The Role of *TCF7L2* in Type 2 Diabetes

Laura del Bosque-Plata,[1] Eduardo Martínez-Martínez,[2] Miguel Ángel Espinoza-Camacho,[1] and Claudia Gragnoli[3,4,5,6]

Diabetes 2021;70:1220–1228 | https://doi.org/10.2337/db20-0573

***TCF7L2* is the most potent locus for type 2 diabetes (T2D) risk and the first locus to have been robustly reported by genomic linkage studies. TCF7L2 is a transcription factor that forms a basic part of the Wnt signaling pathway. This gene has highly conserved sequence regions that correspond to functional domains. The association of *TCF7L2* with T2D is one of the most powerful genetically discovered in studies of complex diseases, as it has been consistently replicated in multiple populations with diverse genetic origins. The mechanisms over which TCF7L2 exerts its effect on T2D are still not well understood. In this article, we describe the main molecular mechanisms of how *TCF7L2* is related to T2D. *TCF7L2* variants associated with T2D risk exert an influence on the initial therapeutic success of the hypoglycemic oral agent sulfonylurea. Thus, it is important to know whether there are other *TCF7L2* variants associated with T2D that can influence treatment with oral hypoglycemic agents. Resequencing of the *TCF7L2* gene in diverse ethnic groups is required to reveal common and rare variations and their role in different pathologies and in adverse reactions to drugs. Identification of *TCF7L2*-susceptibility disease variants will permit, at a given moment, offering of therapies to patients according to their genotype.**

The transcription factor 7-like 2 (TCF7L2) (previously TCF4-transcription factor 4) is a member of the T-cell factor/lymphoid enhancer binding factor family (TCF/LEF), a group of transcription factors binding to DNA through a high-mobility group (HMG) domain. The *TCF7L2* gene has been the object of much attention due to its strong genetic association with type 2 diabetes (T2D) (1,2). The *TCF7L2* gene forms a basic part of the Wnt signaling pathway, which is made up of a complex network of interacting proteins having cellular intercommunications regulated at multiple levels, generating numerous effects, and which was initially related to the biology of development. Proteins involved in the Wnt network, as is the case of TCF7L2, have been related to various and diverse common diseases, as well as to different models of cancer, thus reflecting the importance of this developmental pathway in the pathogenesis of human diseases (3–5).

Characteristics of the *TCF7L2* Gene

The human *TCF7L2* gene was mapped to chromosome 10q25.3 (6) and initially sequenced in colorectal cancer (CRC) cell lines (7). *TCF7L2* has 18 exons, which present a complex splicing pattern in different tissues. This gene has highly conserved sequence regions that correspond to functional domains. The β-catenin binding domain corresponds to exon 1, and the HMG box binding domain corresponds to exons 10 and 11 of human *TCF7L2* (*hTCF4*). Both domains are highly conserved between species. In addition, *TCF7L2* possesses highly conserved sequences in the 3′ region of exon 18, with conserved splicing patterns similar to those of the transcription factor T-cell factor 1 (*TCF1*) gene. These spliced transcripts present two reading frames conserved in *Drosophila melanogaster* and *Caenorhabditis elegans*, and two other reading frames are related to the chicken *TCF* genes. There are two binding motifs in the COOH-terminal region of the *TCF7L2*

[1]Laboratory of Nutrigenetics and Nutrigenomics, National Institute of Genomic Medicine, Mexico City, Mexico
[2]Laboratory of Cell Communication and Extracellular Vesicles, National Institute of Genomic Medicine, Mexico City, Mexico
[3]Division of Endocrinology, Department of Medicine, School of Medicine, Creighton University, Omaha, NE
[4]Division of Endocrinology, Diabetes, and Metabolic Disease, Department of Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA
[5]Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA
[6]Molecular Biology Laboratory, Bios Biotech Multi-Diagnostic Health Center, Rome, Italy
Corresponding author: Laura del Bosque-Plata, ldelbosque@inmegen.gob.mx

Received 27 May 2020 and accepted 19 March 2021

isoforms that are conserved through evolution. The complex *TCF7L2* splicing pattern suggests that the alternative use of isoforms in the 3′ region generates distinct protein isoforms with agonistic as well as antagonistic transactivation activities (7) (Fig. 1).

T2D

TCF7L2 is the most potent locus for T2D risk and the first locus to have been robustly reported by genomic linkage studies (1) and genome-wide association studies (2). deCODE genetics initially detected linkage to T2D in the Icelandic population on a chromosome 10 locus (8). However, the TCF7L2 at-risk allele present in ~28% of control subjects and 36% of T2D case subjects did not explain the linkage signal. The exact gene variants contributing to T2D were not determined because some of these variants were in linkage disequilibrium (LD), as well as being located in a noncoding region without evident functional effects. The most probable candidate risk variants with the greatest odds ratio, ~1.4, were the single nucleotide polymorphisms (SNPs) rs7903146 and rs12255372, in strong LD with the microsatellite marker DG10S478, whereas alleles rs7903146-T and rs12255372-T showed the most statistically significant association with T2D (1). Early in 2007, by analyzing 392,935 SNPs in a French cohort, Froguel and colleagues (2) reported *TCF7L2* as a diabetogene. Afterward, in a second cohort they followed up the variants, with the most statistically significant differences between T2D and control subjects. This group confirmed the association of *TCF7L2* with T2D risk and found the zinc-transporter gene *SLC30A8* and two LD blocks that contain genes insulin degrading enzyme (*IDE*), kinesin family member 11 (*KIF11*), and hematopoietically expressed homeobox (*HHEX*), and exostosin glycosyltransferase 2 (*EXT2*) and Aristaless-like homeobox 4 (*ALX4*), associated with T2D. These associations explained a considerable component of disease and established a proof of principle for the genome-wide association study (GWAS) approach to the enlightenment of complex genetic traits (2). Replication of the association in a population of European origin was achieved jointly to the discovery of other diabetogenes (9). With use of genotyping data of 32 European descent GWAS (74,124 T2D case and 824,006 control subjects), >240 loci were reported for T2D, including *TCF7L2* (10).

