*Brief Genetics Report*

# *TCF7L2* Variation Predicts Hyperglycemia Incidence in a French General Population

## The Data From an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) Study

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**Recently, case-control studies demonstrated that a *TCF7L2* (transcription factor 7–like 2 gene) noncoding variant (rs7903146 T at-risk allele) was strongly associated with an increased risk of type 2 diabetes. However, the predictive value of this marker in a nonselected general population remains unknown. In this study, our aim was to assess the contribution of this variant to the prevalence and incidence of hyperglycemia (type 2 diabetes and impaired fasting glucose) and insulin regulation in a 9-year prospective study of 4,976 middle-aged participants in the French DESIR (Data from an Epidemiological Study on the Insulin Resistance Syndrome) cohort. Our data support previous studies associating the T at-risk allele with a higher prevalence of hyperglycemia at baseline ($P = 0.049$) and a higher incidence of hyperglycemia after 9 years of follow-up ($P = 0.014$). The population-attributable risk to develop hyperglycemia due to the T at-risk allele was estimated to be 10.4% at the end of the prospective study. The most likely inheritance model was found to be additive ($P = 0.002$) rather than deviating from linearity ($P = 0.098$). An increase in the incidence of hyperglycemia was confirmed by survival analyses among C/C, C/T, and T/T carriers during the 9 years of follow-up ($P = 0.028$ by log-rank test). Interestingly, in control individuals, there was weak evidence of association of the T at-risk allele with reduced fasting insulin levels and insulin secretion index (homeostasis model assessment of β-cell function) in control individuals. We conclude that the *TCF7L2* T at-risk allele variation (rs7903146) predicts hyperglycemia incidence in a general French population, possibly through a deleterious effect on insulin secretion. *Diabetes* 55: 3189–3192, 2006**

Recently, a strong association was found in individuals of European origin between type 2 diabetes and the DG10S478 microsatellite within intron 3 of the transcription factor 7–like 2 (*TCF7L2*) gene (1). The rs7903146 T at-risk allele variation was then strongly correlated with this microsatellite ($r^2 = 0.78$), and it was shown to be the allele most associated with type 2 diabetes (relative risk 1.54, $P = 2.1 \times 10^{-17}$). The potentially large contribution of this gene variant to type 2 diabetes risk was further confirmed in 2,367 type 2 diabetic participants and 2,499 control subjects of French-Caucasian descent (odds ratio [OR] 1.69 [95% CI 1.55–1.83], $P = 6.0 \times 10^{-35}$) (2). In nonobese type 2 diabetic participants, the association was even stronger (1.89 [1.72–2.09], $P = 2.1 \times 10^{-38}$), suggesting that *TCF7L2* may contribute to insulin secretion defects rather than to insulin resistance resulting from adiposity. In these type 2 diabetic participants, the T at-risk allele was also significantly associated with lower BMI and younger age at diagnosis. In control individuals, however, no association with any metabolic parameter was found, supporting the hypothesis that the effects of *TCF7L2* on type 2 diabetes risk are not mediated by an interaction with adiposity, as previously described for another type 2 diabetes susceptibility gene (3).

Although large scale case-control studies are very sensitive in detecting genetic effects, they are not sufficient to evaluate the true contribution of disease-associated genes in nonselected general populations (4). Therefore, the objective of this study was to examine whether the T at-risk allele predicted hyperglycemia (type 2 diabetes and impaired fasting glucose [IFG]) in the prospective Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort, a French general middle-aged population. This cohort offers the opportunity to analyze both the risk factors for hyperglycemia at baseline and during the 9 years of follow-up. Variant influence on insulin secretion/sensitivity indexes (homeostasis model assessment [HOMA] of β-cell function [HOMA-B] and insulin resistance [HOMA-IR]), BMI, fasting glucose and

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Additional information for this article can be found in an online appendix at http://diabetes.diabetesjournals.org.

DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome; HOMA, homeostasis model assessment; HOMA-B, HOMA of β-cell function; HOMA-IR, HOMA of insulin resistance; IFG, impaired fasting glucose; PAR, population-attributable risk.

