r² values between SNPs were also calculated.

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%) | 0.60(0.39–1.19) | 0.182 |
| LEPR | rs1322837 | A | 17 (15.8%) | 106 (21.5%) | 0.62(0.35–1.08) | 0.094 |
|      | rs8179183 | G | 97 (89.8%) | 454 (91.9%) | 1.28(0.63–2.59) | 0.480 |
|      | rs1137100 | A | 11 (10.2%) | 40 (8.1%) | 1.92 (1.02-1.19) | 0.025 |
|      | rs1137101 | G | 10 (94%) | 421 (85%) | 1.13 (1.05-1.23) | 0.019 |
|      |            | A | 7 (6%) | 73 (15%) | 1.19 (1.04–2.37) | 0.067 |

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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 homeostasis. It has been reported to play an important role in regulation of body weight, fat metabolism, and glucose uptake [11,15].}

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/m²) | 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, %) | 20 (6.9%) | 6 (2.3%) | 0.244 |
| Acute rejection (n, %) | 13 (25.4%) | 44 (17.2%) | 0.197 |

The r² values between rs8179183 and rs1137100, and between rs8179183 and rs1137101, between rs1137100 and rs1137101 were 0.328, 0.509, and 0.647, respectively.

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, CJK22A, HDL, HCN11, KCNQ1, SLC30A8, and TCF7L2 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 PPARG and POR polymorphisms are significantly associated with PTDM in renal transplant patients treated with tacrolimus. The CYF4F2 gene, which is known to be the main gene involved in creation of 20-hydroxyecosatetraenoic acid, was also reported as an independent risk factor for PTDM [30]. These genes are associated with decreased insulin secretion through β-cell impairment.
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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 |
|      | 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]             |
|        | rs150129   | 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]            |
| CNDK2A/B | rs16811661 | 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]            |
| 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]             |
| IL1B   | rs3136558  | Asian (Korean)    | 53        | 253     | Kim et al. [23]             |
| IL2    | rs2069762  | Asian (Korean)    | 53        | 253     | Kim et al. [23]             |
| IL4    | rs2070874  | 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. [23]             |
| IRS1   | rs1801278  | Hispanic          | 133       | 170     | Yang et al. [32]            |
| KCNJ11 | rs5219     | Caucasian         | 115       | 205     | Tavira et al. [34]          |
| 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]             |
| LEF    | rs2175720  | Caucasian         | 45        | 280     | Romanowski et al. [30]      |
| MMP2   | rs1122896  | 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]           |
| PPARa  | 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]          |
| 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; CNDK2A/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 1; 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; PPARα, peroxisome 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.

