

The new type 2 diabetes gene *TCF7L2*

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Purpose of review

Common variants in the gene that encodes the transcription factor 7-like 2 (*TCF7L2*) have been strongly associated with type 2 diabetes. This highly reproducible association may uncover novel mechanisms of glycemic pathophysiology.

Recent findings

The initial publication of an association of common variants in *TCF7L2* with type 2 diabetes in people of European descent has been followed by an avalanche of replication reports. These papers not only confirm the original finding, but also extend it to other populations, fine map the source of the association signal, describe its effect on metabolic parameters in humans, open the door to a more precise molecular characterization, and provide an insight into its possible impact on diabetes therapy.

Summary

The discovery of *TCF7L2* as a diabetes gene illustrates that novel true diabetes genes can be found, their association with type 2 diabetes replicated and their effect incorporated into risk prediction models. It is hoped that the detection of other such genes in genome-wide association scans will help elucidate the genetic architecture of this disease.

Keywords

genetic association, single nucleotide polymorphisms, *TCF7L2*, type 2 diabetes

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Abbreviation

SNP single nucleotide polymorphism

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Introduction

Over the past few years, candidate gene studies have uncovered the association of several common single nucleotide polymorphisms (SNPs) with type 2 diabetes [1]. The P12A polymorphism in *PPARG*, the gene that encodes the peroxisome proliferator-activated receptor- γ , was the first genetic variant to be definitively implicated in the common form of type 2 diabetes, an intriguing association given that *PPAR γ* is a target for thiazolidinedione medications [2]. Subsequently, the E23K polymorphism in *KCNJ11*, the gene that encodes the islet ATP-dependent potassium channel Kir6.2 (the target for sulfonylurea medications), was also reproducibly associated with type 2 diabetes [3]. SNPs in the gene that encodes calpain 10 (*CAPN10*) also appear to be associated with type 2 diabetes [4–6], and promoter SNPs in the hepatocyte nuclear factor 4 α gene (*HNF4A*) may confer a modest genetic risk as well [7–9]. Nevertheless, given the substantial resources invested in the search for causal genetic variants in type 2 diabetes, the low yield of traditional linkage approaches for this disease, and the modest effects conferred by these highly reproducible genetic associations (which together explain only a small fraction of the overall genetic risk), the field of type 2 diabetes genetics truly seemed to need an infusion of optimism at the beginning of 2006.

While several genome-wide association scans were commenced – with the natural trepidation brought about by uncertainty over the eventual outcome – investigators at deCODE Genetics provided a reason for new-found excitement: their discovery of a robust genetic association of common variants in the gene that encodes the transcription factor 7-like 2 (*TCF7L2*) with type 2 diabetes, its subsequent confirmation by virtually every other diabetes genetics group, and the exploration of possible mechanisms of action and their impact on metabolic phenotypes in humans, have indeed illuminated the field of diabetes genetics over the past few months, and further illustrate several general principles about the genetics of this complex disease.

The discovery of *TCF7L2* as a type 2 diabetes gene

In 2003, deCODE Genetics scientists published a genome-wide linkage scan for type 2 diabetes [10]. After genotyping 906 microsatellite markers in 763 patients with type 2 diabetes from 227 families, the authors reported suggestive evidence for linkage to a region in chromosome 5q34–q35.2, with a nonparametric

multipoint linkage logarithm of the odds (LOD) score which increased from 2.90 to 3.64 after stratification for BMI. Additional sites with suggestive linkage in nonobese diabetic subjects included loci in chromosomes 6q, 10q and 12q (LOD scores 1.80, 1.69 and 1.44, respectively); when the interaction between the linkage peaks at 5q34 and 10q was studied, the authors observed that the LOD score at chromosome 10q increased to 4.06 if the analysis was restricted to families with a negative score at 5q34. Fine mapping with eight additional markers did not increase this LOD score significantly, and simulation testing produced only marginal statistical significance ($P=0.074$).

Presumably, many of these findings in multiple genomic locations were pursued at deCODE with detailed fine mapping and laborious association testing. What one imagines to be a tremendous amount of painstaking and costly work finally yielded its fruit, not as a susceptibility gene in chromosome 5q34 but as a novel result in chromosome 10q. In early 2006, Grant *et al.* [11^{••}] reported that a common microsatellite in the *TCF7L2* gene region (DG10S478) was associated with type 2 diabetes in an Icelandic case–control sample ($n=2116$), and replicated this result in two additional case–control white cohorts ($n=1658$). The overall estimated allelic relative risk was 1.56, with an impressive P value of 7.8×10^{-15} (after Bonferroni correction for the number of alleles tested). The noncoding SNPs rs12255372 and rs7903146 were in strong linkage disequilibrium with DG10S478 ($r^2=0.95$ and 0.78 , respectively), and showed comparably robust associations with type 2 diabetes. Interestingly, this strong association did not seem to explain the original linkage signal. Nevertheless, the statistical evidence was compelling, and the effect size was greater than that of any other bona-fide diabetes gene described to date.