TCF7L2 association with T2D has been consistently replicated in multiple populations with diverse genetic origins, thus representing one of the most powerful genetic associations discovered in studies of complex diseases. A meta-analysis of the genetic associations found in different populations showed that the *TCF7L2* variants associated with T2D exert their effects under a multiplicative genetic model. It suggested that *TCF7L2* is involved in nearly one-fifth of T2D cases (11).

Soon after the first genetic association of *TCF7L2* with T2D risk, other SNPs in the *TCF7L2* gene were reported to be associated with this disease by different research groups. Haddad et al. (12) reported in African Americans a new signal in SNP rs114770437, which was independent of the index SNP rs7903146. The variant rs114770437 is monomorphic in the 1000 Genomes Project, which includes European, East Asian, and South Asian populations, thus explaining why it has not been found in previous GWAS of European and Asian ancestry subjects (13). The MEta-analysis of type 2 DIabetes in African Americans (MEDIA) Consortium reported a group of SNPs—SNPs rs7896811, rs11196199,

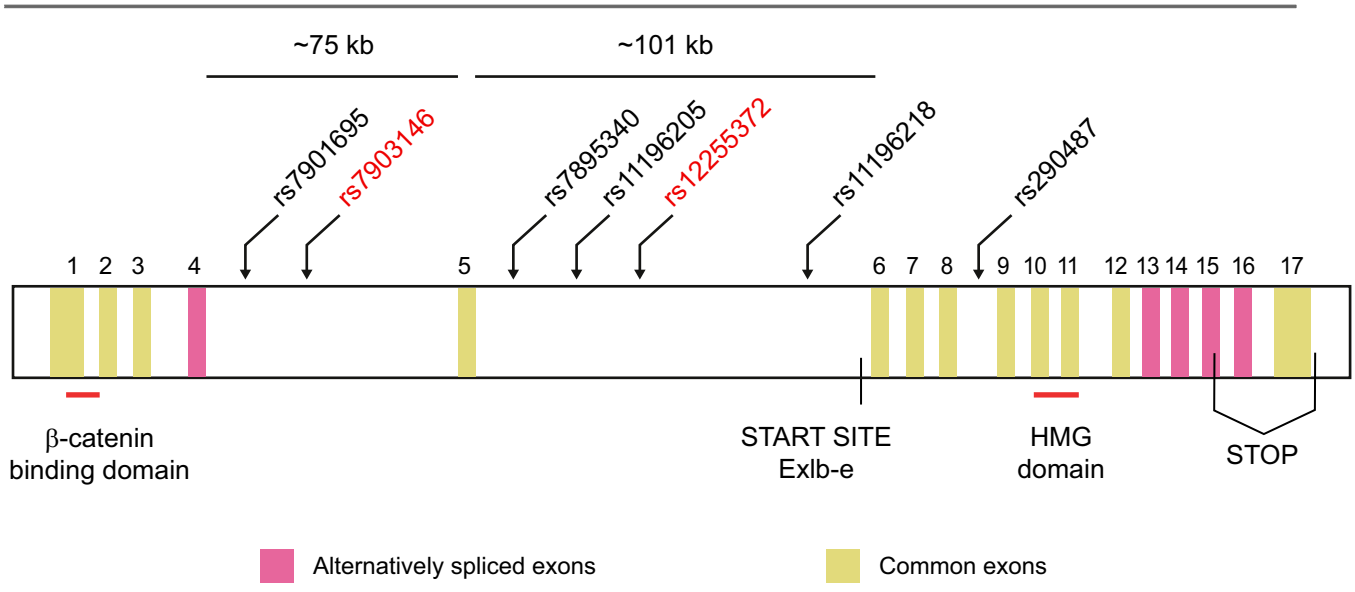

Figure 1—Structure of the *TCF7L2* gene. Localization of at risk intron 4, 5, and 8 SNPs. Modified from Duval et al. (7).

and rs11196203, uncorrelated with the index SNP rs7903146 ($r^2 < 0.05$)—that correlate moderately ($r^2 = 0.3$) with rs114770437, indicating that they may be tagging the same causal SNP or that they may each one alone or in combination contribute to T2D in the African ancestry population (13).

Chang et al. (14) analyzed *TCF7L2* in the Chinese Han population by amplifying 13 SNPs with allelic frequencies >20% and covering >90% of all haplotypes. They found that rs290487-C, located in an LD block close to the 3′ region of the gene, is associated with T2D in the Chinese Han population, in which the allelic frequency is ≤40% and the population-attributable risk fraction (PAR) is 18.7% (14). Another study in the Chinese population replicated the T2D association of SNP rs11196205, which resides within an LD block of 92.1 kb. In the same population, SNP rs11196218, localized downstream of rs11196205, was identified within another LD block, thereby conferring risk in an independent manner (population-attributable risk fraction = 42%) (15). Studies on a Mexican American population also found independent associations with T2D for additional *TCF7L2* SNPs in the 5′ and 3′ regions of the same LD block in which the originally identified risk variants are located (16).

Analysis of other ethnic groups has suggested differences among races in terms of the contributions of genetic and environmental factors to T2D (17). In European populations, *TCF7L2* SNPs associated with T2D susceptibility vary greatly in terms of allelic frequencies at global levels, with use of the International Haplotype Project (HapMap), Human Genome Diversity Project, Centre d'Etude du Polymorphisme Humain (CEU) databases and The ALlele FREquency Database (ALFRED). In addition, the risk SNPs allelic frequencies vary at regional levels; for example, the frequency of *TCF7L2* rs11196218-A is highest in Eurasia, while it is reduced in sub-Saharan African and Native American populations, indicating that these variants may differently contribute to T2D incidence worldwide. Additional studies of gene-gene and gene-environment interactions are needed to elucidate the multifactorial contributions in diverse populations (17).

