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ARTICLE

TCF7L2 in the Go-DARTS study: evidence for a gene dose effect on both diabetes susceptibility and control of glucose levels

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Abstract
Aims/hypothesis The gene encoding transcription factor 7-like 2 (*TCF7L2*) has been identified as a type 2 diabetes locus from genome-wide linkage studies and subsequent association analysis. We investigated the role of two common variants in *TCF7L2* in a large case-control study recruited from the Tayside region of Scotland, UK.
Subjects and methods We genotyped 6,516 participants for rs12255372 and rs7903146 and analysed the role in type 2 diabetes susceptibility using binary logistic regression. Age, sex and obesity status were examined as covariates. The distribution of the genotypes within different treatment groups of cases was examined.
Results Both variants were associated with type 2 diabetes ($p<10^{-13}$). The variants were present at very similar frequencies and were in strong linkage disequilibrium ($R^2=0.88$, $D'=0.89$). A gene dosage effect of the rare allele of both variants was observed, the heterozygote CT group of rs7903146 having an odds ratio of 1.36 (95% CI 1.2–1.5, $p = 1.54 \times 10^{-7}$) for type 2 diabetes and the TT homozygote having a greater risk (OR=2.03, 95% CI 1.7–2.5, $p = 1.40 \times 10^{-12}$). An interaction with sex was observed, the males displaying a higher degree of genotype-associated risk compared with the females ($p=0.023$). The T allele was associated with increased HbA_{1c} levels in both cases and controls, and with decreased BMI and waist circumference in case but not controls. The T allele was overrepresented in individuals requiring insulin treatment and underrepresented in the patients being managed by diet alone ($p=0.006$).
Conclusions We have confirmed *TCF7L2* to be a diabetes locus in a large case-control study in Tayside, UK. Our data suggest that variants of *TCF7L2* may be associated with increased disease severity and therapeutic failure.

Keywords Body mass index · Disease severity · Genetics · Glucose control · HbA_{1c} · Insulin · Susceptibility · Transcription factor · Type 2 diabetes

Abbreviations

Go-DARTS	Genetics of Diabetes Audit and Research Tayside Study
OR	odds ratio
PAR	population attributable risk
SNP	single-nucleotide polymorphism

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Introduction

The polygenic basis of type 2 diabetes has been intensely investigated by large consortia worldwide, and consensus on a range of valid susceptibility genes has emerged. Such genes, for example *PPARG*, *KCNJ11* and *CPN10*, appear to contain common variation that confers only 10–20% additional risk of type 2 diabetes, and only studies with large numbers of case and controls have had sufficient statistical power to examine their role robustly [1]. Recently, Grant et al. investigated the role of variation in a region of chromosome 10 that had been implicated as a weak susceptibility locus by linkage analysis using whole-genome microsatellite markers in several studies [2]. Intensive single-nucleotide polymorphism (SNP) analysis and resequencing revealed that *TCF7L2* gene variants, including microsatellite DG10S478, SNP rs12255372 and rs7903146, are in tight linkage disequilibrium and were associated with type 2 diabetes [3]. This relationship was replicated in three studies providing robust statistical evidence for association with type 2 diabetes ($p<10^{-15}$). This finding has now been replicated in several studies of both case-control and prospective study design [4–10]. Importantly, the risk alleles of *TCF7L2* have also been shown to confer risk of conversion from impaired glucose tolerance to diabetes in the Diabetes Prevention Program [8]. In addition, the results of the Diabetes Prevention Program suggest that variation in this gene is associated with impaired beta cell function rather than insulin resistance.

In order to provide large-scale, population-based evidence for the role of this variant in type 2 diabetes, and to further characterise the role of these variants in the aetiology of diabetes, we have genotyped 6,516 individuals from Tayside, UK, who have been enrolled in the Wellcome Trust UK case-control study of type 2 diabetes. We have also examined the phenotypic and treatment profiles of the individuals with type 2 diabetes who harbour the risk variants.

Subjects and methods

Study population We studied type 2 diabetic patients and non-diabetic controls from the Wellcome Trust UK type 2 diabetes case-control collection (Go-DARTS2), which is a substudy of Diabetes Audit and Research Tayside (DARTS) [11–17]. All type 2 diabetes patients were physician-diagnosed with type 2 diabetes and were recruited at primary or secondary care diabetes clinics, or invited to participate from primary care registers, and had not been characterised for GAD antibodies or MODY gene mutations. The controls were invited to participate through their primary care physicians or their workplace occupational health departments. None of the controls had a previous diagnosis of diabetes and their glucose tolerance status was unknown. All individuals in this ongoing study were recruited in Tayside between 1 October 2004 and 1 July 2006. All study participants were white. This study was approved by the Tayside Medical Ethics Committee and informed consent was obtained from all participants.