Confirmation of the original finding

In complex human genetics, replication of an initial report of association is essential [12]. This has not always been easy, as a result of the proliferation of false positive results and the modest effects of true positive associations, which require very large sample sizes for detection [13]. Fortunately, the relatively high frequency of the associated *TCF7L2* variants (around 30% in white and black populations), their generous effect size and the general maturity of the field enabled diabetes geneticists to confirm the original finding within a short space of time. Indeed, a quick succession of positive replication studies followed: the multiethnic cohort of the Diabetes Prevention Program [14^{••}], large case–control and family-based white samples from the United Kingdom [15[•]], nested case–control cohorts from two prospective United States studies [16], a Finnish case–control sample from the FUSION study [17[•]], the Amish Family Diabetes

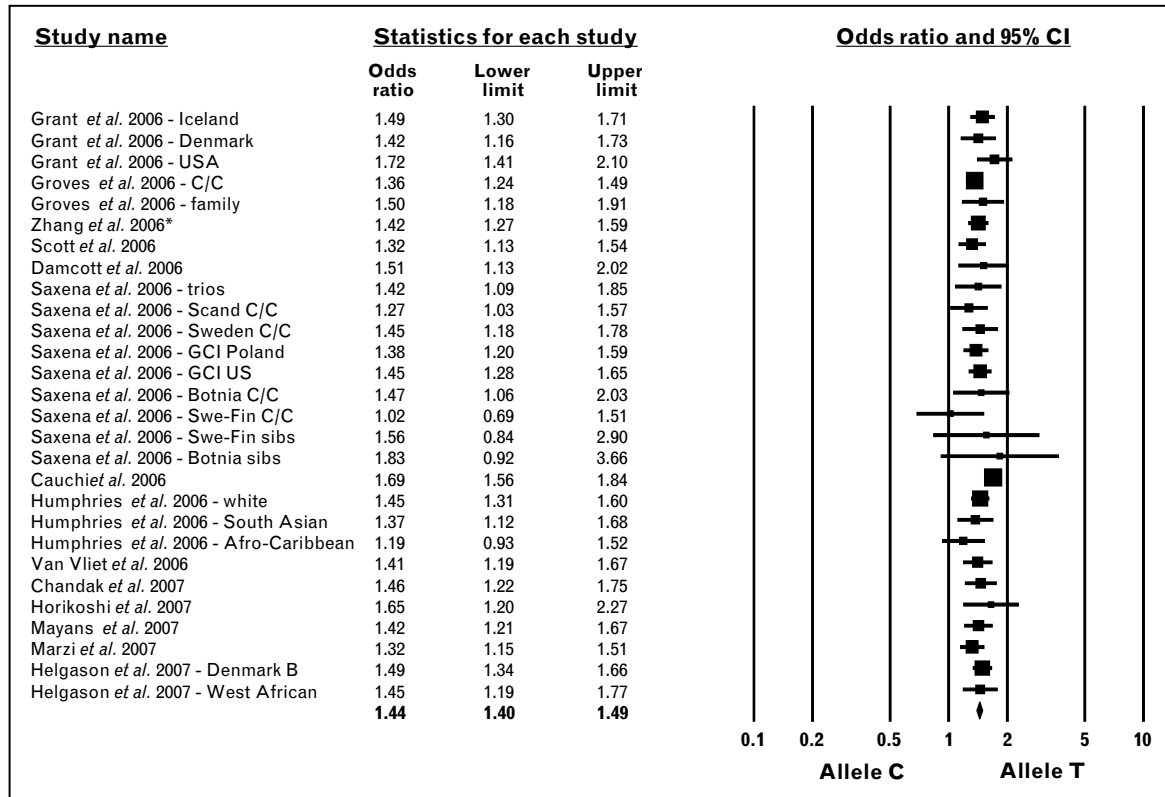
Study [18[•]], large case–control and family-based white samples from Scandinavia, the United States and Poland [19[•]], and a large French case–control sample [20[•]] all simultaneously showed convincing association of the tested variants with type 2 diabetes, with very low P values and essentially identical effect sizes. The preponderance of the evidence indicated an additive effect, with a single copy of the risk allele conferring ~40% risk, and two copies (carried by ~10% of the white population) conferring ~80% risk of type 2 diabetes (Fig. 1).