In a population-based cohort study of U.S. Hispanic/Latino adults (21–76 years old), a protective effect of *TCF7L2* rs7930146-T on BMI was detected at ages 21 and 45 years, as well as a significant positive association between rs7903146-T and T2D onset in both middle and late adulthood. The results suggest that a complicated biologic mechanism underlies the functional consequences of *TCF7L2* on obesity and T2D across the life course (18).

The mechanisms over which TCF7L2 exerts its effect on T2D are still not well understood. To determine whether the *TCF7L2* rs7903146 variant has *cis*-regulatory properties, a detailed map of *cis*-regulatory elements within the 92-kb T2D association interval of the GWAS *TCF7L2* locus has been made using a systematic cell-based enhancer strategy for *cis*-regulatory activity in a panel of cell lines. The chromatin state was evaluated in HCT-116 and U2OS cells, and allelic-specific enhancer properties were examined at the associated *TCF7L2* rs7903146. A *cis*-regulatory variation leading to T2D predisposition and SNP rs7903146s allelic-specific effects in multiple cell lines were detected, indicating a peripheral defect in disease etiology (19). The use of the same strategy with additional cell lines will allow a clearer picture of the *cis*-regulatory elements involved in the disease pathogenesis.

Wnt Signaling Pathway

The Wnt signaling pathway consists of 19 secreted glycoproteins containing 22 or 24 highly conserved cysteine residues as well as seven transmembrane domains acting as ligands of receptors mediating human developmental and adult processes (20). The Wnt/β-catenin pathway generates numerous tissue-specific responses, including acting on multiple nuclear-effector proteins, which have different functional properties (e.g., TCF proteins), and regulating gene transcription and transduction in the pathway (Fig. 2). These TCF/LEF transcription factors respond to Wnt signals via a transcriptional interrupter that partially modulates the binding with β-catenin and the recruitment of coactivator complexes; the specificity and fine regulation of this interrupter are achieved by the cellular content–dependent expression of four members of the TCF/LEF family (transcription factor 7 [TCF7], transcription factor 7-like 1 [TCF7L1], TCF7L2, and LEF1) and their numerous isoform variants, exhibiting differences in the affinity and specificity of DNA binding, repression, activation, and regulation (21).

TCF7L2 and Adipogenesis

TCF7L2 has fundamental developmental and metabolic roles in adipose tissue. The regulation of adipogenesis by TCF7L2 and Wnt signaling is more complex than previously recognized, and the in vivo inactivation of adipocyte TCF7L2 promotes adipocyte hypertrophy and peripheral and hepatic insulin resistance (22). Qin et al. (23) studied the mechanisms of the Wnt signaling pathway and miRNA-mediated regulation of adipogenesis in the 3T3-L1 cell line. By inhibiting the Wnt signaling with a differentiation cocktail and activating it with the glycogen synthase kinase-3β (GSK-3β) inhibitor, which blocks β-catenin phosphorylation, they identified 18 miRNAs that promote adipogenesis by repressing Wnt signaling and other miRNAs that activate Wnt signaling. In particular, bioinformatics analysis and corroboration experiments predicted that miRNA210 bound to the gene *TCF7L2* repressed Wnt signaling, thereby promoting adipogenesis (23) (Fig. 3). Furthermore, miR-181a-5p promotes 3T3-L1 preadipocyte differentiation and adipogenesis by regulating TGFβ/Smad, and it promotes the Wnt signaling pathway by directly targeting Smad7 and Tcf7l2 (24). This information offers a deeper understanding of the mechanisms by which miRNAs regulate adipogenesis.

