# A Variant of the Transcription Factor 7-Like 2 (*TCF7L2*) Gene and the Risk of Posttransplantation Diabetes Mellitus in Renal Allograft Recipients

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**OBJECTIVE** — Posttransplantation diabetes mellitus (PTDM) is a major complication associated with kidney transplantation. Defects in insulin secretion play a pivotal role in the pathogenesis of PTDM. A polymorphism in the transcription factor 7-like 2 (*TCF7L2*) gene was reported to be associated with type 2 diabetes and possibly associated with an insulin secretion defect. The aim of this study was to investigate the association between genetic variations in *TCF7L2* and PTDM in renal allograft recipients.

**RESEARCH DESIGN AND METHODS** — A total of 511 unrelated renal allograft recipients without previously known diabetes were enrolled. Six single nucleotide polymorphisms (rs11196205, rs4506565, rs12243326, rs7903146, rs12255372, and rs7901695) were genotyped in the cohort, which consisted of 119 PTDM patients and 392 non-PTDM subjects. The genotyping of *TCF7L2* polymorphisms was performed using real-time PCR.

**RESULTS** — rs4506565, rs7901695, and rs7903146 were found to be in complete linkage disequilibrium. The rs7903146 genotype distribution was CC 94.3% and CT 5.7%. The incidence of PTDM was significantly higher in patients with the CT genotype than in patients with the CC genotype (41.4 vs. 22.2%) (odds ratio 2.474 [95% CI 1.146–5.341]; $P = 0.024$). The effect of this genotype remains significant after adjustment for age, sex, amount of body weight gain, and type of immunosuppressant (2.655 [1.168–6.038]; $P = 0.020$).

**CONCLUSIONS** — These data suggest that the *TCF7L2* rs7903146 genetic variation is associated with an increased risk of PTDM in renal allograft recipients.

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**Abbreviations:** FPG, fasting plasma glucose; MAF, minor allele frequency; PTDM, posttransplantation diabetes mellitus; SNP, single nucleotide polymorphism.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.



The development of posttransplantation diabetes mellitus (PTDM) is an important metabolic complication of renal transplantation that is associated with cardiovascular morbidity and mortality (1,2) and contributes to reducing graft and patient survival (3). PTDM increases the risk of long-term cardiovascular events between 1.34 and 3.27 times, compared with patients without PTDM (4). The incidence of PTDM ranges from 2 to 53% (5). Various risk factors for the development of PTDM have been described, including older age, ethnicity, obesity, family history of diabetes, donor type (cadaver versus live), acute rejection, hepatitis C infection, polycystic kidney disease as the underlying renal disease, corticosteroid dose, and type of immunosuppressant therapy given following transplantation (2,3,6–9). Identifying patients at high risk of PTDM is beneficial for preventing PTDM and improving long-term patient outcome by allowing personalized immunosuppressant regimens and managing cardiovascular risk factors.

Our previous studies (10,11) have shown that defects in insulin secretion play a pivotal role in the pathogenesis of PTDM. Moreover, many recent studies have shown that a specific transcription factor 7-like 2 (*TCF7L2*) polymorphism (12) is associated with type 2 diabetes (12–19). Many reports suggest that this genetic variation influences insulin secretion (17,18,20). The aim of this study was to determine the association between *TCF7L2* polymorphisms and PTDM in a renal allograft cohort.

## RESEARCH DESIGN AND METHODS

— A total of 681 unrelated transplant recipients were recruited between 1989 and 2006. PTDM was diagnosed according to American Diabetes Association criteria (21) after the third posttransplantation month, and patients who began and continued an antidiabetes medication (oral medication or insulin) after transplantation were included in the PTDM group. The remaining patients be-

longed to the non-PTDM group. No patients had any previous diagnosis of diabetes or a recorded fasting plasma glucose (FPG) level <100 mg/dl. Patients were eligible to participate in the study if they were the recipients of a kidney allograft with no previous history of organ transplantation.

In accordance with our previous study (11), both persistent PTDM (diagnosed in patients who developed diabetes within 1 year following transplantation and remained diabetic) and late PTDM (diagnosed in patients who developed diabetes later than 1 year posttransplantation) patients were classified in the PTDM group. Transient PTDM patients (who developed diabetes during the first year following transplantation but eventually recovered to normoglycemia without medication) were classified as non-PTDM.

Patients were excluded if they had a history of diabetes before transplantation, had severe metabolic or infectious disease, had received multiple organ transplants, or had repeated kidney transplants. A total of 511 unrelated renal allograft recipients were enrolled in this study. The study protocol was approved by the ethics committee of the Yonsei University College of Medicine. All subjects were provided adequate information about the study and gave informed consent.