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TABLE 1
*TCF7L2* rs7903146 T at-risk allele association with hyperglycemia during a 9-year follow-up of a general French population

| Analysis | C/C (HG/control) | C/T (HG/control) | T/T (HG/control) | Allelic OR (95% CI) | *P* |
|---|---|---|---|---|---|
| A1 | 252/2,176 = 0.116 | 226/1,878 = 0.120 | 64/380 = 0.168 | 1.14 (1.00–1.31) | 0.049 |
| A2 | 200/1,472 = 0.136 | 215/1,200 = 0.179 | 45/253 = 0.178 | 1.20 (1.04–1.40) | 0.014 |
| A3 | 452/1,472 = 0.307 | 441/1,200 = 0.368 | 109/253 = 0.431 | 1.19 (1.07–1.33) | 0.002 |

The genotypic distributions were in agreement with Hardy-Weinberg equilibrium. A1: At baseline, all participants. A2: Control: participants followed 9 years and remaining normoglycemic over the 9 years. HG: incident cases of hyperglycemia over the 9 years. A3: Control: participants followed 9 years and remaining normoglycemic over the 9 years. HG: participants hyperglycemic at baseline and incident cases of hyperglycemia.

insulin, triglycerides, and total, LDL, and HDL cholesterol was also investigated.

In the studied samples, rs7903146 genotypic distributions did not deviate from the Hardy-Weinberg equilibrium. Genotypic/phenotypic data were analyzed by comparing relevant quantitative traits in three different ways. At baseline (A1: prevalence analysis), we compared the control subjects ($n$ = 4,434) with hyperglycemic participants ($n$ = 542). Individuals who were control subjects at baseline were then reanalyzed after 9 years of follow-up (A2: incidence analysis), and we compared those who remained nonaffected at the end of the study ($n$ = 2,925) with the incident hyperglycemic participants ($n$ = 460). In the third analysis (A3: prospective analysis), individuals who remained nonaffected after 9 years of follow-up ($n$ = 2,925) were compared with all hyperglycemic participants (both baseline and incident cases, $n$ = 1,002). In all three analyses (A1–A3), we found that the T at-risk allele was associated with hyperglycemia risk (OR 1.14 [95% CI 1.00–1.31], $P$ = 0.049; 1.20 [1.04–1.40], $P$ = 0.014; and 1.19 [1.07–1.33], $P$ = 0.002, respectively) (Table 1). In two of the three analyses (A2 and A3), the T at-risk allele was associated with type 2 diabetes risk (1.37 [1.10–1.70], $P$ = 0.006; and 1.30 [1.10–1.55], $P$ = 0.003, respectively) (supplementary Table 1 of the online appendix [available at http://diabetes.diabetesjournals.org]). At baseline, the proportions of type 2 diabetes among hyperglycemic participants were 26% for C/C, 24% for C/T, and 30% for T/T carriers, respectively. After 9 years of follow-up, the proportions of type 2 diabetes among hyperglycemic participants were 31% for C/C, 31% for C/T, and 39% for T/T carriers, respectively. During 9 years of follow-up, among individuals with IFG, 21% of C/C, 27.0% of C/T, and 34% of T/T carriers converted to type 2 diabetes. While more men than women had type 2 diabetes and IFG, no statistical heterogeneity was found between the ORs for men and women (supplementary Table 2 of the online appendix). The population-attributable risk (PAR) to develop hyperglycemia and type 2 diabetes resulting from the T at-risk allele was 10.4 and 13.3%, respectively, at the end of the prospective study (A3 analysis). At the end of the follow-up (A3 analysis), the most likely inheritance model was found to be additive ($P$ = 0.002), with no deviation from linearity ($P$ = 0.098). An increase in hyperglycemia incidence (A2 analysis) was confirmed by survival analyses among C/C, C/T, and T/T carriers during the 9 years of follow-up (hazard ratio 1.21 [95% CI 1.05–1.39], $P$ = 0.008) (Fig. 1). At the end of the study, the prevalences of hyperglycemia (A3 analysis) were found to be 23% for C/C, 27% for C/T, and 30% for T/T carriers, respectively (Table 1).

