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Analysis of the Type 2 Diabetes Gene, *TCF7L2*, in 13,795 Type 1 Diabetes Cases and Controls

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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 affect 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 since no such locus has emerged from type 2 diabetes genetics studies. However, recently 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; $P = 2.1 \times 10^{-9}$ 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 is in lower LD with the DG10S478 ($r^2 = 0.75$), for the minor allele (T) of this SNP they obtained odds ratios (ORs) of 1.41-1.71 in the three populations and *P* values from 0.0018 - 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 $P = 3.6 \times 10^{-10}$, MAF = 0.31 in control

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

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subjects) but that the T allele of rs12255372 was also associated (OR = 1.29, 95% CI = 1.18-1.41; $P = 2.2 \times 10^{-6}$, MAF = 0.30 in control subjects) [3]. These results have also been confirmed by other studies in Finnish and American 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 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, 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 controls ($P \geq 0.05$). 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).

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, which 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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Table 1

Association of *TCF7L2* SNPs rs12255372 and rs7903146 with type 1 diabetes in a total of 5,819 type 1 diabetic subjects and 7,092 control subjects. We assumed a multiplicative model of effect. OR – odds ratio, 95% CI – 95% confidence interval.

rs12255372					
	Cases (%)	**Controls (%)**	**OR**	**95% CI**	***P***
Alleles (2 × number of subjects).					
G	7,964 (0.72)	9,764 (0.71)	1.00	(reference)	-
T	3,112 (0.28)	3,984 (0.29)	0.95	0.90 - 1.01	0.10
Genotypes (number of genotypes achieved)					
G/G	2,827 (0.51)	3,446 (0.50)	1.00	(reference)	-
T/G	2,310 (0.42)	2,872 (0.42)	0.98	0.91 - 1.06	0.18
T/T	401 (0.07)	556 (0.08)	0.88	0.77 – 1.01	0.18
rs7903146					
	Cases (%)	Controls (%)	OR	95% CI	*P*
Alleles (2 × number of subjects).					
C	7,869 (0.72)	9,591 (0.71)	1.00	(reference)	-
T	3,131 (0.28)	3,927 (0.29)	0.97	0.92 - 1.03	0.35
Genotypes (number of genotypes achieved)					
C/C	2,805 (0.51)	3,412 (0.50)	1.00	(reference)	-
T/C	2,259 (0.41)	2,767 (0.41)	0.99	0.92 - 1.07	0.42
T/T	436 (0.08)	580 (0.09)	0.91	0.80 - 1.04	0.42