TCF7L2 and diabetes – A transcription gene with prescription hope?

M. Balasubramanyam

There is a growing feeling in the biomedical community that the efforts of geneticists to identify the specific genetic variants underlying polygenic diseases such as type-2 diabetes have been less successful than had been promised. Genetic susceptibility to the common form of type-2 diabetes involves a number of variants, each with a modest effect on the risk of disease in an individual person. The genetic web of type-2 diabetes is particularly tangled. Despite important advances in understanding the genetic determinants of the relatively rare monogenic forms of diabetes, the pace of definitive identification of genes that increase the risk of common type-2 diabetes has been slow.

However, slow does not mean an end to the efforts. This was reflected in the recent identification of a common allele in the transcription factor 7-like 2 (*TCF7L2*) gene that increases the risk of type-2 diabetes[1]. The risk of diabetes among carriers of a single copy of the risk allele is increased by a factor of 1.45, and among carriers of two risk alleles, by an impressive factor of 2.41. This is the largest odds ratio that we are aware of for a gene associated with susceptibility to type-2 diabetes. Florez *et al.*[2] studied participants in the Diabetes Prevention Program (DPP) and examined whether the *TCF7L2* genotype (variants *rs12255372* and *rs7903146*) influences the risk of progression from impaired glucose tolerance to diabetes over a three-year period. They found that participants who were homozygous for the high-risk allele had 55% greater rate of conversion from impaired glucose tolerance to diabetes over a three-year period than those who were homozygous for the low-risk alleles. Wang *et al.*[3] also observed that variants of the *TCF7L2* gene predicted conversion to type-2 diabetes in the Finnish Diabetes Prevention Study.

TCF7L2, also known as *TCF-4* is a nuclear receptor for β-catenin, which in turn mediates the canonical WNT (Wingless-type MMTV integration site family) signalling pathway (Figure 1). The WNT signalling pathway is critical for normal embryogenesis, cell proliferation and motility, as well as cell fate determination. While a role of WNT signalling in myogenesis and adipogenesis is also known, a tightly regulated WNT signalling is required for normal development of the pancreas and islets during embryonic growth. Little is known about the physiological implication of *TCF7L2* in glucose homeostasis. It has been suggested that intestinal proglucagon gene expression may be regulated by the WNT/*TCF7L2* pathway in enteroendocrine cells[4]. Thus, *TCF7L2* variants may modify type-2 diabetes susceptibility through alterations in glucagon-like peptide-1 (GLP-1) that is linked to physiololgical insulin secretion. A putative role for *TCF7L2* in β-cell differentiation was also suggested by the strong correlation between neurogenin-3 (NGN-3, an upstream marker of differentiation) and *TCF7L2* expression during the early steps of rat pancreas development[5]. In this regard, attenuated WNT signalling is expected to restrict pancreatic growth.

Although *TCF7L2* seems to be a diabetes-associated gene in which common polymorphisms primarily affect the β-cell[2], it might have a role in insulin resistance[6–8]. Interestingly, *TCF7L2* is highly expressed in most human tissues, including pancreatic β-cells and adipocytes, with the exception of lowest mRNA expression in skeletal muscle[5,8]. This suggests that the common polymorphisms of *TCF7L2* might influence skeletal muscle insulin sensitivity via indirect pathways. Since *TCF7L2* is highly expressed in adipose tissue, the relationship between polymorphisms of *TCF7L2* and insulin resistance could be mediated through altered endocrine function of adipocytes, which needs to be addressed in tissue-specific investigations. In subcutaneous and omental fat from obese, type-2 diabetic subjects, *TCF7L2* expression was significantly decreased compared with obese normoglycaemic individuals[5]. One intriguing observation reported across several studies is that in cases (but not controls), the type-2 diabetes susceptibility variants in *TCF7L2* were associated with reduced body mass index (BMI). As suggested by Zeggini and McCarthy[9], this may reflect an ascertainment effect, i.e. reduction in β-cell function is so profound that carriers tend to develop type-2 diabetes at a lower BMI than otherwise. If it is true that *TCF7L2* polymorphism carriers develop diabetes at lower levels of BMI, the functional consequences of *TCF7L2* variants may have a potential impact on Asian Indians who are thin (low BMI) but have higher adiposity (percentage body fat), and are more centrally obese. It is plausible that a potentially increased WNT signalling in carriers of the *TCF7L2* risk variants could be expected to influence adipose tissue growth and development, and thus BMI. While studying the elderly population, Melzer *et al.*[10] have observed that patients with diabetes carrying *TCF7L2* variants are less likely to have metabolic syndrome features, but may be at a higher risk from more microvascular complications, including renal impairment and (vascular) dementia. Thus, *TCF7L2* studies continue to pose problems in its physiological and pathological roles.