Genotyping We genotyped rs12255372 and rs7903146 by Taqman allelic discrimination assays (Applied Biosystems, Foster City, CA) using the following labelled probes and primers: rs12255372 forward primer, TGCAAATCCAGCA GGTTAGCT; rs12255372 reverse primer, GCAGAGGCC TGAGTAATTATCAGAA; probe 1, FAM-CCAGGAATAT CCAGGCAAGAATGACCA-BHQ-1; probe 2, Yakima-Yellow-CCCAGGAATATCCAGGCAAGAATTACCA-BHQ-1; rs7903146 forward primer, CCTCAAAACCTAG CACAGCTGTTAT; rs7903146 reverse primer, TGAAAA CTAAGGGTGCCTCATACG; probe 1, FAM-TAAGCAC TTTTTAGATATTATAT-MGB/NFQ; probe 2, VIC-CTAA GCACTTTTTAGATACTATAT-MGB/NFQ. The call rate for both assays was ~98% and the duplicate concordance rate was >99%.

Statistical analysis Allele frequencies were calculated by gene counting. Hardy–Weinberg equilibrium was seen in both SNP distributions ($p>0.1$). Binary logistic regression was used to compare the SNP frequencies in case and controls, and age, sex and obesity status were used as covariates. General linear modelling was used to compare quantitative parameters between disease status groups and between genotypic groups. All statistics were performed using SPSS v11 (SPSS Inc., Chicago, IL) for the Macintosh.

Table 1 Characteristics of study group

Characteristic	Controls	Cases	*p* value
Number of participants	3,291	3,225	
Sex (male/female) (*n*)	1,720/1,571	1,821/1,404	<0.001
Current smoker (*n*)	557	562	0.592
Age (years)	60.7±13.0	65.3±11.2	<0.001
BMI (kg/m^2)	26.8±4.6	31.3±6.2	<0.001
HbA_{1c} (%)	5.6±0.4	7.7±1.5	<0.001
Cholesterol (mmol/l)	5.3±1.1	4.5±0.9	<0.001
Triacylglycerol (mmol/l)	1.6±1.1	2.2±1.4	<0.001
HDL-cholesterol (mmol/l)	1.7±0.5	1.4±0.4	<0.001
LDL-cholesterol (mmol/l)	3.0±1.0	2.2±0.8	<0.001

All values were determined from the clinical visit at study entry. Biochemical measures were obtained through the National Health Service clinical biochemistry system from blood taken at study entry.

Table 2 *TCF7L2* genotypes in the type 2 diabetes cases and controls

rs2255372 genotype	Controls	Type 2 diabetes cases	rs7903146 genotype	Controls	Type 2 diabetes cases
GG	1,735 (52.7)	1,434 (44.5)	CC	1,714 (52.1)	1,405 (43.7)
GT	1,323 (40.2)	1,432 (44.4)	CT	1,329 (40.4)	1,459 (45.2)
TT	233 (7.1)	359 (11.1)	TT	248 (7.5)	361 (11.2)
Total	3,291	3,225 $p = 2.05 \times 10^{-14}$		3,291	3,225 $p = 5.10 \times 10^{-14}$
Minor allele frequency	0.272	0.333		0.277	0.338

Results

This study involved a total of 6,516 individuals; 3,225 of these were cases who had been diagnosed with type 2 diabetes, and the remaining 3,291 individuals were population controls with no history of type 2 diabetes at the time of recruitment. The characteristics of the study population are shown in Table 1.

All individuals were typed for both rs12255372 and rs7903146 of *TCF7L2* (Table 2). The allele frequencies of both SNPs in the controls were very similar to the reported frequencies in the Icelandic and Danish populations in the index studies, and the corresponding increased allele frequency was observed in the cases (Pearson χ^2 for rs12255372=58.48; $p = 2.05 \times 10^{-14}$; rs7903146=56.69; $p = 5.10 \times 10^{-14}$). The increase for both SNPs was almost identical, tight linkage disequilibrium (D'=0.89, R^2=0.88) being observed. The high linkage disequilibrium in the Scottish population means that neither SNP provides significantly greater information than the other in this case-control comparison, although this may not be the case in other populations.

