Prime suspect: the *TCF7L2* gene and type 2 diabetes risk

Andrew T. Hattersley

Commentary

Transcription factor-7–like 2 (*TCF7L2*) is the most important type 2 diabetes susceptibility gene identified to date, with common intronic variants strongly associated with diabetes in all major racial groups. This ubiquitous transcription factor in the Wnt signaling pathway was not previously known to be involved in glucose homeostasis, so defining the underlying mechanism(s) will provide new insights into diabetes. In this issue of the *JCI*, Lyssenko and colleagues report on their human and isolated islet studies and suggest that the risk allele increases *TCF7L2* expression in the pancreatic β cell, reducing insulin secretion and hence predisposing the individual to diabetes (see the related article beginning on page 2155).

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heme moieties would somehow trigger Foxo3 translocation to the nucleus and induction of its targets in terminal differentiation. This as yet untested hypothesis emphasizes the importance of determining both the direct targets of Foxo3 and its own regulation in helping us understand how a red blood cell lacking a nucleus knows exactly when to die.

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Prime suspect: the *TCF7L2* gene and type 2 diabetes risk

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Transcription factor-7–like 2 (*TCF7L2*) is the most important type 2 diabetes susceptibility gene identified to date, with common intronic variants strongly associated with diabetes in all major racial groups. This ubiquitous transcription factor in the Wnt signaling pathway was not previously known to be involved in glucose homeostasis, so defining the underlying mechanism(s) will provide new insights into diabetes. In this issue of the *JCI*, Lyssenko and colleagues report on their human and isolated islet studies and suggest that the risk allele increases *TCF7L2* expression in the pancreatic β cell, reducing insulin secretion and hence predisposing the individual to diabetes (see the related article beginning on page 2155).

Over 170 million people in the world can blame their type 2 diabetes, at least in part, on their genes. It has been hoped for over 2 decades that identifying the "guilty" genes would help us to understand the fundamental pathophysiology of this common and important disorder. Now, at last, not only are common gene variants being reproducibly associated with type 2 diabetes, but work such as that of Lyssenko and colleagues, reported in this issue of *JCI*, is turning this genetic information into novel biological insights (1).

Early genetic studies in type 2 diabetes

Early attempts to identify the genes responsible for type 2 diabetes were slow and unsuccessful: faced with 30,000 suspects, geneticists were only able to examine less than 5% and, in most cases, the coverage of the gene and sample size were too small to detect modest effects. The choice of genes studied was primarily based on evidence that these genes played biologically important roles in glucose homeostasis. By the end of 2005, despite considerable research throughout the world, only 2 polymorphisms were considered guilty beyond a reasonable doubt of predisposing to type 2 diabetes: P12A in *PPARG* (2) and E23K in *KCNJ11* (3). One advantage of using biological candidacy to choose genes for further study was that we already knew the critical science of the proteins encoded by these genes — the nuclear transcription factor PPARγ and the potassium inward-rectifying 6.2 subunit (Kir6.2) of the potassium ATP channel. Both genes were diabetes drug targets, and mutations in both could cause monogenic diabetes (4, 5). This meant that once the association with disease was established, understanding the associated pathophysiology was relatively straightforward. However, the very reasoning that led to the genes being chosen also meant there was not a lot of new scientific insights to be learned from identifying these two genes.

TCF7L2: the most important type 2 diabetes gene

At the start of 2006, transcription factor-7–like 2 (*TCF7L2*) was revealed as an unexpected suspect for a type 2 diabetes gene by the DECODE group in Iceland (6). This gene had initially drawn attention during follow-up research on a small linkage signal on chromosome 10, but it turned out that, despite not explaining this linkage, multiple polymorphisms within the gene showed strong association with diabetes in multiple cohorts. The initial study was rapidly followed by widespread replication not only in white Europeans (7) but also in Indian and Japanese people (8–10), Mexican Americans (11), and West Africans (12) — representing the major racial groups with a high prevalence of type 2 diabetes. In all populations, *TCF7L2* showed strong association, with the odds of developing type 2 diabetes being increased by 30%–50% for each allele inherited — approximately double the odds ratio seen with most other diabetes susceptibility polymorphisms.