Since the initial report in early 2006, we have now more than 20 robustly reproducible studies to indicate that *TCF7L2* might be a strong candidate for conferring susceptibility to type-2 diabetes across different ethnicities[11,12]. The speed of confirmation and reproducibility of the findings with *TCF7L2* has certainly been unprecedented. Unlike *TCF7L2*, the other two type-2 diabetes susceptibility variants, notably the P12A variant in *PPAR*γ and *E23K* in *KCNJ11*, have only modest effects on disease risk (odds ratios ~1.2), far too small to offer (either individually or in combination) clinically useful predictive testing. Since these variants lie within genes whose products are already known to be therapeutic targets, genetic studies with *PPAR*γ and *KCNJ11* have also had limited capacity to deliver novel pathophysiological insights. The paradoxical link of *TCF7L2* with diabetes suggests that many more type-2 diabetes susceptibility variants with large effect sizes do exist and can be revealed by genome-wide association mapping. *TCF7L2* may not be the most attractive of drug targets, since it is closely involved in fundamental developmental processes. There is also skepticism in that the main effect of the high-risk single-nucleotide

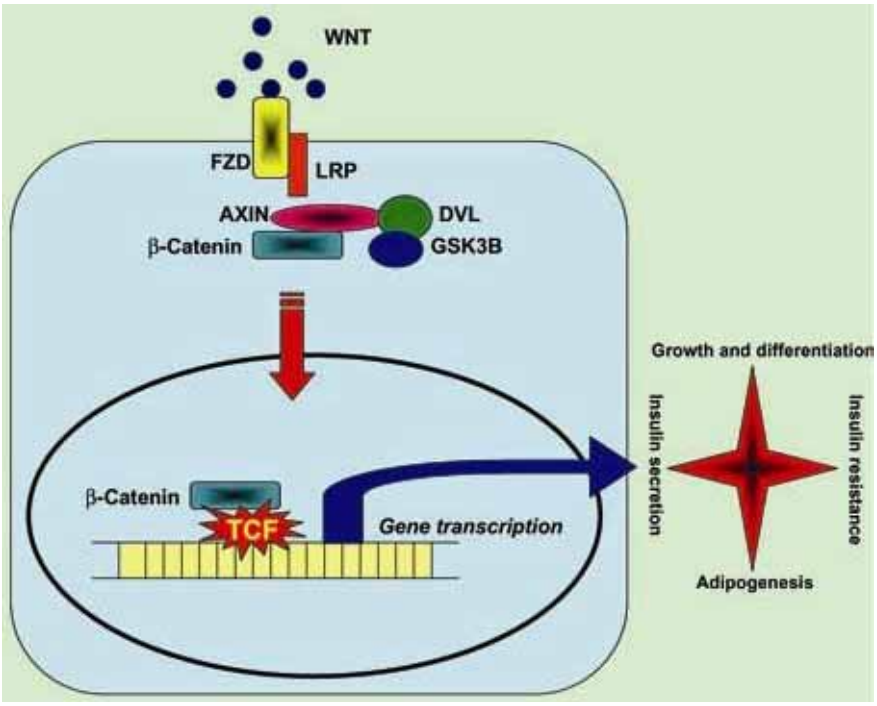

Figure 1. Schematic representation of WNT/TCF signalling. Secreted WNTs bind to FZD and LRP receptors, which in turn inactivate the degradation complex comprising AXIN, DVL and GSK3B. This results in non-phosphorylated β-catenin entering into the nucleus and binding to *TCF7L2*, thus activating a wide variety of genes. *TCF7L2* could regulate several genes – tissue specifically influencing both insulin secretion and insulin sensitivity. For example, *TCF7L2* regulates β-cell growth and differentiation. *TCF7L2* also activates the expression of proglucagon gene, which encodes the GLP-1 (glucagons like peptide-1) and thus promotes insulin secretion. Alterations in this pathway (in *TCF7L2* risk variants) could lead to reduced secretion of GLP-1 and hence defective insulin secretion. In addition, altered WNT signalling (in *TCF7L2* risk variants) could be expected to influence adipose tissue growth and development and thus BMI. Increased pro-inflammatory signals (IL-6, TNF-α) and altered adiponectin from the adipocytes (through their endocrine function) might result in skeletal muscle insulin resistance. With regard to microvascular complications of diabetes, *TCF7L2* may also influence mesangial cell expansion and retinal neovascularization.

polymorphisms in relation to diabetes may be developmental and may not be amenable to therapeutic manipulation in adult patients. Nevertheless, the pharmaceutical industry will be looking carefully at agents that modulate the signalling pathways of WNT/*TCF7L2*. Moreover, the critical role of *TCF7L2* in glucose homeostasis points out the need for improved understanding of the role played by WNT signalling in metabolic processes, and exploration of the possibilities for novel therapeutic modalities.