### Immunosuppression

The main immunosuppressive regimens consisted of calcineurin inhibitors (cyclosporine A or tacrolimus) and glucocorticoids. Immunosuppressive regimens and schedules were as reported previously (11) (online appendix [available at http://dx.doi.org/10.2337/dc07-1005]).

### Measurements

Anthropometric measurements were taken using standard techniques at the time of transplantation, then 3, 6, and 12 months after transplantation. All measurements were taken using the same equipment and by the same personnel. All samples were taken the morning after overnight fasting. FPG level was determined using an enzymatic colorimetric assay.

### DNA extraction and *TCF7L2* genotyping

Genomic DNA was isolated from peripheral blood lymphocytes. The genotyping of *TCF7L2* polymorphisms (rs4506565, rs7901695, rs7903146, rs11196205, rs12243326, and rs12255372) was performed using the TaqMan fluorogenic 5′ nuclease assay (Applied Biosystems, Foster City, CA). These polymorphisms were chosen from a screen of 15 single nucleotide polymorphisms (SNPs) and were selected because their minor allele frequency (MAF) was >2% or because they were reported to be associated with type 2 diabetes in previous studies (12–19,22–27).

Specific methods are shown in the online appendix. Duplicate samples and negative controls were included to ensure the accuracy of genotyping. On average, 99.3% of attempted genotypings were successful (success rates from 98.8 to 99.6% for each SNP).

### Statistical analyses

Statistical analyses were performed using SPSS for Windows software (version 12.0; SPSS, Chicago, IL). All continuous variables were expressed as the mean ± SD. The genotype frequencies were tested for Hardy-Weinberg equilibrium using a $\chi^2$ test. The Student's *t* test was used to compare the continuous variables between the PTDM and non-PTDM groups. To control for age and sex effects, multiple regression and logistic regression tests were used. The Pearson's $\chi^2$ test was used to evaluate differences in the incidence of diabetes between genotypes. A multivariable logistic regression test was used to identify risk factors for PTDM development and calculate the adjusted odds ratio and 95% CIs. Pairwise linkage disequilibrium between *TCF7L2* SNPs was assessed and patient baseline characteristics were assessed on the transplant day. A *P* value <0.05 was considered statistically significant.

## RESULTS

### Clinical characteristics of PTDM patients

Overall PTDM incidence in this study population was 23.3%. Baseline clinical characteristics of the population are shown in Table 1. The mean age of patients at transplantation was 36.9 ± 10.7 years. Patients in the PTDM group were older than those in the non-PTDM group (aged 41.1 ± 9.3 vs. 35.6 ± 10.8 years; $P = 0.001$). Follow-up duration was longer in the PTDM group compared with the non-PTDM group ($P = 0.003$). Although initial mean body weight was not different, patients in the PTDM group gained more weight than those in the non-PTDM group after 3 and 6 months following transplantation. These differences remained significant after adjustment for age and sex (Table 1). Initial FPG levels were not significantly different, but FPG levels between the two groups were significantly different at 3, 6, and 12 months after transplantation, despite antidiabetes treatment (Table 1). The duration of dialysis, incidence of acute rejection, percentage of tacrolimus use as an immunosuppressive agent, and serum creatinine levels were not different between the two groups (Table 1).

### Genotype distribution

Genotype distribution was in agreement with Hardy-Weinberg equilibrium (Table 2 and online appendix Table A1). Because rs4506565, rs7901695, and rs7903146 were in complete linkage ($D' = 1$, $r^2 = 1$) (online appendix Table A2) and the MAFs of rs11196205 (MAF = 0.023), rs12243326 (MAF = 0.002), and rs12255372 (MAF = 0.006) were too small to perform statistical analysis, only rs7903146 was further investigated (online appendix Table A1). The rs7903146 CC genotype was present in 94.3% of the samples and the CT genotype in 5.7% (Table 2).

### Association between the *TCF7L2* rs7903146 genotype and PTDM

PTDM developed in 119 patients (23.3%). The distribution of *TCF7L2* genotypes was significantly different between patients with and without diabetes. The CT genotype was more common in patients with PTDM (10.1%) than without (4.3%). The incidence of PTDM was significantly higher in patients with the CT genotype than in patients with the CC genotype (41.4 vs. 22.2%) (odds ratio 2.474 [95% CI 1.146–5.341]; $P = 0.024$) (Table 3). Unlike other studies on *TCF7L2*, no patients with the TT genotype were identified in this study. There was no difference between genotypes with regard to age at transplantation; initial body weight; FPG at baseline, 3, 6, and 12 months after transplantation; duration of dialysis; percentage of initial tacrolimus use; incidence of acute rejection; and serum creatinine levels (Table 3).