Logistic regression analysis was used to correct the association of rs7903146 and rs2255372 for age, sex and obesity status (Table 3). The susceptibility conferred by the risk alleles was clearly codominant, the rs7903146 heterozygote CT group having an odds ratio (OR) of 1.36 (95% CI 1.2–1.5, $p = 1.54 \times 10^{-7}$) relative to the CC individuals, and the TT homozygote having a greater risk (OR= 2.03, 95% CI 1.6–2.4; $p = 1.40 \times 10^{-12}$) (Fig. 1). This represents an increased risk of type 2 diabetes in the TT individuals compared with the CT individuals (OR=1.48, 95% CI 1.2–1.8; $p = 9.89 \times 10^{-5}$). The population attributable risk (PAR) observed for rs7903146 in this study was 18.9%, in agreement with previous reports [6, 7].

Greater genotype-associated risk was observed in men compared with women, the odds ratios in the separate sexes being almost identical to those observed by Zhang et al. [6] (men, TT vs CC, OR=2.3, 95% CI 1.8–3.1; $p = 1.26 \times 10^{-10}$; women, TT vs CC, OR=1.6, 95% CI 1.2–2.2; p=0.001). The additional power of our study, however, allowed detection of a significant interaction between genotype and sex (p=0.023).

Linear regression was used to examine associations of rs7903146 with biochemical measures and adiposity in the controls and cases separately (Table 4). The results obtained with rs12255372 were very similar; the corresponding p values (p^1) are shown in Table 4. No association was observed for either SNP with creatinine or any measure of dyslipidaemia in the cases or controls. In the cases, individuals with the T allele of rs7903146 were slimmer by BMI and waist circumference measures. HbA_{1c} was higher in the T-bearing individuals in both case and controls. BMI is a major determinant of HbA_{1c} in individuals with type 2 diabetes and we therefore included BMI as a covariate. There was a clear allelic association with HbA_{1c} in the cases and controls, indicating that the association between rs7903146 and HbA_{1c} is independent of BMI. This indicates that the T-allele carriers had increased HbA_{1c} despite being thinner. Individuals carrying

Table 3 *TCF7L2* genotype is associated with type 2 diabetes after adjustment for age, sex and obesity in a binary logistic regression model

rs12255372	OR (95% CI)	p value	rs7903146	OR (95% CI)	p value
GT	1.35 (1.20–1.51)	$2.80e^{-7}$	CT	1.36 (1.21–1.52)	$1.54e^{-7}$
GG	2.11 (1.73–2.57)	$2.17e^{-13}$	TT	2.03 (1.67–2.47)	$1.40e^{-12}$
Age (55–65 years)	2.09 (1.80–2.44)	$1.45e^{-21}$	Age (55–65 years)	2.09 (1.88–2.53)	$2.93e^{-21}$
Age (>65 years)	3.31 (2.88–3.80)	$3.10e^{-63}$	Age (over 65 years)	3.29 (2.86–3.79)	$6.28e^{-63}$
Overweight	2.29 (1.98–2.64)	$1.27e^{-29}$	Overweight	2.28 (1.97–2.63)	$2.74e^{-29}$
Obese	9.42 (8.08–10.97)	$2.45e^{-182}$	Obese	9.39 (8.07–10.94)	$3.31e^{-182}$
Male	1.21 (1.09–1.36)	$4.27e^{-4}$	Male	1.22 (1.09–1.36)	$4.27e^{-4}$

Obese, BMI ≥30 kg/m^2 and above; overweight, 25–30 kg/m^2
Referent categories: rs7903146 C/C; age under 55 years; individuals with BMI <25 kg/m^2

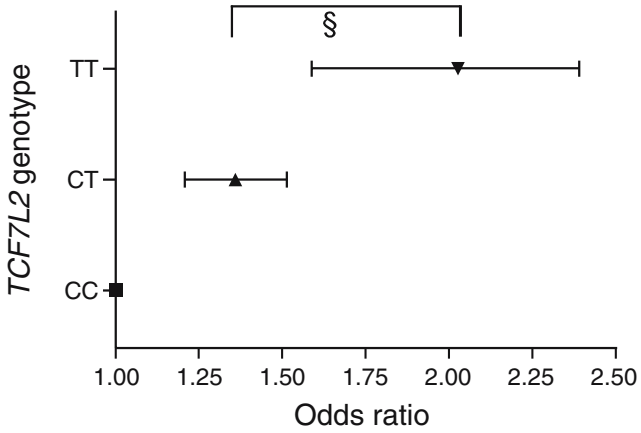

Fig. 1 *TCF7L2* genotype demonstrates a clear codominant association with type 2 diabetes. Shown are the point estimates of the odds ratios for rs7903146 CT and TT vs the CC referent genotype. *Error bars* are 95% confidence intervals. $^{\S}p = 9.89 \times 10^{-5}$