The tracking of criminals and the tracking of genes have both been greatly helped by new technologies. Because of techno-
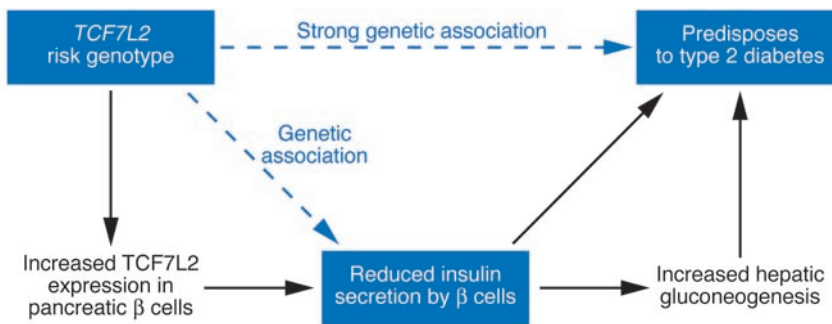
Figure 1
From genetic association to pathophysiology in *TCF7L2* genotypes predisposing to type 2 diabetes. Diagram of proposed pathophysiological pathway explaining how *TCF7L2* risk genotypes predispose to type 2 diabetes. The risk genotype results in overexpression of TCF7L2 in pancreatic β cells, which in turn results in reduced insulin secretion. Reduced insulin secretion results in a predisposition to type 2 diabetes directly and also indirectly by increasing hepatic glucose output. Dotted arrows represent previous genetic associations. Solid arrows show observations reported by Lyssenko and colleagues in the current issue of the *JCI* (1).

logical advances, the majority of common genetic variations can be assessed on a single chip at a very reasonable cost. This directly led to a whole new series of large-scale genome-wide genetic studies. As with many other polygenic conditions, this approach has been dramatically successful in studying type 2 diabetes, and within a few months, the number of established associated polymorphisms increased from 3 to 9 (13–17). A key result was that *TCF7L2* polymorphisms have been most strongly associated with type 2 diabetes in the initial scan in 4 of the 5 recently published genome-wide scans (13–17).

Defining the mechanism by which *TCF7L2* alleles predispose to diabetes

Defining the biological functions of polygenes found through genetic approaches can be very hard. Calpain 10 was the first type 2 diabetes susceptibility gene to be defined through linkage rather than a candidate gene route (18). Calpain 10 had not been previously thought to be involved in the pathogenesis of diabetes; it showed initial association with intronic SNPs, and replication required large studies (19, 20). We now recognize that these three characteristics are typical of the majority of type 2 diabetes susceptibility genes, and this may mean that the biological function of such genes will be difficult to define. In the case of Calpain 10, it was 5 years before the gene was shown to play a role in apoptosis in pancreatic islets (21).

TCF7L2 polymorphisms are clearly guilty of predisposing to type 2 diabetes on the basis of strong, reproducible association in multiple populations and would appear to be the leader among a gang of susceptibility genes. The next challenge, as with all genome-wide scans, is to define how the polymorphism predisposes to disease. The associated TCF7L2 haplotype was in the noncoding region of the gene without obvious function in gene regulation, so it was uncertain how or even whether such variants alter TCF7L2 expression. What is the critical variant of the large number of polymorphisms that are coinherited as a haplotype? Is the risk variant altering the gene it is situated in, or does it have a distant regulatory function? What biological pathway are the altered gene or genes acting in and how does this predispose to diabetes? These are the fundamental questions that need to be answered if we are to move forward from the genetic association to gain new insights into diabetes.

It is the hypothesis-free results from genome-wide association studies that have the potential to create major breakthroughs in our understanding of disease, but there are intrinsic difficulties in working on these leads. Most polymorphisms are in genes on which there has been little previous work, and the leading scientists working in cell biology and rodent models already have funding for worthy work in other areas, so why should they risk time and money working on a gene whose role is not 100% certain?