Although most of these studies were carried out in samples of European descent, the association has been extended to other populations as well: South Asian Indians [21[•],22], Japanese [23] and United States Hispanics [14^{••},24] all exhibit a higher burden of type 2 diabetes when carrying the risk alleles. Similar results have been subsequently published in independent Dutch [25], German [26] and Swedish [27] samples. While initial explorations in samples of African ancestry were underpowered (and thus yielded consistent but not significant results) [14^{••},21[•]], a recent follow-up report from deCODE indicates that a similar risk applies to Africans as well [28^{••}].

All of these reports firmly establish *TCF7L2* as the strongest genetic contributor to risk of type 2 diabetes studied thus far, and illustrate how real effects can be detected in adequately sized samples when they are sufficiently frequent and/or large: a meta-analysis of the accumulated evidence (nearly 50 000 subjects) reveals the remarkable consistency of this finding, and yields an overall P value $<10^{-80}$ (Fig. 1). Once the genetic association was established beyond reasonable doubt, the fascinating (but not simple) twin tasks of determining which specific variant gives rise to the association signal, and how it might increase risk of type 2 diabetes, could be undertaken.

Fine mapping of the association signal

Although the original deCODE publication focused on the DG10S478 microsatellite, subsequent studies refined the association signal to the two noncoding SNPs rs12255372 and rs7903146 reported to be in strongest linkage disequilibrium with DG10S478. The FUSION investigators genotyped 12 additional SNPs in linkage disequilibrium with rs12255372 (the SNP most highly correlated with DG10S478), and found that none of them yielded a stronger association signal than rs12255372 [17[•]]. Our group similarly genotyped 13 tag SNPs that captured 32 of 44 variants (with $r^2>0.8$) in the 65 kb linkage disequilibrium block spanning intron 3, exon 4 and intron 4 of *TCF7L2*: no SNP produced a stronger association signal than rs7903146 when tested by logistic regression [19[•]], suggesting that the association stems from rs7903146 or from a closely correlated variant.

Figure 1 Random-effects meta-analysis of published studies on *TCF7L2* rs7903146

After combining data for nearly 50 000 samples, the risk conferred by the T allele is 1.44 (95% confidence interval (CI) 1.40–1.49, $P < 10^{-80}$); there was no evidence of publication bias. C/C, case–control; GCI, Genomics Collaborative. *The Zhang *et al.* study [16] only genotyped rs12255372; however, because the true association signal seems to stem from rs7903146, the odds ratio and 95% CI reported for this study are likely to represent an underestimate of the true effect, so including parameters for rs12255372 in this meta-analysis is conservative. The Florez *et al.* study [14**] is not included because the Diabetes Prevention Program enrolled participants with impaired glucose tolerance and/or impaired fasting glucose at baseline, randomized them to interventions designed to lower diabetes incidence, and the hazard ratio was calculated in a prospective fashion, thus, it does not lend itself to case–control analyses. The Lehman *et al.* study [24] is not included because no genotype counts were available for that publication. Figures prepared with Comprehensive Meta-Analysis software version 2.0 (Biostat, Englewood, NJ, USA).

Nevertheless, given the strong linkage disequilibrium between rs7903146 and rs12255372, which SNP tagged the causal variant could not be distinguished on statistical grounds.

In the Diabetes Prevention Program, we had noted that linkage disequilibrium between rs7903146 and rs12255372 broke down in African Americans. While r^2 between the two SNPs was 0.78 in white participants, it was as low as 0.01 in those of African descent [14**]. Thus, one could take advantage of the weaker linkage disequilibrium in this population to resolve the true source of the association signal, although the number of African-American participants in the Diabetes Prevention Program was not sufficiently high to provide enough power to perform a conclusive test. A recent follow-up publication from deCODE which included additional European and new African samples suggests that the haplotype tagged by the T allele at rs7903146 is the source of the association [28**]. Deep resequencing of all *TCF7L2* exons and

the region surrounding rs7903146, however, has not uncovered clear functional variants [11**,28**]: the precise molecular mechanisms by which this SNP in the third intron of *TCF7L2* gives rise to a glycemic phenotype, and whether it affects gene expression or protein function, is currently unknown.

What does *TCF7L2* do?