Quantitative trait analyses were then performed in control individuals (Table 2). At baseline (A1 analysis), only two traits differed significantly; between homozygotes C/C and T/T, we found a 0.07 decrease in ln(fasting insulinemia) (3.68 ± 0.51 for C/C, 3.66 ± 0.51 for C/T, and 3.61 ± 0.53 for T/T; $P$ = 0.04) and a 0.06 decrease in ln(HOMA-B) (4.41 ± 0.52 for C/C, 4.38 ± 0.52 for C/T, and 4.35 ± 0.53 for T/T; $P$ = 0.04). Because of the number of statistical tests carried out, a simple Bonferroni correction was

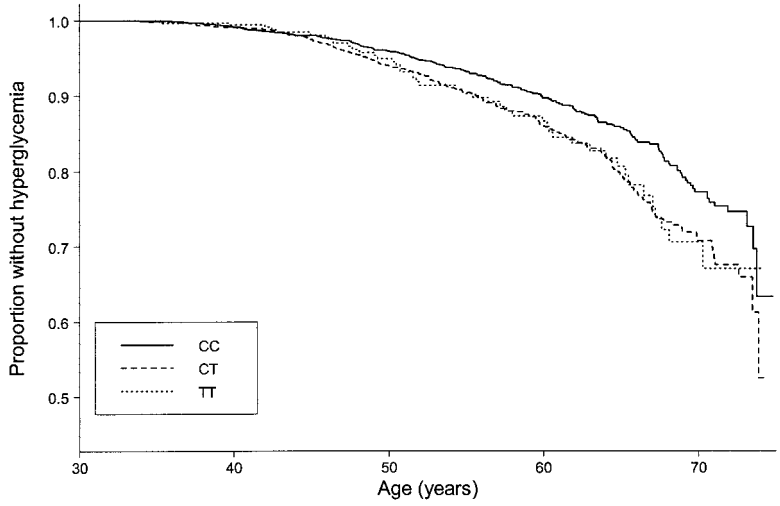


**FIG. 1. Hyperglycemia incidence, by age at baseline, in a French general population according to the *TCF7L2* genotype. The genotype could be considered a risk factor present since birth. The time scale is represented by age, in order to be in a continuous scale. The proportion with hyperglycemia was calculated within each genotypic class to assess the impact of the genotype on hyperglycemia incidence. An increase of the incidence of hyperglycemia (A2 analysis) was confirmed by Cox survival analysis (adjusted for BMI, age, and sex) among C/C, C/T, and T/T carriers during the 9 years of follow-up (hazard ratio 1.21 [1.05–1.39], $P$ = 0.008).**

TABLE 2
Quantitative trait means (±SD) by *TCF7L2* rs7903146 genotype at different times of the prospective study in control subjects

| Quantitative trait | A1 ($n$ = 4,434) | | | | A2 and A3 ($n$ = 2,925) | | | |
|---|---|---|---|---|---|---|---|---|
| | C/C | C/T | T/T | *P* | C/C | C/T | T/T | *P* |
| BMI (kg/m$^2$) | 24.49 ± 3.67 | 24.51 ± 3.70 | 24.23 ± 3.52 | 0.39 | 25.29 ± 3.89 | 25.27 ± 3.74 | 25.14 ± 3.76 | 0.84 |
| ln(Fasting insulin) (pmol/l) | 3.68 ± 0.51 | 3.66 ± 0.51 | 3.61 ± 0.53 | 0.04* | 3.90 ± 0.57 | 3.89 ± 0.53 | 3.82 ± 0.55 | 0.09 |
| ln(HOMA-B) (AU) | 4.41 ± 0.52 | 4.38 ± 0.52 | 4.35 ± 0.53 | 0.04* | 4.73 ± 0.54 | 4.71 ± 0.52 | 4.66 ± 0.60 | 0.18 |
| ln(HOMA-IR) (AU) | 0.41 ± 0.55 | 0.39 ± 0.55 | 0.34 ± 0.56 | 0.07 | 0.61 ± 0.60 | 0.60 ± 0.56 | 0.52 ± 0.58 | 0.09 |
| Fasting glucose (mmol/l) | 5.17 ± 0.47 | 5.18 ± 0.47 | 5.16 ± 0.49 | 0.61 | 5.03 ± 0.43 | 5.03 ± 0.45 | 5.01 ± 0.44 | 0.87 |
| Cholesterol (mmol/l) | 5.72 ± 1.01 | 5.69 ± 0.99 | 5.72 ± 0.94 | 0.69 | 5.72 ± 0.90 | 5.73 ± 0.91 | 5.69 ± 0.93 | 0.77 |
| HDL cholesterol (mmol/l) | 1.64 ± 0.42 | 1.64 ± 0.43 | 1.66 ± 0.44 | 0.74 | 1.54 ± 0.36 | 1.53 ± 0.36 | 1.55 ± 0.39 | 0.67 |
| LDL cholesterol (mmol/l) | 3.56 ± 0.93 | 3.55 ± 0.90 | 3.57 ± 0.90 | 0.84 | 3.66 ± 0.79 | 3.67 ± 0.77 | 3.63 ± 0.77 | 0.73 |
| Triglycerides (mmol/l) | 1.14 ± 0.76 | 1.12 ± 0.79 | 1.10 ± 0.66 | 0.59 | 1.14 ± 0.59 | 1.16 ± 0.61 | 1.10 ± 0.61 | 0.25 |