Multivariable logistic regression tests revealed that age at transplantation, amount of body weight gain during the first 6 months, and *TCF7L2* genotype are important risk factors of the development of PTDM (Table 4). The effect of the ge-

**Table 1—*Clinical characteristics of the study population***

| | Non-PTDM | PTDM | *P* | *P** |
|---|---|---|---|---|
| *n* (% female) | 392 (36.5) | 119 (34.5) | 0.744† | — |
| Age (years) at transplantation | 35.64 ± 10.80 | 41.10 ± 9.33 | 0.001 | — |
| Family history of diabetes (%) | 224 (59.3) | 68 (59.1) | 1.000† | 0.465 |
| Follow-up duration (months) | 104.13 ± 60.93 | 122.47 ± 57.40 | 0.003 | <0.001 |
| Body weight (kg) | | | | |
| At transplantation | 57.12 ± 10.98 | 58.29 ± 9.52 | 0.258 | 0.426 |
| At 3 months after transplantation | 57.24 ± 9.88 | 59.43 ± 8.92 | 0.023 | 0.469 |
| At 6 months after transplantation | 59.74 ± 10.15 | 62.45 ± 8.13 | 0.003 | 0.181 |
| ΔBody weight (kg) | | | | |
| At 3 months after transplantation | 0.12 ± 4.30 | 1.14 ± 5.48 | 0.035 | 0.004 |
| At 6 months after transplantation | 2.62 ± 5.62 | 4.16 ± 6.22 | 0.017 | 0.001 |
| FPG (mg/dl) | | | | |
| At transplantation | 91.92 ± 24.70 | 95.49 ± 27.78 | 0.242 | 0.304 |
| At 3 months after transplantation | 96.39 ± 17.50 | 114.28 ± 57.27‡ | <0.001 | <0.001 |
| A t 6 months after transplantation | 94.53 ± 14.10 | 110.47 ± 24.82‡ | <0.001 | <0.001 |
| At 12 months after transplantation | 96.24 ± 16.99 | 123.22 ± 54.35‡ | <0.001 | <0.001 |
| Duration of dialysis (months) | 20.79 ± 34.39 | 14.83 ± 22.70 | 0.077 | 0.055 |
| Patients with acute rejection (%) | 89 (22.7) | 34 (28.6) | 0.221† | 0.128† |
| Patients with tacrolimus use (%) | 91 (23.2) | 29 (24.4) | 0.806† | 0.941† |
| Creatinine (mg/dl) | | | | |
| At 3 months after transplantation | 1.39 ± 0.75 | 1.35 ± 0.42 | 0.488 | 0.600 |
| At 6 months after transplantation | 1.30 ± 0.34 | 1.35 ± 0.37 | 0.693 | 0.621 |
| At 12 months after transplantation | 1.31 ± 0.42 | 1.29 ± 0.42 | 0.557 | 0.709 |

Data are means ± SD or *n* (%) unless otherwise indicated. *P* values are calculated from *t* test. **P* values are adjusted for age and sex; †*P* values are calculated from $\chi^2$ test. ‡Included patients treated with antidiabetes medications.

notype remains significant after multivariable logistic regression for PTDM after adjustment for age and sex (model 1, $P = 0.012$), after adjustment for age, sex, and amount of weight gain (model 2, $P = 0.016$), and after adjustment for age, sex, amount of weight gain, and type of immunosuppressant use (model 3, $P = 0.020$). Although male sex and use of tacrolimus seemed to be risk factors for PTDM, they were not statistically significant (Table 4).

**CONCLUSIONS** — Various risk factors of the development of PTDM have been studied, but there are few reports on its genetic risks. We have previously reported that defects in insulin secretion play a pivotal role in the pathogenesis of PTDM (10,11). Many recent studies have suggested that TCF7L2 may play a role in insulin secretion (17,18). Therefore, we investigated the genetic influence of the *TCF7L2* polymorphism on the development of PTDM in a renal transplant cohort.

We initially selected six SNPs in the *TCF7L2* gene that are reported to be associated with type 2 diabetes in many populations (12–19,22–27). However, MAFs were significantly lower in this cohort than in populations of European ancestry. Moreover, we did not observe minor allele homozygotes for rs4506565, rs12243326, rs7903146, rs12255372, or rs7901695. This result is consistent with recently reported haplotype structures in East Asians (23). The frequency of the rs7903146 CT genotype was only 5.7% in the study population herein compared with up to 48% in Caucasian populations. This frequency is similar to that seen in Japan, where the heterozygote accounts for 8.47% (27).