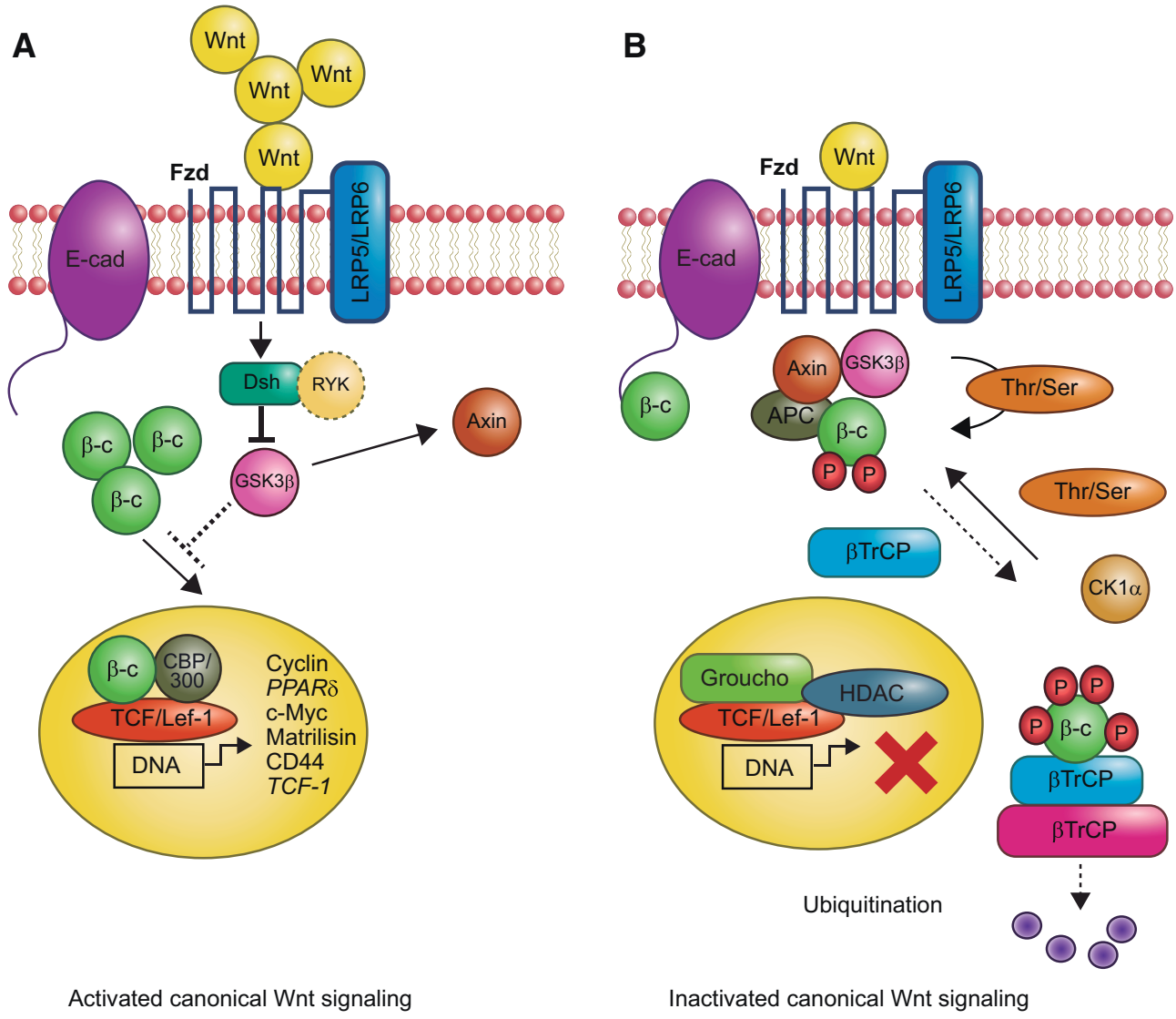

Figure 2—Canonical Wnt signaling pathway. *A*: Activated Wnt pathway. β-c, β-catenin; CK1α, casein kinase Iα; Fzd, Frizzled receptor; GSK3β, glycogen synthase kinase 3β; Lef-1, lymphoid enhancer factor-1; LRP5/LRP6, low-density lipoprotein–related receptors 5 and 6; β-TrCP, β-transducin repeat–containing protein; TCF, T-cell factor (TCF7, TCF7L1, TCF7L2). *B*: Inactivated Wnt pathway. Modified from Ding et al. (50).

The expression of miRNAs in adipose tissue can be modulated by inflammation. Proinflammatory factors can impair insulin secretion as well as insulin sensitivity in peripheral organs (25), and these inflammatory processes are associated with the defect of glucose homeostasis that leads to T2D.

TCF7L2 functions as central transcriptional regulator of the adipocyte metabolic program by directly regulating the expression of genes involved in lipid and glucose metabolism (26). *TCF7L2* regulates adipocyte size, adipocyte endocrine function, and glucose metabolism. *TCF7L2* expression in white adipose tissue is suppressed in genetic and high fat diet–induced models of obesity. Analysis of genome-wide distribution of *TCF7L2* binding and gene expression in adipocytes shows that *TCF7L2* directly regulates genes implicated in cellular metabolism and cell cycle control. When an animal model of conditional deletion of *TCF7L2* in adipocytes is challenged with a high-fat diet, there is progression to impaired glucose intolerance, impaired insulin sensitivity, weight gain, and increased subcutaneous adipose tissue mass. In addition, triglyceride-hydrolase expression is reduced and fasting-induced free fatty acids are released. High-fat feeding results in glucose intolerance after 3 days and reduced insulin sensitivity after 3 months. The findings suggest that the early loss of *TCF7L2* predisposes mice to diabetes when challenged with a high-fat diet (26).