Data are means ± SD. A1: At baseline, all control participants. A2 and A3: Participants followed 9 years and remaining normoglycemic over the 9 years. *P* values are from linear regression models and are adjusted for BMI, age, and sex (BMI being adjusted for age and sex only). *No *P* values remained significant after Bonferroni correction. AU, arbitrary units.

applied, and none of the *P* values remained significant. In participants who remained nonaffected after 9 years of follow-up (A2 and A3 analyses), none of the analyzed traits were significantly different among the three genotypes. No significant association was found within control subjects with any other quantitative traits such as BMI, fasting glucose, HOMA-IR, triglycerides, or total, HDL, or LDL cholesterol.

Numerous gene variants have been associated with type 2 diabetes, but information about their predictive value has been hampered, as very few variants have been assessed in long large-scale prospective observational studies (5–7). The *TCF7L2* rs7903146 T at-risk allele has been strongly associated with type 2 diabetes in several populations of European origin (1,2). The minor allelic frequency is quite high (~30%) in these populations, and it confers a relative risk ranging between 1.5 and 1.9, with an attributable risk ranging between 20 and 35% (1,2). The major interest of the present study is to provide further information on this gene variant for both hyperglycemia prevalence and incidence during a 9-year follow-up of a middle-aged cohort from a French general population. However, the ORs (1.2–1.3) and PARs (10.4% for hyperglycemia and 13.3% for type 2 diabetes) are lower in the DESIR study than in French case-control cohorts. The PAR is probably better estimated in a general population than in control subjects from case-control studies. However, the ORs in DESIR correspond to only 1 decade of exposure, whereas the case-control analysis gives a more composite value of a lifetime exposure. Although the allelic ORs are substantially lower than in other studies, the CIs of the genotypic ORs (C/C versus C/T and C/T versus TT, one being the wild-type allele) overlap with previously published estimations (1,2). An explanation for these differences may lie in the physiological role of the *TCF7L2* transcription factor in glucose homeostasis. It has been suggested that intestinal proglucagon gene expression may be regulated by the Wnt/*TCF7L2* pathway in enteroendocrine cells (8), and we found that *TCF7L2* was also expressed in human β-cells (2). In the present study, we found only weak evidence of association with limited reduction of fasting insulin levels and HOMA-B values in control subjects during the 9 years of follow-up (no post–glucose load data were available in the DESIR study), suggesting a potential impact of the T at-risk allele on insulin secretion. After simple Bonferroni corrections, no *P* values remained significant. However, the pathogenic traits monitored during our study (BMI, insulin, glucose, and lipid traits) are not independent, and they have been shown to be related in type 2 diabetes (9); thus, it is unlikely that the effect of a variant on these parameters would occur only by chance. The results need to be confirmed in other cohorts in order to clarify the physiological consequences of the rs79013146 T at-risk allele. Interestingly, neither BMI nor any quantitative traits related to atherosclerosis were found to be associated with the T at-risk allele, which makes it unlikely that the *TCF7L2* diabetogenic effect directly involves insulin sensitivity or fat deposition.

In conclusion, this study shows that the *TCF7L2* T at-risk allele variation (rs7903146) predicts hyperglycemia in a nonselected, prospectively followed, general, middle-aged, French population. This is probably due to a continuous impairment in insulin secretion. Further studies should be directed at determining the molecular and physiological mechanisms by which *TCF7L2* contributes to glucose homeostasis and type 2 diabetes development.

