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Transcription Factor 7-Like 2 (TCF7L2) Polymorphism and Hyperglycemia in an Adult Italian Population-Based Cohort

OBJECTIVE — To assess whether TCF7L2 polymorphism has a role in the deterioration of glycemic control.

RESEARCH DESIGN AND METHODS — Metabolic variables were evaluated at baseline and after 6-year follow-up in 1,480 Caucasian subjects from a population-based cohort.

RESULTS — At baseline, T-allele carriers showed significantly lower BMI and homeostasis model assessment for β-cell function (HOMA-B) values and higher fasting glycemia and diabetes prevalence. At follow-up, fasting glucose and HOMA-B index were increased and reduced, respectively, in carriers of the T-allele. Incident impaired fasting glucose (IFG) and incident diabetes were 5.7, 10.7, 16.9% and 1.6, 1.7, 3.0% in the CC, CT, and TT genotypes, respectively. In a multiple logistic regression model, the association between incident IFG and the T-allele was significant (odds ratio [OR] 2.08 [95% CI 1.35–3.20] and 3.56 [2.11–5.98] in CT and TT genotypes, respectively).

CONCLUSIONS — The T-allele of TCF7L2 rs7903146 polymorphism was independently associated with increasing fasting glucose values toward hyperglycemia in the follow-up.

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due to the higher prevalence of hyperglycemia in these subjects.

Incident diabetes was almost double in homozygous for the T-allele, but the association was not significant due to the low case number. Incident IFG was two-fold and threefold higher in the heterozygous and homozygous T carriers, respectively (OR 2.08 [95% CI 1.35–3.20] and 3.56 [2.11–5.98] in CT and TT genotypes, respectively). Adjustments for smoking habits, lipid parameters, or HOMA-B values did not significantly affect the results. The AUCs of the ROC curves for the TT genotype were 0.56 for incident IFG and 0.54 for incident diabetes.

**CONCLUSIONS** — The major findings of the present study are: 1) a high prevalence of the defective T-allele in an Italian population-based cohort; 2) a significant association between the T-allele and hyperglycemia and β-cell dysfunction at baseline and follow-up; 3) a two-to threefold higher risk of incident IFG in the T-allele carriers at follow-up; and 4) an increased prevalence of MS in the T-allele carriers.

The minor T-allele is strongly associated with reduced HOMA-B levels, suggesting that the polymorphism could affect the ability of the β-cells to secrete insulin. These data indicate that SNP rs7903146 polymorphism may modulate the degree of insulin secretion to offset the prevailing level of insulin resistance without being a cause of insulin resistance. SNP rs7903146 acts like other TCF7L2 SNPs in playing a central role in the pathophysiology of type 2 diabetes. It has been reported that the pathway of incretins by itself can fail and individually by modulating incretin action or secretion.

An increased prevalence of MS in subjects carrying the TT genotype was about twofold higher at follow-up when compared with the prevalence at baseline. This increment was almost exclusively due to the significantly higher prevalence of hyperglycemia in this subgroup. The AUC values are similar to those reported in literature dealing with one single SNP (11).

The prevalence of MS in subjects carrying the TT genotype was about twofold higher at follow-up when compared with the prevalence at baseline. This increment was almost exclusively due to the significantly higher prevalence of hyperglycemia in this subgroup. The AUC values are similar to those reported in literature dealing with one single SNP (11).

Our study confirms an effect of the widely replicated TCF7L2 rs7903146 polymorphism on hyperglycemia in an adult Italian population-based cohort both in cross-sectional and longitudinal evaluation. The independent association of TCF7L2 polymorphism with increasing fasting glucose values in the follow-up may represent a marker for higher metabolic risk, which is useful for developing
more closely tailored lifestyle preventive approaches as we have recently reported (12).