How might current findings on *TCF7L2* benefit patients? The good news from the study of Florez *et al.*[2] is that you can overcome your genetic risk, at least when it comes to this particular gene. People with two copies of the variation who lost weight and exercised (moderately for 30 min a day at least five times a week) reduced their increased risk of type-2 diabetes to 15%, compared to 80% for those on a placebo. This finding emphasizes that people at risk of diabetes, whether they are overweight, have elevated blood glucose levels, or have this particular genetic variant, can benefit greatly by implementing a healthy lifestyle. Here, it is worth noting that current public health recommendations for physical activity are for 30 min of moderate–intensity activity/day, which provides substantial benefits across a broad range of health outcomes for sedentary adults. Therefore, *TCF7L2* might qualify to be called as a 'lifestyle-friendly' gene.

Will this transcription gene imply a prescription hope? Together with deCODE diagnostics, DNA Direct is now offering deCODE T2, a genetic test that examines the presence of the 'T' allele of SNP *rs7903146*, located within the *TCF7L2* gene. deCODE T2 is the first of several DNA-based predisposition tests that are being developed for common diseases. According to deCODE, it is believed that as individuals, doctors and healthcare providers begin to integrate these tests as a part of healthcare, these tests may provide major benefit to public health. Given that type-2 diabetes is a multifactorial disease caused by many different genetic and lifestyle factors, having one genetic test done on one specific gene variant may not tell much about one's risk for the disease. If the test is positive, one's risk of developing type-2 diabetes is twice as high as someone who does not have two copies of the *TCF7L2* gene variant. However, the cumulative risk still depends on other risk factors such as weight, lifestyle habits, diet and other genetic variants. In other words, one should not be deluded into thinking to be free of risk if the test is negative.

Genetic testing to pre-determine disease risk and the design of preventative therapeutic regimens, will have a place in future medical care. Although *TCF7L2* variants do have predictive value beyond other measurements that can also foretell diabetes, further studies are needed to determine whether a routine genetic test would drastically improve the results that are achieved using current treatments, or if developing and administering such a test would be cost-effective. The indication that the deCODE T2 genetic test will cost several hundreds US dollars, is certainly a profound limitation. Nevertheless, future predictive testing might include testing a battery of common genetic variants, followed by computational joint assessment of traditional, environmental and lifestyle risk factors, which may assist physicians and patients in choosing a preventive strategy. Recent theoretical studies have emphasized that as few as 20 susceptibility variants on the scale of those in *TCF7L2*, *PPARγ* and *KCNJ11* may suffice to explain as much as 50% of the burden of the disease[13,14]. If personalized medicine is to be realized in the future for complex diseases, such models will be required. However, the question still remains – what will it cost and whether 'gene-prescription' knowledge of the possibility of developing a particular disease be enough to motivate some patients to modify that risk? More than genetic testing, for developing countries like India, *TCF7L2* studies send a clear message – 'lifestyle modifications to prevent diabetes' – the same philosophical teachings of our ancient saints, now with a flavour of molecular evidence in the post-genomic era.

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M. Balasubramanyam is in the Madras Diabetes Research Foundation, 4 Conran Smith Road, Gopalapuram, Chennai 600 086, India.
e-mail: drbalu@mvdsc.org

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Contact: Dr Y. C. Goswami
Coordinator, National Seminar
Institute of Technology & Management
ITM Campus, Opp. Sithouli Railway Station
NH 75, Jhansi Road, Sithouli
Gwalior 474 001
Phone: 0751-2432977-216, 244005
Fax: 0751-2432988
Mobile: 94251 21044
E-mail: itmphysics@yahoo.co.in
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Department of Immunology
Sanjay Gandhi Postgraduate Institute of
Medical Sciences
Raebareli Road
Lucknow 226 014
Phone: 91-522-2668700/800/900 Ext 2284
E-mail: cytometry2007@sgpgi.ac.in
Website: www.cytometry2007.com