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RESEARCH LETTER

Analysis of the type 2 diabetes gene, *TCF7L2*, in 13,795 type 1 diabetes cases and control subjects

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To the Editor: The two most common forms of diabetes that have been classified are type 1 diabetes and type 2 diabetes. Type 1 diabetes is characterised by infiltration of the pancreas by autoreactive T cells and autoimmune destruction of pancreatic beta cells, leading to a complete loss of insulin production, whereas type 2 diabetes is associated with the gradual increase of insulin insensitivity in tissues leading to hyperglycaemia and beta cell failure. However, it has been suggested that type 1 diabetes and type 2 diabetes may share a common genetic aetiology [1]. For example, the accelerator hypothesis suggests that type 1 diabetes and type 2 diabetes are the same disease of hyperglycaemia-induced beta cell damage but that type 1 diabetes has the added effect of autoimmunity [1].

One way of testing the hypothesis that there is a common causal pathway between type 1 and type 2 diabetes is to analyse a type 2 diabetes gene with a large effect in a large type 1 diabetes sample. Until very recently [2] this has not been possible, as no such locus has emerged from type 2 diabetes genetics studies. Recently, however, the transcription-factor-7-like 2 (*TCF7L2*) gene region on chromosome 10q25.2 has been found to contribute substantially to the risk of type 2 diabetes with convincing statistical support (relative risk [RR]=0.67; $p=2.1\times10^{-9}$ for the 0 allele of the microsatellite marker DG10S478) [2]. This study was carried out in three different populations: Icelandic, Danish and white American. Two single nucleotide polymorphisms (SNPs) were also genotyped in this study: rs12255372 (G>T, minor allele frequency [MAF] 0.36 in control subjects) and rs7903146 (C>T, MAF=0.28 in control subjects). rs12255372 was found to be in high linkage disequilibrium (LD) with DG10S478 ($r^2=0.95$ for the major G allele of the SNP with the 0 allele of the microsatellite marker). rs7903146 was in lower LD with the DG10S478 ($r^2=0.75$): for the minor allele (T) of this SNP the authors obtained odds ratios (ORs) of 1.41–1.71 in the three populations and p values from 0.0018 to 1.6×10^{-9} [2]. These results were independently replicated in 2,158 white UK type 2 diabetic subjects, 2,574 geographically matched white control subjects and 388 parent–offspring trios [3]. In this population it was found that the T allele of rs7903146 was the most associated with type 2 diabetes susceptibility (OR=1.36, 95% CI=1.24–1.48 and $p=3.6\times10^{-10}$, MAF=0.31 in control subjects), but that the T allele of rs12255372 was also associated (OR=1.29, 95% CI=1.18–1.41; $p=2.2\times10^{-6}$, MAF=0.30 in control subjects) [3]. These results have also been confirmed by other studies in Finnish and US populations [4, 5]. A study on type 2 diabetes progression suggests that *TCF7L2* may be associated with insulin secretion [6].

Therefore, as *TCF7L2* is a major gene in type 2 diabetes we can now test if it affects type 1 diabetes susceptibility. We analysed the two SNPs, rs12255372 and rs7903146, in 6,199 white UK type 1 diabetic subjects (5,872 from the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory's Genetic Resource

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Investigating Diabetes study (http://www-gene.cimr.cam.ac.uk/ucdr//grid.shtml) and 327 from the Oxford Regional Prospective Study [7]) and 7,596 geographically matched white control subjects (from the 1958 British Birth Cohort [8]) using TaqMan 5′ nuclease assay (Applied Biosystems, Warrington, Cheshire, UK). All type 1 diabetic subjects were diagnosed under the age of 17 years. Given the reported MAF of 0.30 (in a sample set from the 1958 British Birth Cohort [3]), our study has 80% power to detect an effect with an OR as low as 1.12 at $\alpha=10^{-3}$. This α level can be considered appropriate assuming that the prior information about common genetic and mechanistic pathways in type 2 diabetes and type 1 diabetes is true. Alternatively, assuming no prior information, on a genome-wide level, $\alpha=10^{-8}$, our study has 80% power to detect an effect with an OR as low as 1.19. In this sample set we obtained a MAF=0.29 for the T alleles of both rs12255372 and rs7903146. The genotype distributions for both of these SNPs were consistent with Hardy–Weinberg equilibrium in the control subjects ($p>0.05$). We found no evidence for association between *TCF7L2* and type 1 diabetes: for rs12255372, OR=0.96 and $p=0.17$, and for rs7903146, OR=0.99 and $p=0.79$, for the minor T alleles of both SNPs (Table 1).

Table 1 Association of *TCF7L2* SNPs rs12255372 and rs7903146 with type 1 diabetes in 6,199 type 1 diabetic subjects and 7,596 control subjects

	Diabetic subjects (%)	Control subjects (%)	OR	95% CI
rs12255372				
Alleles (2×number of subjects), $p=0.17$				
G	8,561 (0.72)	10,461 (0.71)	1.00	(reference)
T	3,377 (0.28)	4,279 (0.29)	0.96	0.91–1.02
Genotypes (number achieved), $p=0.33$				
G/G	3,033 (0.51)	3,687 (0.50)	1.00	(reference)
T/G	2,495 (0.42)	3,087 (0.42)	0.97	0.91–1.05
T/T	441 (0.07)	596 (0.08)	0.90	0.79–1.03
rs7903146				
Alleles (2×number of subjects), $p=0.79$				
C	8,404 (0.71)	10,306 (0.71)	1.00	(reference)
T	3,400 (0.29)	4,224 (0.29)	0.99	0.94–1.05
Genotypes (number achieved), $p=0.84$				
C/C	2,991 (0.51)	3,669 (0.50)	1.00	(reference)
T/C	2,422 (0.41)	2,968 (0.41)	1.01	0.93–1.08
T/T	489 (0.08)	628 (0.09)	0.97	0.85–1.10

These data do not support a model of a shared major causal pathway in type 2 diabetes and type 1 diabetes. However, as more and more causal variants for common multifactorial diseases are established they will provide a panel of markers that can be used to elucidate the functions and physiology of other diseases. Thus, in this study, we have found that a variant that increases the risk for type 2 diabetes [2–5] and may affect insulin secretion [6] does not alter susceptibility to the immune-mediated destruction of beta cells in type 1 diabetes to any measurable extent in this British population.

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Duality of interest The authors have no duality of interest in regard to this study.

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