References
1. Ghishal L, Van Laecke S, Abramowicz MJ, Vanholder R, Abramowicz D (2012) New-onset diabetes after renal transplantation: risk assessment and management. Diabetes Care 35: 181-188. [Crossref]
2. McCaughan JA, McKnight AJ, Maxwell AP (2014) Genetics of new-onset diabetes after transplantation. J Am Soc Nephrol 25: 1037-1049. [Crossref]
3. Kesiaju S, Paritila P, Rao Ch UM, Saharai S (2014) New onset of diabetes after transplantation - an overview of epidemiology, mechanism of development and diagnosis. Transplant Immunol 30(1): 52-58.
4. van Hooft JP, Christiaans MH, van Duijnhoem EM (2004) Evaluating mechanisms of post-transplant diabetes mellitus. Nephrol Dial Transplant 19 Suppl 6: v8-v8v12. [Crossref]
5. Palepu S, Prasad GV (2015) New-onset diabetes mellitus after kidney transplantation. Transplant Infect Dis 17: 151-163. [Crossref]
6. Benson KA, Maxwell AP, McKnight AJ (2016) A HuGE Review and Meta-Analyses of Reference are needed.
7. McCaughan JA, McKnight AJ, Maxwell AP (2014) Genetics of new-onset diabetes after transplantation. J Am Soc Nephrol 25: 1037-1049. [Crossref]
8. Wauters M, Mertens I, Rankinen T, Chagnon M, Bouchard C, et al. (2001) Leptin receptor gene polymorphisms are associated with insulin in obese women with impaired glucose tolerance. J Clin Endocrinol Metab 86: 3227-3232. [Crossref]
9. Romankiewicz G, Domanski L, Pawlik A, Osekowska B, Drziedziuk V, et al. (2015) Interleukin-17 gene polymorphisms in patients with post-transplant diabetes mellitus. Mol Genet Genomic Med 3: 70-78. [Crossref]
10. Dutkiewicz G, Domanski L, Pawlik A, Osekowska B, Drziedziuk V, et al. (2015) Association of interleukin-17 gene polymorphism and type 2 diabetes mellitus in kidney transplant patients medicated with tacrolimus. Pharmacogenomics 16: 159-168. [Crossref]
11. Wauters M, Considne RV, Van Gaal LF (2000) Human leptin: from an adipocyte hormone to an endocrine mediator. Eur J Endocrinol 143: 293-311. [Crossref]
12. Dardeno TA, Chou SH, Moon HS, Chamberland JP, Fiorenza CG, et al. (2010) Leptin receptor gene polymorphisms and type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Res Clin Pract 91: 279-288. [Crossref]
13. Gottlieb MG, Bodanese LC, Leite LE, Schwane CH, Piccoli Jda C, et al. (2009) Association between the Glu223Arg polymorphism of the leptin receptor and metabolic syndrome in free-living community elderly. Metab Syndr Relat Disord 7: 341-348. [Crossref]
14. Fangos D, Taka N, Iyamauchi T, Natsuhara K, Kimura R, et al. (2010) The 842C/T polymorphism in LEPR is associated with obesity in Pacific Islanders. Hum Genet 127: 287-294. [Crossref]
15. Lakka TA, Rankinen T, Weinselag SJ, Chagnon YC, Lakka HM, et al. (2004) Leptin and leptin receptor gene polymorphisms and changes in glucose homeostasis in response to regular exercise in nondiabetic individuals: the HERITAGE family study. Diabetes 53: 1603-1608. [Crossref]
16. Lee, Sr., Moon JY, Lee SH, Ihm CG, Lee TW, et al. (2013) Angiotensinogen gene polymorphisms and post-transplantation diabetes mellitus in Korean renal transplant subjects. Kidney Blood Press Res 37: 95-102. [Crossref]
17. Kim YG, Ihm CG, Lee TW, Lee SH, Jeong KH, et al. (2012) Association of genetic polymorphisms of interleukins with new-onset diabetes after transplantation in renal transplant. Transplantation 93: 906-907. [Crossref]
18. Ong S, Kang SW, Kim YH, Kim TH, Jeong KH, et al. (2016) Matrix Metalloproteinase Gene Polymorphisms and New-Onset Diabetes After Kidney Transplantation in Korean Renal Transplant Subjects. Transplant Proc 48: 855-863. [Crossref]
19. Kim JS, Kim SK, Park JY, Kim YG, Moon JY, et al. (2016) Significant Association between Toll-like Receptor Gene Polymorphisms and Posttransplantation Diabetes Mellitus. Nephron 133: 279-286. [Crossref]
20. Kim ES, Kim MS, Kim CH, Nam CM, Han SJ, et al. (2009) Association of common type 2 diabetes risk gene variants and posttransplantation diabetes mellitus in renal allograft recipients in Korea. Transplantation 88: 653-698. [Crossref]
21. Gervasini G, Luna E, Garcia-Cerrada M, Garcia-Pino G, Cubero JJ (2016) Risk factors for posttransplant diabetes mellitus in renal transplant: Role of genetic variability in the CYP450-mediated anionic acid metabolism. Mol Cell Endocrinol 419: 158-164. [Crossref]
22. Yang J, Hutchinson, II, Shah T, Min DI (2011) Genetic and clinical risk factors of new-onset diabetes after transplantation in Asian Indian population. Genes & Diseases 2: 276-282. [Crossref]
23. Jeong KH, Moon JY, Chung JH, Kim YH, Lee TW (2010) Significant associations between CCL5 gene polymorphisms and post-transplantational diabetes mellitus in Korean renal allograft recipients. Am J Nephrol 32: 536-536. [Crossref]
24. Wauters M, Mertens I, Rankinen T, Chagnon M, Bouchard C, et al. (2001) Leptin receptor gene polymorphisms are associated with insulin in obese women with impaired glucose tolerance. J Clin Endocrinol Metab 86: 3227-3232. [Crossref]
40. Kang ES, Kim MS, Kim YS, Hur KY, Han SJ, et al. (2008) A variant of the transcription factor 7-like 2 (TCF7L2) gene and the risk of posttransplantation diabetes mellitus in renal allograft recipients. *Diabetes Care* 31: 63-68.

41. Bamoulid J, Courivaud C, Deschamps M, Mercier P, Ferrand C, et al. (2006) IL-6 promoter polymorphism -174 is associated with new-onset diabetes after transplantation. *J Am Soc Nephrol* 17: 2333-2340. [Crossref]