TCF proteins belong to a family of transcription factors which contain high mobility group box DNA-binding domains. TCF4, encoded by *TCF7L2*, plays a key role in the Wnt signalling pathway: its binding by β catenin after Wnt activation of its receptor (or in the absence of the inactivating molecule adenomatous polyposis coli (APC)) leads to the formation of a TCF4/ β catenin transcriptional complex which induces the expression of TCF4 target genes. Thus, while mutations in APC and related genes have been implicated in colorectal cancer, the controlled regulation of this signalling

mechanism is thought to direct normal cellular proliferation and differentiation [29].

Tcf7l2 homozygous null mice die shortly after birth. While grossly normal in body weight and anatomical structures, they exhibit a marked deficit in intestinal development due to the absence of epithelial stem cells [30]. Among the specialized cell compartments derived from such cells is the enteroendocrine system: these cells are responsible for the manufacture of incretins, a set of hormones secreted by the gut in response to a meal which regulate such key functions as gut motility, satiety and energy homeostasis in the whole organism [31].

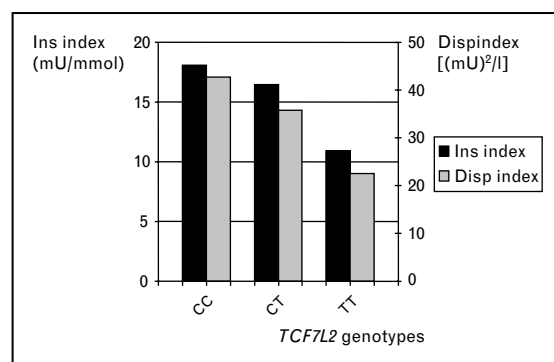
The link between *TCF7L2* and incretins provides a plausible mechanism of action for its impact on type 2 diabetes: if variants in *TCF7L2* compromise its expression or function, one might postulate that enteroendocrine processes might be affected in patients who carry such variants. These individuals could exhibit abnormalities in nutrient absorption and metabolic regulation, for example via defects in the glucagon-like peptide 1 (GLP-1)-induced increment in insulin secretion after a carbohydrate load [32]. A direct molecular connection was offered by the observation that TCF4 activates transcription of the proglucagon gene encoding GLP-1 [33]; taken together, these various lines of evidence could be combined into an attractive and testable hypothesis.

Genotype-phenotype correlations

As mentioned above, knowledge of the function of *TCF7L2* and its association with the gut incretin system gave rise to a testable speculation: lower expression or defective function of the *TCF7L2* protein product might lead to decreased transactivation of the proglucagon gene, reduced GLP-1 levels in the circulation and decreased insulin secretion in response to an enteral glucose challenge. The prediction, therefore, was that carriers of the risk allele at rs7903146 would suffer from impaired insulin secretion *in vivo*.

The Diabetes Prevention Program provided data consistent with this hypothesis. At baseline, the presence of one or two T alleles at rs7903146 led to lower levels of insulin secretion during the initial phase of an oral glucose tolerance test in individuals with impaired glucose tolerance and/or impaired fasting glucose. On the other hand, T carriers displayed a paradoxical increase in insulin sensitivity, indicating that rs7903146 increases risk of diabetes by affecting insulin secretion, not insulin resistance [14^{••}]. These differences were much more pronounced in normoglycemic individuals in whom the insulinogenic index showed a 40% decrease in TT homozygotes when compared with CC homozygotes (Fig. 2) [19[•]]. Consistent with our results, the insulin disposition index appeared to be lower in a small group ($n = 4$) of TT

Figure 2 Insulin secretion measures in 995 nondiabetic Scandinavian individuals, by genotype at *TCF7L2* rs7903146



Ins index, insulinogenic index; Disp index, insulin disposition index. Differences among genotypic groups are statistically significant at $P < 0.005$. Data obtained from Saxena *et al.* [19[•]].

homozygotes when evaluated by an intravenous glucose tolerance test [18[•]]. A similar but nonsignificant trend was observed in white and African-American women [34]. Whether these effects are due to a direct impact of *TCF7L2* variants on incretin expression in the gut, or to a more complex interaction with related peptides in the pancreas – where *TCF7L2* is also expressed [20[•]] – awaits genotype-stratified measurement of GLP-1 circulating levels and examination of this and other transcripts in specific tissues and cell types.