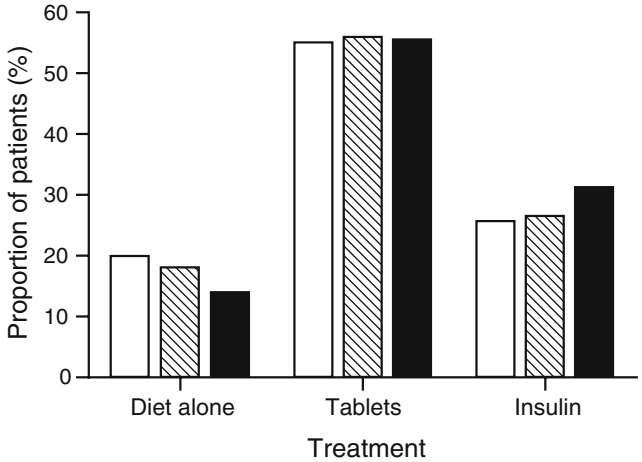

Fig. 2 Association of treatments for the diabetic patients and their genotypes. Shown is the proportion of each genotype group of rs7903146 in each treatment class: CC (*open bars*); CT (*hatched bars*); TT (*black bars*). Tablets group constitutes individuals on oral hypoglycaemic agents without insulin. Insulin group contains insulin monotherapy and combined insulin/oral hypoglycaemic agent treated individuals. Similar results were obtained with rs12255372. χ^2 test for trend=7.37, p=0.007

the T allele of rs7903146 were also diagnosed slightly younger than the CC individuals (1.4 years difference between CC and TT; p=0.031). As an additional measure of disease severity and therapeutic control, we examined the distribution of rs7903146 alleles within the three major treatment modalities for type 2 diabetes, i.e. diet alone, oral hypoglycaemics and insulin treatment (Fig. 2). This demonstrates that the individuals bearing the T allele of rs7903146 were less likely to have been managed on diet alone, and were more likely to have received insulin treatment (χ^2 test for trend, p=0.007), and this remained significant after adjustment for age, sex, BMI and smoking status (p=0.006). The odds ratio for rs7903146 TT homozygotes for insulin treatment vs non-insulin treatment was 1.32 (95% CI 1.02–1.7; p=0.038) relative to the common CC homozygote. In addition, the association of the TT homozygote with active medication vs diet alone was significant (OR=1.55, 95% CI 1.12–2.16; p=0.01).

Discussion

This study provides evidence of the robust nature of the association between common variation in the *TCF7L2* gene and type 2 diabetes. This association has been more readily replicated than the other previous candidate gene variants as the allele frequency of the variant is more than 30% and

Table 4 Characteristics of control and case populations by *TCF7L2* genotype

	Controls					Cases				
Rs7903146	CC	CT	TT	p value[a]	p value[c]	CC	CT	TT	p value[a]	p value[c]
BMI (kg/m^2)	26.9 (4.5)	26.8 (4.6)	26.7 (4.7)	0.802	0.507	31.6 (6.3)	31.3 (6.0)	30.4 (6.3)	0.002[b]	0.008[b]
Waist (cm)	92.9 (13.1)	92.5 (13.0)	91.7 (13.4)	0.549	0.334	104.8 (14.3)	104.3 (13.6)	102.1 (14.5)	0.001[b]	0.002[b]
HbA_{1c} (%)	5.56 (0.4)	5.60 (0.4)	5.63 (0.5)	0.003[b, d]	0.13[b]	7.64 (1.5)	7.72 (1.5)	7.88 (1.4)	0.012[b, d]	0.002[b]
Cholesterol (mmol/l)	5.32 (1.1)	5.35 (1.1)	5.25 (1.0)	0.375	0.480	4.48 (0.9)	4.45 (0.9)	4.46 (0.9)	0.757	0.354
HDL-cholesterol (mmol/l)	1.65 (0.5)	1.64 (0.5)	1.66 (0.5)	0.563	0.730	1.37 (0.4)	1.37 (0.4)	1.39 (0.4)	0.306	0.346
LDL-cholesterol (mmol/l)	2.98 (1.0)	2.98 (1.0)	2.92 (0.9)	0.632	0.852	2.17 (0.8)	2.12 (0.8)	2.14 (0.8)	0.393	0.024[b, e]
Triacylglycerol (mmol/l)	1.56 (1.0)	1.64 (1.3)	1.56 (1.0)	0.326	0.406	2.21 (1.5)	2.25 (1.4)	2.21 (1.4)	0.756	0.225
Serum creatinine (μmol/l)	94.5 (19.4)	95.2 (18.4)	93.3 (19.5)	0.419	0.277	98.8 (24.1)	99.8 (27.0)	97.5 (23.4)	0.252	0.834
Age at diagnosis (years)						57.5 (11.4)	57.1 (11.5)	56.1 (12.1)	0.031[b, e]	0.114