A number of previous reports showed that the *TCF7L2* rs7903146 variant is associated with type 2 diabetes in the general population. In this study, *TCF7L2* rs7903146 was significantly associated with the development of PTDM. The incidence of PTDM was significantly higher in patients with the CT genotype than in patients with the CC genotype (41.4 vs. 22.2%) (odds ratio 2.474 [95% CI 1.146–5.341]; $P = 0.024$).

In monovariable analysis, age, the amount of body weight gain, and the *TCF7L2* genotype were associated with the development of PTDM. The effect of genotype remains significant after multivariable logistic regression for PTDM. Sex and type of immunosuppressant were not shown to be independent risk factors. These results suggest that the *TCF7L2* gene is one of the susceptibility genes for PTDM.

**Table 2—*Allele and genotype frequencies of* TCF7L2 *rs7903146***

| Allele | PTDM | Non-PTDM | Genotype | PTDM | Non-PTDM | *P* |
|---|---|---|---|---|---|---|
| C | 94.96 | 97.83 | C/C | 107 (89.9) | 375 (95.7) | 0.509 |
| T | 5.04 | 2.17 | C/T | 12 (10.1) | 17 (4.3) | 0.024* |
| | | | T/T | 0 (0) | 0 (0) | |

Data are % or *n* (%). *P* value was assessed by Hardy-Weinberg equilibrium $\chi^2$ test. **P* value was assessed by $\chi^2$ test between the CC and CT genotypes.

**Table 3—*Characteristics of patients according to rs7903146 genotype***

| | CC | CT | *P* |
|---|---|---|---|
| *n* | 482 | 29 | |
| Number of PTDM patients (%) | 107 (22.2) | 12 (41.4) | 0.024* |
| Age (years) at transplantation | 36.92 ± 10.73 | 36.72 ± 10.74 | 0.925 |
| Family history of diabetes (%) | 272 (58.5) | 20 (71.4) | 0.235* |
| Follow-up duration (months) | 108.22 ± 59.78 | 111.34 ± 73.74 | 0.825 |
| Body weight (kg) | | | |
| At transplantation | 57.53 ± 10.64 | 55.06 ± 10.91 | 0.243 |
| At 3 months after transplantation | 57.82 ± 9.71 | 56.62 ± 9.73 | 0.526 |
| At 6 months after transplantation | 60.45 ± 9.81 | 59.06 ± 9.34 | 0.443 |
| ΔBody weight (kg) | | | |
| At 3 months after transplantation | 0.28 ± 4.61 | 1.57 ± 4.63 | 0.157 |
| At 6 months after transplantation | 2.92 ± 5.81 | 4.01 ± 5.63 | 0.321 |
| FPG (mg/dl) | | | |
| At transplantation | 92.94 ± 25.68 | 88.86 ± 20.62 | 0.381 |
| At 3 months after transplantation | 100.58 ± 32.30 | 101.55 ± 38.14 | 0.913 |
| At 6 months after transplantation | 98.10 ± 17.47 | 93.07 ± 26.73 | 0.454 |
| At 12 months after transplantation | 102.52 ± 32.14 | 103.51 ± 31.74 | 0.868 |
| Duration of dialysis (months) | 19.32 ± 31.02 | 18.43 ± 46.12 | 0.910 |
| Patients with acute rejection (%) | 123 (25.31) | 3 (10.34) | 0.069* |
| Patients with tacrolimus use (%) | 110 (22.8) | 10 (34.5) | 0.175* |
| Creatinine (mg/dl) | | | |
| At 3 months after transplantation | 1.39 ± 0.70 | 1.26 ± 0.36 | 0.104 |
| At 6 months after transplantation | 1.31 ± 0.35 | 1.23 ± 0.31 | 0.226 |
| At 12 months after transplantation | 1.31 ± 0.42 | 1.22 ± 0.31 | 0.172 |

Data are means ± SD or *n* (%). *P* values are calculated from *t* test. **P* values are calculated from $\chi^2$ test.

Patients with PTDM gained more weight during the follow-up period. This difference may be due to medications (e.g., insulin or thiazolidinediones) rather than reduced kidney function in PTDM patients or older age (online appendix Table A3). It is unlikely that PTDM patients had less improved kidney function, as there was no significant difference in serum creatinine levels between the two groups. It is also unlikely that the difference in weight gain is simply due to the older age of the PTDM patients since, after adjustment for age and sex, the difference in body weight gain remained significant (Table 1).

