

Variation of the Transcription Factor 7-Like 2 (TCF7L2) Gene Predicts Impaired Fasting Glucose in Healthy Young Adults

The Cardiovascular Risk in Young Finns Study

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Recently, Grant et al. (1) reported an association between type 2 diabetes and variation in the transcription factor 7-like 2 (TCF7L2) gene. Thereafter, the relation has been replicated in several populations (2–11). The mechanisms by which TCF7L2 variants contribute to the development of type 2 diabetes are incompletely understood. To gain insight on potential mechanisms, we examined the effects of TCF7L2 on the incidence of impaired fasting glucose (IFG) in young adults.

RESEARCH DESIGN AND METHODS

The Young Finns Study is a longitudinal study that included 3,596 healthy children and adolescents at baseline in 1980 (12–14). In the present analysis, we used data collected in 1986 and 2001 to assess the effect of the TCF7L2 gene on IFG incidence. Details of methods have been described (15–18). IFG was defined as fasting glucose 5.6–7.0 mmol/l (19,20). Homeostasis model assessment (HOMA) was used to assess β -cell function (HOMA-B) and insulin resistance

(HOMA-IR) (21). We genotyped two TCF7L2 single nucleotide polymorphisms (SNPs): 47833C>T (rs7903146) and 98368G>T (rs12255372) (22). These two SNPs were shown to have robust associations with type 2 diabetes and were recommended to be genotyped in attempts at replication (1). Both genotype frequencies were in Hardy-Weinberg equilibrium. Linkage disequilibrium analysis showed that the alleles of the two polymorphisms are tightly associated ($D' = 0.9$, $r^2 = 0.7$, $P < 0.001$, χ^2 test). Haplotypes were estimated using the PHASE program (23,24). Statistical methods included ANOVA, χ^2 test, and logistic regression. Statistical tests were performed with SAS version 8.1, and statistical significance was inferred at a two-tailed P value < 0.05 .

RESULTS

There were 11 subjects with type 2 diabetes. TCF7L2 rs7903146 genotype was significantly related with the prevalence of type 2 diabetes: CC 0.3%, CT 0.7%, and TT 2.8% ($P = 0.007$). The age- and sex-adjusted odds ratios (ORs) were 3.50

(95% CI 1.02–12.02, $P = 0.047$) between CC versus CT/TT groups and 10.9 (1.96–60.9, $P = 0.006$) between CC versus TT homozygote groups. In further analysis, the subjects with type 2 diabetes were excluded.

In cross-sectional data (year 2001), the TCF7L2 rs7903146 genotype at risk T-allele was significantly related with higher prevalence of IFG ($P = 0.046$) and lower HOMA-B index ($P = 0.042$). Fasting glucose, insulin, HOMA-IR, obesity indexes, serum lipids, C-reactive protein, adiponectin, and leptin did not differ across the genotypes.

There were 1,658 subjects with longitudinal data on fasting glucose that were normoglycemic in 1986 (glucose < 5.6 mmol/l). Of these subjects, 172 developed IFG during the follow-up. The relations of rs7903146 and rs12255372 genotypes on IFG incidence are shown in Table 1. The adjusted ORs indicate that the homozygotes for the at-risk T allele at both SNPs had over double the risk of developing IFG compared with the homozygotes for the more common CC or GG alleles. The population-attributable risk of developing IFG due to the rs7903146 at-risk T-allele was 9.0%. None of the haplotypes provided stronger associations with incidence of IFG than either SNP alone.

CONCLUSIONS — We found that TCF7L2 variation predicts IFG incidence in a population of nondiabetic young adults. The mechanism by which the TCF7L2 gene is related to the risk of type 2 diabetes is unknown, but there is evidence indicating influence on insulin secretion. The gene product of TCF7L2 is human T-cell transcription factor 4, which plays a role in the Wnt signaling pathway (25). T-cell transcription factor 4 regulates the transcription of the proglucagon gene in enteroendocrine cells, the gene encoding insulinotropic hormone glucagon-like peptide 1 in vitro (26). Glucagon-like peptide 1 has been demonstrated to exert effects on glucose homeosta-

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Abbreviations: IFG, impaired fasting glucose; HOMA, homeostasis model assessment; HOMA-B, HOMA for β -cell function; HOMA-IR, HOMA for insulin resistance; SNP, single nucleotide polymorphism.

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

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Table 1—Incidence of IFG and ORs for the development of IFG during 15 years of follow-up in 1,663 adolescents and young adults according to TCF7L2 genotype

	n	Incidence (%)*	OR (95% CI)†	OR (95% CI)‡	OR (95% CI)§	OR (95% CI)	OR (95% CI)¶
rs7903146							
CC	1,102	9.4	1.0	1.0	1.0	1.0	1.0
CT	502	12.0	1.4 (1.0–1.9)	1.4 (1.0–2.0)	1.3 (1.0–1.9)	1.4 (1.0–2.0)	1.4 (1.0–2.1)
TT	54	14.8	2.1 (0.9–4.6)	2.2 (1.0–5.0)	2.1 (1.0–4.7)	2.3 (1.0–5.2)	2.3 (1.0–5.3)
rs12255372							
GG	1,167	9.9	1.0	1.0	1.0	1.0	1.0
GT	445	10.6	1.2 (0.8–1.7)	1.2 (0.8–1.7)	1.1 (0.8–1.7)	1.1 (0.8–1.6)	1.1 (0.8–1.6)
TT	46	19.6	2.4 (1.1–5.2)	2.8 (1.3–6.2)	2.4 (1.1–5.3)	2.9 (1.3–6.4)	2.9 (1.3–6.6)

*Unadjusted; †adjusted for age and sex; ‡adjusted for age, sex, and waist circumference; §adjusted for age, sex, and physical activity index; ||adjusted for age, sex, and insulin; ¶adjusted for age, sex, waist circumference, physical activity, and insulin.

sis. It can lower glucose levels through the stimulation of insulin secretion and biosynthesis and the inhibition of glucagon release and gastric emptying (26). Our finding that insulin secretion is decreased in carriers of the risk-conferring genotype lends indirect support to this hypothesis. Previous reports have shown that the carriers of the susceptibility variants have increased risk of type 2 diabetes due to impaired insulin secretion (2,27,28).

The effect of TCF7L2 variation on hyperglycemia incidence has been previously studied in the French general population in a 9-year prospective study (28), where the population-attributable risk to develop hyperglycemia due to the rs7903146 T-allele was 10.4%. In the present study, in a substantially younger population, the estimated population-attributable risk to develop hyperglycemia due to the rs7903146 T-allele was 9.0%.

TCF7L2 has been implicated as a member of the Wnt signaling pathway, which plays a role in regulating adipogenesis (29,30). Therefore, increased Wnt signaling in carriers of the TCF7L2 risk variants could potentially influence adipose tissue development. In general, previous studies have reported similar or lower levels of obesity in the carriers of the risk variants. In the present study, however, we were unable to demonstrate significant relations between TCF7L2 variation and obesity indexes, serum lipids, or adipokines, including leptin and adiponectin.

Due to the young age of the cohort, the number of subjects with type 2 diabetes was limited. However, even with these low numbers, we observed a statistically significant many-fold increased risk of type 2 diabetes associated with rs7903146. This indicates that TCF7L2 variation may

play an important role, especially in cases of early-onset type 2 diabetes.

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