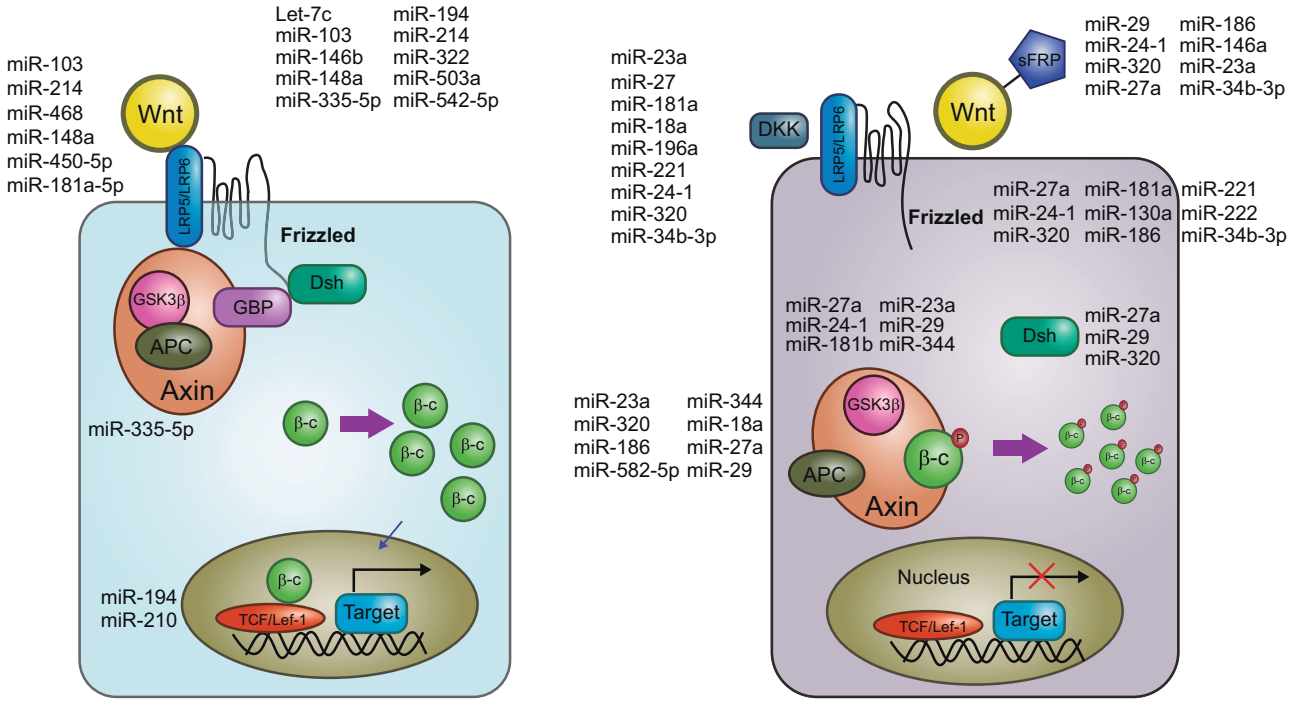

Figure 3—Regulation of adipogenesis through modulation of the canonical Wnt/β-catenin signaling pathway with miRNA. Left: MiRNAs and their predicted targets in the Wnt signaling pathway: Wnt, LRP, Axin, and TCF, which activate adipogenesis. Right: Predicted miRNAs with targets in the Wnt signaling pathway causing repression of adipogenesis, including sFRP, DKK, Frizzled, GSK3β, APC, and Dsh. Modified from Qin et al. (23).

While it has been known that Wnt signaling impairs adipogenesis, the *TCF7L2* gene was recently shown to fulfill, during adipogenesis, very complex regulatory functions that may depend on several factors, including the balance between TCF7L2 and β-catenin levels, the timing of their interaction, and the interaction between TCF7L2 and other cofactors at specific gene regions (22).

Clinical Translation of *TCF7L2* Signals in T2D Association Studies

Physiological characterization of *TCF7L2* risk variants for T2D will aid understanding of the role of TCF7L2 in the regulation of glycemia and in the secretion of insulin and its action. In addition, the identification of *TCF7L2*-interacting partners and target genes can lead to the detection of new metabolic pathways potentially involved in pathogenesis of T2D. The majority of the variants known at present to confer risk for T2D and/or continuous glycemic traits primarily impact the function of the pancreatic β-cell rather than sensitivity to insulin (27,28).

When *TCF7L2* was discovered, it was known that *TCF7L2*-knockout mice die 24 h after birth and that they lack the intestinal epithelial stem cell compartment (27). It was also known that TCF7L2 regulates the preproglucagon (*GCG*) gene that encodes glucagon-like peptide 1 (GLP-1); thus, it was postulated that *TCF7L2* variants modifying GLP-1 levels in endocrine cells could influence susceptibility to T2D (29). Successive studies in humans support this hypothesis (30). Silencing *TCF7L2* exerts a strong negative effect on glucose-mediated insulin secretion. It has been suggested that the defect may lie in the fusion of insulin-secretory granules. Defective insulin exocytosis may thus underlie increased T2D incidence in carriers of the at-risk *TCF7L2* alleles (31). *TCF7L2*-silencing studies and studies on the in vitro overexpression of gluconeogenic precursors that used chromatin immunoprecipitation combined with massive DNA sequencing (ChIP-Seq) through the genome showed that TCF7L2 is a key regulator of hepatic glucose metabolism; thus, risk variants may affect both fasting and postprandial glycemia in carriers of T2D risk genotypes (32). Most of the *TCF7L2* variants are found in noncoding regions, suggesting that they exert their effects by modulating expression. The TCF7L2 molecular mechanism of action was found while exploring the patterns of open chromatin, an evolution-conserved indicator of regulatory activity. The DNA of human islets was analyzed by high-performance sequencing of formaldehyde-assisted isolation of regulatory elements (FAIRE-seq), and the *TCF7L2* at-risk alleles were mapped at open chromatin sites, at which rs7903146, one of the *TCF7L2* variants with greatest risk for T2D, was selected. The heterozygotes of rs7903146 showed an altered intrinsic enhancer activity, indicating that the variant confers risk through *cis* regulation and modification of local chromatin structure in the pancreatic islet (33).

Additional studies in different cohorts worldwide have detected the role of the TCF7L2 risk variants in glucose metabolism and T2D. In 2007, the Finnish Diabetes Prevention Study showed that some *TCF7L2* variants predict T2D onset and are associated with impaired glucose regulation and insulin secretion (34). In 2011, the French cohort data from the Epidemiological Study on the Insulin Resistance Syndrome showed the impact of *TCF7L2* genetic risk on the evolution of T2D: *TCF7L2* variants were associated with a more rapid reduction of pancreatic β-cell function, increased glycemia, and decreased insulin secretion. These effects related to familial history of T2D, and *TCF7L2* variants indicate the familial genetic predisposition to the development over time of impaired glycemia and T2D (35). Physiological studies found that variant rs290487 contributed to insulin resistance, implicating Wnt signaling in insulin resistance (36).

The GWAS utilizing microarrays used to identify T2D risk variants reported most of the associated variants affecting pancreatic β-cell function by means of molecular mechanisms not yet known in detail. However, we know that one group of these genes affects glucose-stimulated insulin secretion, another group affects incretin-stimulated insulin secretion, and the remaining group has a defect that impairs the conversion of proinsulin into insulin. *TCF7L2* risk variants interfere with each of the three above-mentioned mechanisms (37).

Carriers of the *TCF7L2* rs7903146-T genotype, in response to an intravenous glucose-tolerance test and a euglycemic-hyperinsulinemic clamp, present phospholipids alterations in plasma metabolic profiles, potentially indicating that phospholipids may mediate metabolic abnormalities prior to the onset of glucose intolerance (38). Of note, phospholipids are the essential components of biological membranes, which provide the cell with a protective barrier that has selective permeability for cellular metabolism. Due to *TCF7L2* association with T2D and its key role in fundamental cell functions, several groups have begun to study the role of *TCF7L2* variants in biological processes such as natural selection and alternative splicing.