The difficulty had been trying to place *TCF7L2* at the scene of the crime, especially as there was some doubt regarding which organ and cell type(s) were involved in the pathophysiology. TCF7L2 is a transcription factor involved in the Wnt signaling pathway and is ubiquitously expressed. The studies from Lyssenko and colleagues (1) confirm earlier studies (22–25) showing that the predisposition to type 2 diabetes is the result of reduced insulin secretion rather than reduced insulin action, making the pancreatic β cell the most likely primary cell target of altered TCF7L2 activity. However, this was contrary to an initial, much-repeated hypothesis, suggesting that the risk genotype was altering insulin secretion indirectly by reducing intestinal *TCF7L2* activity, which in turn reduced the secretion of incretins, glucagon intestinal peptide (GIP), and glucagon-like peptide 1 (GLP-1) (6). Lyssenko et al. (1), in their detailed studies, show that insulin secretion in subjects with the at-risk genotype was reduced in response to a variety of stimuli including i.v. glucose and arginine and not just oral glucose. In addition, GIP levels were not reduced, suggesting that even though GLP-1 levels were not measured, there was a reduced β cell response to incretin secretion rather than reduced incretin secretion.

The final question is how exactly the "crime" is performed within the β cell — and here there is a final twist in the story. Lyssenko et al. (1) show that *TCF7L2* expression was increased 5-fold in type 2 diabetes islets, rather than being reduced. This vital and surprising observation came from studies of pancreatic islets carefully purified from type 2 diabetic and nondiabetic human cadavers. In addition, there was some suggestion that in the nondiabetic islets that the risk genotype was associated with increased *TCF7L2* expression, but the numbers are small and caution must be exercised in interpreting these data until a greater number of islets are examined. Finally, in a reconstruction of the crime, overexpressing *TCF7L2* in human islets using an adenovirus system reduced insulin secretion. As with much of science that has been reported in the study of type 2 diabetes, there are bits of the story that do not fit: insulin gene mRNA was positively correlated with *TCF7L2* mRNA, out of keeping with the reduced insulin secretion observed, and the overexpression of *TCF7L2* did not result in the increased glucagon secretion seen in the type 2 diabetic islets.

Conclusion

So the interim verdict is that *TCF7L2* risk alleles predispose to type 2 diabetes by crimes against the β cell (Figure 1). The risk allele results in overexpression of *TCF7L2* in the pancreatic β cell, which reduces insulin

secretion in response to a variety of stimuli (1). The reduced insulin secretion in turn explains the increased hepatic glucose production observed. There are still many unanswered questions: Is the concentration of TCF7L2 protein increased in the β cell in addition to TCF7L2 RNA? How is expression increased by intronic variants? How does increased *TCF7L2* expression reduce insulin secretion? This is the first in a series of steps toward understanding the associated pathophysiology. In the end, what is desired from scientific breakthroughs is improved prevention of type 2 diabetes and improved treatment of those who develop the disease. We are still a long way from this, but there is now a new β cell pathway to be further investigated to see if it can be manipulated by drugs or lifestyle changes.

Acknowledgments

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Proteinuria: is it all in the foot?

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Despite significant advances in our understanding of the molecular structure and composition of the glomerular filtration barrier, the mechanisms underlying the presence of excess protein in the urine (proteinuria) in acquired human kidney diseases remain elusive. In a study appearing in this issue of the *JCI*, Sever and associates use a combination of biochemical, genetic, and in vivo approaches in mice to demonstrate a pivotal role of cathepsin L and its substrate the GTPase dynamin, in the induction of proteinuria and associated foot process effacement in glomerular podocytes (see the related article beginning on page 2095).

One main function of the kidney is to filter low-molecular-weight plasma waste products into the urine while restricting the passage of albumin and larger molecules that are necessary for maintaining normal homeostasis. This occurs in special filtration units called glomeruli, which consist of a capillary tuft inside the Bowman capsule and every day form about 180 liters of primary urine virtually devoid of macromolecules. The glomerular capillary wall is characterized by an extremely high permeability to water, small solutes, and ions, contrasting with a very low permeability to plasma proteins of the size of albumin and larger. The essential components of the glomerular capillary wall are the fenestrated endothelium, the glomerular basement membrane (GBM), and the podocytes (Figure 1). The latter cells have a voluminous body and long primary processes that extend toward the capillaries to which they affix by numerous foot processes. The foot processes of neighboring podocytes regularly interdigitate, forming filtration slits between them that are bridged by slit