**Table 4—*Multivariable logistic regression analysis for risk factors associated with PTDM***

| Variable | OR (95% CI) | *P* |
|---|---|---|
| Model 1 | | |
| Age at transplantation | 1.054 (1.032–1.076) | <0.001 |
| Sex (0 = male, 1 = female) | 0.776 (0.494–1.218) | 0.270 |
| rs7903146 genotype (0 = CC, 1 = CT) | 2.798 (1.255–6.238) | 0.012 |
| Model 2 | | |
| Age at transplantation | 1.058 (1.035–1.081) | <0.001 |
| Sex (0 = male, 1 = female) | 0.718 (0.453–1.139) | 0.159 |
| ΔBody weight at 6 months after transplantation | 1.060 (1.020–1.101) | 0.003 |
| rs7903146 genotype (0 = CC, 1 = CT) | 2.741 (1.211–6.205) | 0.016 |
| Model 3 | | |
| Age at transplantation | 1.058 (1.035–1.081) | <0.001 |
| Sex (0 = male, 1 = female) | 0.704 (0.442–1.119) | 0.137 |
| ΔBody weight at 6 months after transplantation | 1.066 (0.978–1.161) | 0.002 |
| Immunosuppressant (0 = cyclosporine A, 1 = tacrolimus) | 1.283 (0.754–2.185) | 0.358 |
| rs7903146 genotype (0 = CC, 1 = CT) | 2.655 (1.168–6.038) | 0.020 |

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, and amount of body weight gain during the first 6 months after transplantation. Model 3: adjusted for age, sex, amount of body weight gain during the first 6 months after transplantation, and type of immunosuppressant use. ΔBody weight, body weight gain between baseline and 6 months after transplantation.

*TCF7L2* is a novel type 2 diabetes susceptibility gene that confers up to a twofold increase in the risk of developing type 2 diabetes. The *TCF7L2* polymorphism is considered to be the most powerfully associated polymorphism with type 2 diabetes to date (18). Our data suggest that *TCF7L2* variation plays an important role in the development of PTDM and type 2 diabetes.

A recent report suggests that this genetic variation increases TCF7L2 expression in the β-cell, reducing insulin secretion and predisposing the subject to diabetes (20). There are few studies on the genetic risk factors for PTDM to date. Bamouulid et al. (28) reported that an interleukin-6 promoter polymorphism is associated with a lower risk of PTDM in 349 renal allograft patients. Numakura et al. (29) reported that a vitamin D receptor (*VDR*) gene polymorphism is associated with PTDM in 70 renal allograft recipients. Interestingly, *VDR* polymorphism is also re-

ported to have an effect on insulin secretion (30,31). These results are consistent with our previous reports (10,11) showing that defects in insulin secretion play a more crucial role in the pathogenesis of PTDM than increased insulin resistance.

Although many clinical studies (3,32,33) have indicated that tacrolimus is approximately five times more diabetogenic than cyclosporine, there was no difference in the incidence of PTDM according to the kind of immunosuppressive agents used in this study. This is probably because the doses of calcineurin inhibitors and glucocorticoids used in this study were different.

A limitation of this study is that an oral glucose tolerance test was not routinely performed before transplantation. It is possible that preexisting impaired glucose tolerance leads to overdiagnosis of PTDM. While genetic variation in TCF7L2 is associated with PTDM in the current study, the contribution of this genetic variation to the development of PTDM in Asians is relatively modest because of the low MAF. The T allele frequency was 2.84% in the Korean population, which is comparable with such frequencies in Chinese individuals from Beijing (2.2%) or Japanese individuals from Tokyo (2.3%) and in contrast to those of Caucasian populations (25%) and African populations (29.2%) in the HapMap database (34). There might be a more substantial impact on Caucasian populations in which MAF is reported to be ~25%.

In conclusion, our study results suggest that the *TCF7L2* rs7903146 variant is associated with an increased risk of PTDM. To our knowledge, this study is the first and the largest genetic study to investigate the association between the *TCF7L2* gene polymorphism and PTDM. The development of PTDM after renal allograft is a critical factor for quality of life and graft survival. Therefore, to minimize the risk of PTDM development in patients carrying this high-risk genotype, it may be critical to consider the use of less diabetogenic immunosuppressants, encourage weight reduction and lifestyle modification, utilize a rapid steroid tapering schedule, or pursue pharmacologic prevention.

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