Natural Selection

The phylogenetic reconstruction of *TCF7L2* intron 4 variants in LD and their related haplotypes, in which T2D risk variants are found, allowed the discovery of two main haplotype lineages: HapA and HapB. Between the two, HapB is the most diverse haplotype, containing all haplotypes carrying the SNP rs7903146 ancestral T allele as a T2D risk variant that is referred to as HapBT2D. The second major lineage, HapA, comprises a cluster of relatively homogeneous haplotypes and is notably divergent from HapB. It exhibits a star-type diversity pattern consistent with a natural selection pattern, and it contains a base haplotype included in 81% of its haploid chromosomes. Among the HapMap populations, the frequency of the HapA lineage presents an unusual degree of divergence that ranges from 10% in the Yoruba population of Nigeria (YRI) to 58% in a population of European ancestry from a Utah pedigree of Centre d'Etude du Polymorphisme Humain (CEU) and 95% in the East Asian group of the Chinese Han of Hong Kong (CHB) and of the Japanese population of Tokyo (JPT). The frequency of the risk variant HapBT2D in the HapMap group of Asians (CHB + JPT) is ∼5% (39).

HapBT2D is the genetic factor conferring the greatest risk for T2D, and it is negatively associated with BMI (39), showing that *TCF7L2* may play a role in T2D, which is usually associated with hyperinsulinemia. In in vitro studies, insulin reduced *TCF7L2* mRNA expression, and this effect was reduced with free fatty acids. In in vivo studies comparing the subcutaneous adipose tissue (SAT) of insulin-resistant subjects versus insulin-sensitive subjects, *TCF7L2* mRNA was significantly more expressed in the SAT of the insulin-resistant individuals, implicating a role for this gene in insulin resistance, although no correlations between *TCF7L2* mRNA expression and obesity measures were observed. Also, *TCF7L2* expression was higher in visceral adipose tissue than in SAT, and in stratifying for haplotypes, this difference was seen in HapA carriers but not in non–HapA carriers, indicating a possible HapA role in the *TCF7L2* expression in visceral adipose (40).

TCF7L2 gene variants may confer a genetic risk for becoming overweight. Men with the HapBT2D variation have a lower BMI, and, in contrast, men with the HapA genetic variation have a higher BMI. Researchers have inferred that individuals with the HapA genetic variation were at an advantage in past centuries because they were able to form fat reserves that allowed them to survive periods of famine (39). To obtain a better picture of the role of natural selection in different ethnic groups, Acosta et al. (41) sequenced the exome of the *TCF7L2* gene using the Sanger method. They reported a lack of diversity in intronic region 4–6 in indigenous populations. This characteristic could be an effect of selective sweeps generated by the selection of neighboring rare variants at T2D-associated variations. The abundance of selective peak sweeps in the downstream region of the *TCF7L2* gene suggests that the gene is part of a region that is in constant recombination between populations (41).

Alternative Splicing

Alternative splicing is a mechanism by which multiple transcripts are generated from a unique gene, increasing the amount of different functional protein isoforms, some of which are associated with metabolic diseases (42). Prokunina-Olsson et al. (42) described tissue-specific *TCF7L2* splicing patterns in various tissues and cells (pancreas, pancreatic islets, skeletal muscle, cutaneous adipose tissue, colon, liver, monocytes, and lymphoblastic cell lines). They identified a unique *TCF7L2* "13-13b" splicing

form expressed in the pancreas, pancreatic islets, and colon; the "13-13b" splicing form is correlated with the concentration of proinsulin in glucose-stimulated pancreatic islets, suggesting its key role in glucose regulation and thus in the development of T2D. Further, *TCF7L2* rs7903146-genotype was associated with alternative splicing patterns in SAT (43). However, when Prokunina-Olsson et al. (44) analyzed *TCF7L2* expression in both visceral adipose tissue and SAT in obese individuals, they found that alternative *TCF7L2* splicing forms have different functions in each of these tissues. Kaminska et al. (45) showed that weight loss after gastric bypass surgery led to the differential expression of *TCF7L2* mRNA isoforms in SAT. Specifically, they found that an adipose tissue–specific variant incorporating exons 12 and 13 was increased after surgery; this splicing form variant is more common in SAT of patients with T2D, and it shows a positive correlation with free fatty acid during insulin clamps. Chen et al. (22) showed that total *TCF7L2* expression is reduced ∼20% in adipose tissue of subjects with impaired glucose tolerance and adipose insulin resistance. Nevertheless, they did not find differential expression of transcripts incorporating exon 12 and 13 because this variant also was reduced in the adipose tissue of subjects with impaired glucose tolerance. Another study also showed reduced *TCF7L2* mRNA levels in adipose tissue of patients with diabetes. The same pattern is observed in carriers of the rs7903146 T2D risk allele (43). These results support the idea that adipose tissue insulin sensitivity does not regulate *TCF7L2* gene splicing (22). More research is needed in this area to define the mechanisms involved in the complicated *TCF7L2* splicing pattern that contributes to the pathophysiology of T2D.

Pharmacokinetics

TCF7L2 rs12255372-T and rs7903146-T variants modestly influence initial therapeutic success with sulfonylureas, a class of oral hypoglycemic agents stimulating insulin release. In one study, the sulfonylurea therapeutic effect mediated by *TCF7L2* rs12255372-T was twofold greater than the treatment failure present in 12% of the population homozygote for the wild-type allele, whereas the association between the *TCF7L2* genotype and metformin treatment was very weak (46). The observed differences in treatment response indicate that diabetogenes may be an important contributor to the interindividual treatment response variability (47). In Chinese T2D patients, the intronic *TCF7L2* SNP rs290487-CT has been reported to influence the therapeutic efficacy of repaglinide, an oral agent of the meglitinide class of short-acting insulin secretagogues (48). Based on available studies, evaluating the correlation of *TCF7L2* gene variants with therapeutic responses is difficult due to differences in study design, definitions of clinical end points, sample sizes, and types and doses of therapies used (47,49).