## RESEARCH DESIGN AND METHODS

The study population (men and women aged between 30 and 65 years [equal amounts of men and women by 5-year age-groups]) participated in the cohort for the DESIR, a 9-year follow-up study that aims to clarify the development of the insulin resistance syndrome (10). Participants were recruited from volunteers insured by the French social security system, which offers 5-yearly periodic health examinations free of charge. They came from 10 health examination centers in the western-central part of France. All participants signed an informed consent. The protocol was approved by the ethics committee at Bicêtre Hospital. Pregnant women, those who did not want their results communicated to their general practitioners, those expecting to shift from the geographical region of the study, and those already participating in another study were excluded. For the 5,212 individuals included in the study, there were examinations every 3 years, and 3,981 (76%) were examined at 9 years. A total of 4,976 participants, genotyped for the rs7903146 T at-risk allele, had data available at baseline. Among them, 4,434 participants were normoglycemic, of whom 3,927 (mean age at recruitment 47 ± 10 years) could be followed for type 2 diabetes and IFG during a 9-year period (response rate 0.89). Three classes of glycemic status were defined according to 1997 American Diabetes Association criteria: normoglycemia, fasting plasma glucose <6.1 mmol/l; IFG, fasting plasma glucose between 6.1 and 6.9 mmol/l; and type 2 diabetes, fasting plasma glucose ≥7.0 mmol/l and/or treatment by antidiabetes agents. Participants were classified as hyperglycemic if they had either type 2 diabetes or IFG (6). The mean BMI was 24.12 ± 3.40 kg/m$^2$ for control subjects, 26.87 ± 4.12 kg/m$^2$ for hyperglycemic (IFG plus type 2 diabetes) participants, and 28.44 ± 4.34 kg/m$^2$ for type 2 diabetic participants.

**Quantitative trait measures.** Weight, height, and waist circumferences were measured by trained personnel, and BMI (weight in kilograms divided by the square of height in meters) was calculated. Venous blood samples were collected in the morning after participants had fasted 12 h. Fasting plasma glucose was assayed by the glucose oxidase method applied to fluoro-oxalated plasma, using a Technicon RA 1000 (Bayer, Puteaux, France) or a Kone

Automate (Evry, France); fasting serum insulin was measured by an enzymo-immunoassay with IMX (Abbott, Rungis, France) (11). Insulin secretion was assessed by calculating the HOMA-B index, defined as (fasting insulin × 20)/(fasting glucose − 3.5) (12). To estimate peripheral insulin resistance, we used the HOMA-IR, defined as (fasting insulin × fasting glucose)/22.5 (12). The HOMA-IR is correlated with insulin resistance as assessed by a euglycemic-hyperinsulinemic clamp. HOMA-B, HOMA-IR, and fasting insulin were transformed by natural logarithm (ln) to normalize their distributions.

**Genotyping.** The rs7903146 SNP was genotyped using an AOD (assay on demand) kit (Applied Biosystems). The PCR was performed with a GeneAmp 9700 PCR system. The conditions for the TaqMan reaction were 95°C for 10 s and 40 cycles of 92°C for 15 s, 60°C for 1 min, and 15°C for 5 s. Allelic discrimination was performed through capillary electrophoresis analysis, using an Applied Biosystems 3730xl DNA analyzer and GeneMapper3.7 software. The genotypes were determined with an ABI PRISM 7900 HT sequence detection system. There was a 98% genotyping success rate, and the genotyping error rate was assessed by sequencing 384 control and 384 hyperglycemic participants and by regenotyping a random 10% sample. No difference was found with the first genotyping results; thus, the genotyping error rate was estimated to be 0%.

**Statistical analysis.** Tests for deviation from Hardy-Weinberg equilibrium and for OR association used the De Finetti program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). A multivariate linear regression model, taking into account age and sex, was performed for BMI, and, for other quantitative traits, age, sex, and BMI were included. Simple Bonferroni corrections were applied to the *P* values for multiple comparisons. To assess whether the effect was linear, recessive, or dominant, we applied a logistic regression test with two variables, v1 (coded 0, 1, 2), reflecting a linear increase in risk, and v2 (coded 0, 1, 0), reflecting a departure from linearity. If v1 is significant and v2 not significant, the linearity of the effects is the most likely model. Survival curves were modeled and analyzed by the Kaplan-Meier and Cox tests using R Foundation statistical software (version 2.2.1). SPSS (version 14.0.2) was used for general statistics.

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## APPENDIX

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