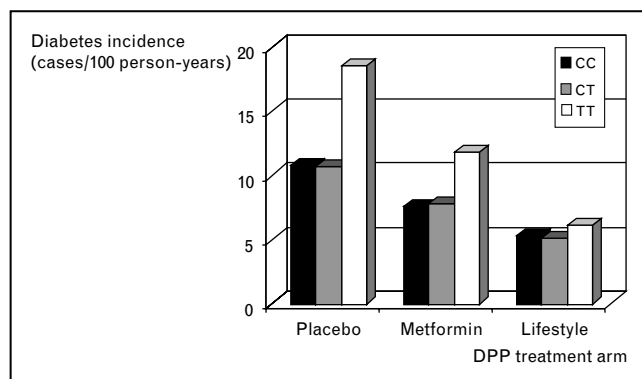
An intriguing relationship of *TCF7L2* with BMI has recently emerged. In the Diabetes Prevention Program, we observed that carriers of the risk genotype had lower BMI and waist circumference at baseline [14^{••}]. As the Diabetes Prevention Program was a clinical trial which required that participants have impaired fasting glucose and/or impaired glucose tolerance at study entry, we reasoned that individuals with the risk genotype at *TCF7L2* would have to be protected from diabetes by other genetic or environmental effects, lest the combination of *TCF7L2* and these other factors render them diabetic and therefore ineligible for enrollment. In other words, if the T allele leads to decreased insulin secretion and a higher risk of diabetes, individuals with additional insulin resistance induced by obesity would be more likely to have diabetes at baseline; thus, the leaner and more insulin-sensitive phenotype of T carriers was thought to be an artifact of ascertainment.

Helgason *et al.* [28^{••}] detected a natural selection signal in the same *TCF7L2* region, which appears to have driven a complementary haplotype (termed HapA, constituted by the alternate allele C at rs7903146 and allele A at rs10885406) to near-fixation in East Asians. HapA was found to be associated with increased BMI ($P = 0.0016$); as the authors acknowledge, the reciprocal BMI results

for HapA and for the haplotype tagged by the diabetes risk T allele at rs7903146 (termed HapB_{T2D}) are not independent, as almost 80% of European haplotypes are captured by one or the other. Because the association with BMI was tested in non-Asian diabetes and control groups separately, the same ascertainment constraints may, however, have been at play: diabetic subjects with the protective C allele at rs7903146 must have been exposed to other genetic or environmental factors that led them to develop diabetes, including those that cause increased BMI, resulting in an overrepresentation of C alleles among heavier cases. Conversely, normoglycemic subjects with the risk T allele at rs7903146 must have been protected from diabetes by analogous genetic or environmental factors which led them to have a lower BMI, resulting in an overrepresentation of T alleles among leaner controls. Therefore, in order to clarify the contribution of this locus to BMI, a thorough evaluation in population samples (without ascertainment of diabetes status) is necessary. In support of this notion, 4434 population controls from the French DESIR cohort showed no BMI differences across rs7903146 genotypes [35].

Be that as it may, an encouraging message can also be gleaned from the Diabetes Prevention Program: participants who carried the high-risk homozygous TT genotype at rs7903146 benefited as much or more from the lifestyle preventive intervention as their wild-type counterparts (Fig. 3); that is, a lifestyle intervention program aimed at $\geq 7\%$ weight loss and ≥ 150 min of physical activity per week was enough to reduce the genetic risk conferred by this variant to baseline levels [14^{**}]. Thus, knowledge of this genetic information may serve to target subjects at greater genetic risk for this highly effective intervention.

Figure 3 Incidence of diabetes (cases/100 person-years) according to genotype at rs7903146 and treatment arm in the Diabetes Prevention Program (DPP)



Data obtained from Florez *et al.* [14^{**}].

Conclusion

The discovery of *TCF7L2* as a diabetes gene, its rapid confirmation by multiple groups and the characterization of possible physiologic mechanisms of action have resulted in several reasons for optimism. To paraphrase Zeggini and McCarthy [36], type 2 diabetes susceptibility variants with large effect sizes can indeed be found and replicated, they can yield novel insights into diabetes pathogenesis, and this new information may impact clinical practice. Indeed, established genetic risk factors can be entered into prospective risk prediction models [37^{*}], and as the Diabetes Prevention Program illustrates, genetic data may help identify a subset of individuals more likely to benefit from successful pharmacological or behavioral interventions. Forthcoming clinical trials should help determine whether knowledge of such genetic information is cost-effective and leads to better patient outcomes: it is hoped that a flurry of similarly exciting results emerges from the impending release of data produced by several recently completed genome-wide association scans.

Addendum

A recent study in an independent white population sample has confirmed that while the risk T allele at *TCF7L2* rs7903146 does indeed affect insulin secretion, it does not appear to influence insulin sensitivity. Similarly, it is not associated with body mass index or waist circumference in this cohort free of ascertainment bias.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 542).

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