Conclusions

TCF7L2 is the most potent locus known for T2D risk. The *TCF7L2* gene is a downstream effector of the canonical Wnt/β-catenin signaling pathway, which permits *TCF7L2* to control a great variety of functions by virtue of the complexity of its expression with numerous mRNA isoforms. This gene has been associated with several fundamental processes, including adipogenesis, natural selection, and alternative splicing, and various and diverse diseases, including different types of cancer. Continued efforts are underway to understand the genomic variation associated with T2D and its functional implications. Future interinstitutional collaborations are needed to guarantee that the clinical translation of this knowledge leads to improved patient care.

Perspectives

Resequencing of the *TCF7L2* gene in diverse ethnic groups will allow identification of common and rare genetic variants that contribute to the pathogenesis of T2D. It will be important to follow up on the newly discovered variants with functional and physiological studies to gain insights into diabetes-related molecular pathways. Developing therapies modulating *TCF7L2* expression may provide opportunities to treat T2D patients carrying a *TCF7L2* risk allele. The role that *TCF7L2* variants play in complex regulatory functions has been little explored, and further studies are required. Despite the *TCF7L2* genetic role in T2D has been widely confirmed in several populations, the relevance of ethnic differences remains to be determined.

To provide more personalized treatments and improve patients' quality of life, it is important to explore the role of new common and rare variants at the *TCF7L2* locus in diverse ethnic groups in combination with the novel clusters reported.

Funding. E.M.-M. is supported by Consejo Nacional de Ciencia y Tecnología (CONACYT) (258589). C.G. is supported by National Institute of Child Health and Human Development grant 5R01HD086911-02 (Principal Investigator).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Grant SF, Thorleifsson G, Reynisdottir I, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 2006; 38:320–323

2. Sladek R, Rocheleau G, Rung J, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature 2007;445:881–885

3. van Amerongen R, Nusse R. Towards an integrated view of Wnt signaling in development. Development 2009;136:3205–3214

4. Lucero OM, Dawson DW, Moon RT, Chien AJ. A re-evaluation of the "oncogenic" nature of Wnt/beta-catenin signaling in melanoma and other cancers. Curr Oncol Rep 2010;12:314–318

5. Wenzel J, Rose K, Haghighi EB, et al. Loss of the nuclear Wnt pathway effector TCF7L2 promotes migration and invasion of human colorectal cancer cells. Oncogene 2020;39:3893–3909