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References
1. Helgason A, Pålsson S, Thorleifsson G, Grant SF, Emilsson V, Gunnarsdottir S, Adeyemo A, Chen Y, Chen G, Reynolds T, Benedictsson R, Hamney A, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Scha¨fer H, Faruque M, Doumatey A, Zhou J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Sigurdsson G, Hebebrand J, Pedersen O, Thorsteinsdottir I, Benediktsson R, Hinney A, Hansen T, Adeyemo A, Chen Y, Chen G, Reynisdottir G, Garvey WT. Polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with reduced insulin secretion in nondiabetic women. Diabetes 2006;55:1112–1117
2. Bo S, Gentile L, Ciccone G, Baldi C, Benini L, Dusio F, Lucia C, Forastiere G, Nuti C, Cassader M, Pagano G. The metabolic syndrome and high C-reactive protein: prevalence and difference by sex in a southern-European population-based cohu. Diabet Metab Res Rev 2005;21:515–524
3. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003;26(Suppl. 1):1–20
4. The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation 2002;106:3143–3421
5. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
6. Munoz J, Lok KH, Gower BA, Fernandez JR, Hunter GR, Lara-Castro C, De Luca M, Garvey WT. Polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with reduced insulin secretion in nondiabetic women. Diabetes 2006;55:3630–3634
7. Kimber CH, Doney AS, Pearson ER, McCarthy MI, Hattersley AT, Leese GP, Morris AD, Palmer CN. TCF7L2 in the Go-DARTS study: evidence for a gene dose effect on both diabetes susceptibility and control of glucose levels. Diabetologia 2007;50:1186–1191
8. Pulizzi N, Lyssenko V, Jonsson A, Osmond C, Saario M, Kajantie E, Barker DJ, Groop LC, Eriksson JG. Interaction between prenatal growth and high-risk genotypes in the development of type 2 diabetes. Diabetologia 2009;52:825–829
9. Scha¨fer SA, Tschritter O, Machicao F, Thamer C, Stefan N, Gallwitz B, Holst JJ, Dekker JM, ‘t Hart LM, ‘t Hart LM, Nijpels G, van Haeften TW, Haring HU, Fritsche A. Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (TCF7L2) gene polymorphisms. Diabetologia 2007;50:2443–2450
10. Musso G, Gambino R, Pacini G, Pagano G, Durazzo M, Cassader M. Transcription factor 7-like 2 polymorphism modulates glucose and lipid homeostasis, adipokine profile, and hepatocyte apoptosis in NASH. Hepatology 2009;49:426–435
11. Weedon MN. The importance of TCF7L2. Diabet Med 2007;24:1062–1066
12. Bo S, Gambino R, Ciccone G, Rosato R, Milanesio N, Villois P, Pagano G, Cassader M, Gentile L, Durazzo M, Cavallo-Perin P. Effects of TCF7L2 polymorphisms on glucose values after a lifestyle intervention. Am J Clin Nutr 2009;90:1502–1508

Table 1—Continued

| At follow-up | CC | CT | TT |
|-------------|----|----|----|
|             | 580| 699| 201|
|             | 391| 472| 137|
| 60.6 ± 5.7  | 60.8 ± 5.6 | 0.51‡ (−0.41 to 0.83) | 60.3 ± 5.8 | 0.50‡ (−0.59 to 1.22) |
| 27.1 ± 4.9  | 26.9 ± 4.6 | 0.41 (−0.72 to 0.29) | 26.2 ± 3.9 | 0.02‡ (−1.65 to −0.17) |
| 93.6 ± 13.1 | 93.4 ± 13.0 | 0.74‡ (−1.63 to 1.15) | 92.1 ± 10.4 | 0.14‡ (−3.56 to 0.52) |
| 134.8 ± 16.8| 136.4 ± 17.8| 0.003§ (0.18–3.66) | 134.6 ± 16.4| 0.34§ (−1.30 to 3.78)|
| 82.9 ± 9.9  | 83.4 ± 9.4 | 0.14‡ (−0.25 to 1.73) | 82.3 ± 8.5 | 0.88§ (−1.56 to 1.34) |
| 3.5 ± 1.0   | 3.6 ± 1.0 | 0.50‡ (−0.07 to 0.15) | 3.6 ± 1.1 | 0.71§ (−0.13 to 0.19) |
| 1.5 ± 0.4   | 1.4 ± 0.4 | 0.39‡ (−0.06 to 0.02) | 1.5 ± 0.4 | 0.51§ (−0.08 to 0.04) |
| 1.3 (0.9)   | 1.3 (0.8) | 0.43‡ (−0.03 to 0.07) | 1.2 (0.8) | 0.75§ (−0.08 to 0.06) |
| 5.3 ± 0.9   | 5.7 ± 1.2 | <0.001§ (0.30–0.54) | 6.1 ± 1.7 | <0.001§ (0.60–0.96) |
| 45.5 (38.8)§| 44.9 (34.3)§ | 0.54‡ (−0.11 to 0.06) | 43.6 (31.1)§ | 0.005§ (−0.30 to −0.06) |
| 97.2 (85.4)§| 85.5 (74.6)§ | −0.25 to −0.05 P = 0.005§ | 75.4 (70.4)§ | −0.50 to −0.20 P < 0.001§ |
| 1.7 (1.6)§  | 1.8 (1.5)§ | 0.12§ (−0.02 to 0.16) | 1.9 (1.3)§ | 0.20§ (−0.04 to 0.22) |
| 4.5         | 7.0     | 0.03§ (1.06–2.99) | 10.5 | <0.001§ (1.63–5.91) |
| 1.6         | 1.7     | 0.75§ (0.48–2.78) | 3.0 | 0.15§ (0.75–6.37) |
| 11.2        | 18.0    | <0.001§ (1.31–2.51) | 25.4 | <0.001§ (1.90–4.39) |
| 5.7         | 10.7    | <0.001§ (1.35–3.20) | 16.9 | <0.001§ (2.11–5.98) |
| 27.9        | 31.5    | 0.04§ (1.02–1.75) | 33.3 | 0.003§ (1.22–2.64) |