BMI was included as a covariate in the analysis of HbA_{1c}.
[a] General linear model analysis with age at recruitment, sex and smoking status as covariates
[b] Nominally significant p values at $p<0.05$
[c] Corresponding p value for rs12255372
[d] p=0.001 overall adjusted for case-control status
[e] Not significant after Bonferroni correction for multiple testing

a clear gene dose effect has been observed, the homozygote rare variant conferring an odds ratio of about 2.0. This has meant, for the first time, that studies containing hundreds, rather than thousands, of cases have had sufficient statistical power to detect this effect reliably. The possibility of this result arising from population stratification was minimised by the use of a relatively homogeneous case-control population of white individuals from a single region of Scotland, and is highly unlikely given the global consistency of the association [18–21] and direct testing of stratification in a whole-genome association study [22]. The use of more than 6,000 individuals in this study has provided the power to separate the three genotypes statistically, the rare homozygote group bearing significantly greater risk than the CT heterozygotes, and has provided power to show that males have a greater genotype-associated risk than females. These data are in agreement with the previous case-control studies and confirm that the lack of gene dosage effects seen in prospective studies is likely to have been due to lack of power. Using binary logistic modelling, we have shown that the association is robust to adjustment for obesity status, sex and age group, the odds ratios for the T homozygotes being similar to those for important conventional risk factors, such as being overweight or middle-aged.

In addition, we also confirm recent studies that suggested that the variants did not have a primary effect on adiposity but were associated with reduced BMI in cases with type 2 diabetes only [7]. This would suggest that the variants predispose individuals to type 2 diabetes at a lower level of adiposity. The mechanism for this may be impaired pancreatic beta cell function, but detailed molecular mechanisms for this are not yet clear. Also, in agreement with earlier studies, we found that the T allele of rs7903146 was associated with a slightly earlier age of diagnosis, and although the association does not stand up to correction for multiple testing within this study, it does provide replication support for earlier observations [9, 23] and is consistent with the observation that the risk alleles of *TCF7L2* are enriched further in groups with early-onset type 2 diabetes [7]. We have extended these observations by demonstrating a relationship with disease severity and therapeutic status. The rs7903146 T allele is associated with higher HbA_{1c} in both controls and individuals with type 2 diabetes, and although the individual observations in case and controls do not withstand correction for multiple testing, the overall association between rs7903146 is highly significant when adjusted for case-control status ($p=0.001$), and this measure is still significant after Bonferroni correction. The association with higher HbA_{1c} in the T-allele carriers with type 2 diabetes is evident despite the more intensive treatment observed in T-allele carriers, and reinforces the notion that the T allele may be associated with greater disease severity.

Prospective studies have demonstrated the role of *TCF7L2* variants in the rate of progression from impaired glucose tolerance to diabetes. Longitudinal studies are also now required to confirm our findings that, even in the diabetic state, this gene may be associated with disease that is managed poorly with standard therapies. Further studies are required to determine the suitability of these individuals for particular oral hypoglycaemic agents. Although the discovery of *TCF7L2* as a major predisposition gene for type 2 diabetes does not immediately inform patient care [24], it is hoped that careful dissection of the performance of current therapies in patients with different *TCF7L2* genotypes may lead to specific treatment strategies based on *TCF7L2* genotype.

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Duality of interest None of the authors has any conflict of interest.

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