6. Duval A, Busson-Leconiat M, Berger R, Hamelin R. Assignment of the TCF-4 gene (TCF7L2) to human chromosome band 10q25.3. Cytogenet Cell Genet 2000;88:264–265
7. Duval A, Rolland S, Tubacher E, Bui H, Thomas G, Hamelin R. The human T-cell transcription factor-4 gene: structure, extensive characterization of alternative splicings, and mutational analysis in colorectal cancer cell lines. Cancer Res 2000;60:3872–3879
8. Reynisdottir I, Thorleifsson G, Benediktsson R, et al. Localization of a susceptibility gene for type 2 diabetes to chromosome 5q34-q35.2. Am J Hum Genet 2003;73:323–335
9. Zeggini E, McCarthy MI. TCF7L2: the biggest story in diabetes genetics since HLA? Diabetologia 2007;50:1–4
10. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet 2018;50:1505–1513
11. Tong Y, Lin Y, Zhang Y, et al. Association between TCF7L2 gene polymorphisms and susceptibility to type 2 diabetes mellitus: a large Human Genome Epidemiology (HuGE) review and meta-analysis. BMC Med Genet 2009;10:15
12. Haddad SA, Palmer JR, Lunetta KL, Ng MC, Ruiz-Narváez EA; MEDIA Consortium. A novel TCF7L2 type 2 diabetes SNP identified from fine mapping in African American women. PLoS One 2017;12:e0172577
13. Uribe-Salazar JM, Palmer JR, Haddad SA, Rosenberg L, Ruiz-Narváez EA. Admixture mapping and fine-mapping of type 2 diabetes susceptibility loci in African American women. J Hum Genet 2018;63:1109–1117
14. Chang YC, Chang TJ, Jiang YD, et al. Association study of the genetic polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes in the Chinese population. Diabetes 2007;56:2631–2637
15. Ng MC, Tam CH, Lam VK, So WY, Ma RC, Chan JC. Replication and identification of novel variants at TCF7L2 associated with type 2 diabetes in Hong Kong Chinese. J Clin Endocrinol Metab 2007;92:3733–3737
16. Lehman DM, Hunt KJ, Leach RJ, et al. Haplotypes of transcription factor 7-like 2 (TCF7L2) gene and its upstream region are associated with type 2 diabetes and age of onset in Mexican Americans. Diabetes 2007;56:389–393
17. Guinan KJ. Worldwide distribution of type II diabetes-associated TCF7L2 SNPs: evidence for stratification in Europe. Biochem Genet 2012;50:159–179
18. Fernández-Rhodes L, Howard AG, Graff M, et al. Complex patterns of direct and indirect association between the transcription factor-7 like 2 gene, body mass index and type 2 diabetes diagnosis in adulthood in the Hispanic Community Health Study/Study of Latinos. BMC Obes 2018;5:26
19. Savic D, Park SY, Bailey KA, Bell GI, Nobrega MA. In vitro scan for enhancers at the TCF7L2 locus. Diabetologia 2013;56:121–125
20. MacDonald BT, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell 2009;17:9–26
21. Mao CD, Byers SW. Cell-context dependent TCF/LEF expression and function: alternative tales of repression, de-repression and activation potentials. Crit Rev Eukaryot Gene Expr 2011;21:207–236
22. Chen X, Ayala I, Shannon C, et al. The diabetes gene and Wnt pathway effector TCF7L2 regulates adipocyte development and function. Diabetes 2018;67:554–568
23. Qin L, Chen Y, Niu Y, et al. A deep investigation into the adipogenesis mechanism: profile of microRNAs regulating adipogenesis by modulating the canonical Wnt/beta-catenin signaling pathway. BMC Genomics 2010;11:320
24. Ouyang D, Xu L, Zhang L, et al. MiR-181a-5p regulates 3T3-L1 cell adipogenesis by targeting Smad7 and Tcf7l2. Acta Biochim Biophys Sin (Shanghai) 2016;48:1034–1041
25. Landrier JF, Derghal A, Mounien L. MicroRNAs in obesity and related metabolic disorders. Cells 2019;8:859
26. Geoghegan G, Simcox J, Seldin MM, et al. Targeted deletion of Tcf7l2 in adipocytes promotes adipocyte hypertrophy and impaired glucose metabolism. Mol Metab 2019;24:44–63
27. Korinek V, Barker N, Moerer P, et al. Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4. Nat Genet 1998;19:379–383
28. Sakhneny L, Rachi E, Epshtein A, et al. Pancreatic pericytes support β-cell function in a Tcf7l2-dependent manner. Diabetes 2018;67:437–447
29. Yi F, Brubaker PL, Jin T. TCF-4 mediates cell type-specific regulation of proglucagon gene expression by beta-catenin and glycogen synthase kinase-3beta. J Biol Chem 2005;280:1457–1464
30. Chiang YT, Ip W, Jin T. The role of the Wnt signaling pathway in incretin hormone production and function. Front Physiol 2012;3:273
31. da Silva Xavier G, Loder MK, McDonald A, et al. TCF7L2 regulates late events in insulin secretion from pancreatic islet beta-cells. Diabetes 2009;58:894–905
32. Norton L, Chen X, Fourcaudot M, Acharya NK, DeFronzo RA, Heikkinen S. The mechanisms of genome-wide target gene regulation by TCF7L2 in liver cells. Nucleic Acids Res 2014;42:13646–13661
33. Gaulton KJ, Nammo T, Pasquali L, et al. A map of open chromatin in human pancreatic islets. Nat Genet 2010;42:255–259
34. Wang J, Kuusisto J, Vänttinen M, et al. Variants of transcription factor 7-like 2 (TCF7L2) gene predict conversion to type 2 diabetes in the Finnish Diabetes Prevention Study and are associated with impaired glucose regulation and impaired insulin secretion. Diabetologia 2007;50:1192–1200
35. Gautier A, Roussel R, Lange C, et al. Effects of genetic susceptibility for type 2 diabetes on the evolution of glucose homeostasis traits before and after diabetes diagnosis: data from the D.E.S.I.R. study. Diabetes 2011;60:2654–2663
36. Liu PH, Chang YC, Jiang YD, et al. Genetic variants of TCF7L2 are associated with insulin resistance and related metabolic phenotypes in Taiwanese adolescents and Caucasian young adults. J Clin Endocrinol Metab 2009;94:3575–3582
37. Schäfer SA, Machicao F, Fritsche A, Häring HU, Kantartzis K. New type 2 diabetes risk genes provide new insights in insulin secretion mechanisms. Diabetes Res Clin Pract 2011;93(Suppl. 1):S9–S24
38. Then C, Wahl S, Kirchhofer A, et al. Plasma metabolomics reveal alterations of sphingo- and glycerophospholipid levels in non-diabetic carriers of the transcription factor 7-like 2 polymorphism rs7903146. PLoS One 2013;8:e78430
39. Helgason A, Pálsson S, Thorleifsson G, et al. Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. Nat Genet 2007;39:218–225
40. Ahlzén M, Johansson LE, Cervin C, Tornqvist H, Groop L, Ridderstråle M. Expression of the transcription factor 7-like 2 gene (TCF7L2) in human adipocytes is down regulated by insulin. Biochem Biophys Res Commun 2008;370:49–52
41. Acosta JL, Hernández-Mondragón AC, Correa-Acosta LC, et al. Rare intronic variants of TCF7L2 arising by selective sweeps in an indigenous population from Mexico. BMC Genet 2016;17:68
42. Prokunina-Olsson L, Kaplan LM, Schadt EE, Collins FS. Alternative splicing of TCF7L2 gene in omental and subcutaneous adipose tissue and risk of type 2 diabetes. PLoS One 2009;4:e7231
43. Mondal AK, Das SK, Baldini G, et al. Genotype and tissue-specific effects on alternative splicing of the transcription factor 7-like 2 gene in humans. J Clin Endocrinol Metab 2010;95:1450–1457
44. Prokunina-Olsson L, Hall JL. Evidence for neuroendocrine function of a unique splicing form of TCF7L2 in human brain, islets and gut. Diabetologia 2010;53:712–716
45. Kaminska D, Kuulasmaa T, Venesmaa S, et al. Adipose tissue TCF7L2 splicing is regulated by weight loss and associates with glucose and fatty acid metabolism. Diabetes 2012;61:2807–2813
46. Florez JC, Jablonski KA, Bayley N, et al.; Diabetes Prevention Program Research Group. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med 2006;355:241–250

47. Zimdahl H, Ittrich C, Graefe-Mody U, et al. Influence of TCF7L2 gene variants on the therapeutic response to the dipeptidylpeptidase-4 inhibitor linagliptin. Diabetologia 2014;57:1869–1875
48. Yu M, Xu XJ, Yin JY, et al. KCNJ11 Lys23Glu and TCF7L2 rs290487(C/T) polymorphisms affect therapeutic efficacy of repaglinide in Chinese patients with type 2 diabetes. Clin Pharmacol Ther 2010;87:330–335
49. Pearson ER, Donnelly LA, Kimber C, et al. Variation in TCF7L2 influences therapeutic response to sulfonylureas: a GoDARTs study. Diabetes 2007;56: 2178–2182
50. Ding M, Wang X. Antagonism between Hedgehog and Wnt signaling pathways regulates tumorigenicity. Oncol Lett 2017;14: 6327–6333