What Can Diabetes-Associated Genetic Variation in *TCF7L2* Teach Us About the Pathogenesis of Type 2 Diabetes?

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Abstract

Type 2 diabetes mellitus (T2DM) is a polygenic metabolic disorder characterized by hyperglycemia occurring as a result of impaired insulin secretion and/or insulin resistance. Among the various genetic factors associated with T2DM, a common genetic variant within the transcription factor 7-like 2 locus (*TCF7L2*) confers the greatest genetic risk for development of the disease. However, the mechanism(s) by which *TCF7L2* predisposes to diabetes remain uncertain. Here we review the current literature pertaining to the potential mechanisms by which *TCF7L2* confers risk of T2DM, using genetic variation as a probe to understand the pathogenesis of the disease.

Keywords: common genetic variation, insulin secretion, insulin action, type 2 diabetes

Introduction

TYPE 2 DIABETES MELLITUS (T2DM) is a widely recognized public health issue affecting more than 170 million individuals worldwide; treatment of the disease and its complications costs in excess of ~\$170 billion/year.¹ It is a disease characterized (and defined) by hyperglycemia that arises from defects in insulin secretion and action,² impaired glucose effectiveness, and impaired postprandial suppression of glucagon.^{3,4} T2DM results from a complex interaction between genes and the environment.

It has been estimated that 30%–70% of T2DM risk can be attributed to heredity,⁵ and over the past decade, candidate gene studies and genome-wide association scans have associated >65 common (defined as a population frequency >5%) single nucleotide polymorphisms (SNPs)⁶ with T2DM. Polymorphisms in loci such as *PPARG* and *KCNJ11*, as well as in *HNF4A*, have been associated with the development of T2DM.⁵ Of the common variants reproducibly associated with T2DM,⁷ transcription factor 7-like 2 (*TCF7L2*) arguably confers the greatest risk of T2DM. The TT genotype at rs7903146 (within the *TCF7L2* locus) increases the risk of T2DM twofold. Although certain uncommon (<5% in a population) variants have greater effects on disease predisposition than does *TCF7L2*,⁸ variants associated with T2DM are usually common and occur in loci previously associated with type 2 diabetes.⁹ Diabetes-

associated variation in *TCF7L2* is not useful in predicting progression to diabetes¹⁰ or individual responses to pharmacotherapy,¹¹ but it can serve as a probe to understand that pathogenesis of T2DM.^{12,13}

The Association of the *TCF7L2* Locus with Type 2 Diabetes

Duggirala et al.¹⁴ first reported linkage of a region on chromosome 10q with T2DM in Mexican Americans. Subsequently, Reynisdottir et al.¹⁵ also found evidence for linkage of this region (10q) with T2DM in an Icelandic cohort. In 2006 Grant et al.¹⁶ genotyped 228 microsatellite markers across this region in an Icelandic population. The microsatellite, DG10S478, located within intron 3 of *TCF7L2*, was associated with T2DM. Fine-mapping of this region identified two SNPs, rs12255372 and rs7903146, in strong linkage disequilibrium with DG10S478 which were most strongly associated with T2DM. When compared with noncarriers, heterozygous and homozygous carriers of the at-risk alleles (38% and 7% of the population, respectively) had relative risks of T2DM of 1.45 and 2.41, respectively, corresponding to a population-attributable risk of 21%.¹⁶

Since then, other efforts at fine-mapping of the association of *TCF7L2* with T2DM have concluded that if rs7903146 is not the disease-causing variant it is indistinguishable from the etiologic variant due to tight linkage

disequilibrium.^{17–19} In Asian populations, polymorphisms at rs7903146 and rs12255372 are infrequent, although an association of T2DM with these variants has been confirmed in two large Japanese cohorts.^{20,21} It is notable that variation in *TCF7L2* does not confer risk for T2DM in Pima Indians,²² suggesting that the pathogenesis of T2DM differs from that in (most) other populations.

rs7903146 is located within an intronic region, raising questions as to the ultimate mechanism by which this variant confers risk of T2DM. One potential mechanism is by affecting the distribution of splice variants of *TCF7L2* in adipose^{23,24} or in pancreatic islets.²⁵ More recently, it has been suggested that rs7903146 resides in an element that controls the expression of *ACSL5*. *ACSL5* encodes an enzyme that is important during the re-esterification of dietary fatty acids into triglycerides.²⁶ However, there are some important caveats to consider before accepting this conclusion²⁷; most notable among them is the observation that *ACSL5*^{−/−} mice exhibit alterations in insulin action. This is a parameter that is not reliably associated with diabetes risk conferred by the T allele at rs7903146.

Latent autoimmune diabetes in adults (LADA) is a clinical presentation of diabetes that shares clinical features with T2DM and with type 1 diabetes mellitus (T1DM). Most of the available evidence suggests that it is a *forme fruste* of T1DM, with an autoimmune etiology, the presence of islet autoantibodies, and a similar genetic predisposition. However, in some cohorts of subjects with LADA a similar increase was observed in the frequency of the T allele at rs7903146 as that observed in T2DM. This has prompted a fresh look at the genetic architecture and pathogenesis of LADA.²⁸

The role of *TCF7L2*-in vitro and in vivo evidence

In both rodent islets and pancreatic β cell lines, *TCF7L2* knockdown decreases glucose induced, but not KCL-induced, insulin secretion. In addition, a pancreas-specific knockout of *TCF7L2*,²⁹ leads to glucose intolerance and decreased β cell mass when animals are fed a high fat diet. *TCF7L2* also affects α cell mass and glucagon expression.³⁰ However, Lyssenko et al.³¹ reported that isolated islets from patients with T2DM had fivefold higher *TCF7L2* RNA concentrations than those from nondiabetic subjects. RNA concentrations increased as a function of the number of T alleles present.

TCF7L2^{−/−} are hypoglycemic at birth, have intestinal hypoplasia, and die within 8–10 hr of birth.³² Heterozygous mice (*TCF7L2*^{+/-}) are viable and grow normally, but have lower circulating glucose and insulin concentrations due to increased insulin action. They are resistant to the effects of a high fat diet.³³ However, mice that overexpress *TCF7L2* are glucose intolerant due to insulin resistance, indicating that overexpression of *TCF7L2* leads to a T2DM phenotype.³⁴ Boj et al.³⁵ reported that β cell-specific deletion of *TCF7L2* generated no effect on metabolic homeostasis. This is in contrast with the results reported by da Silva Xavier²⁹ and Mitchell et al.,³⁶ who found that β cell-specific deletion of *TCF7L2* resulted in impaired β cell function. The reasons for these differences are uncertain but could be attributable to differences in the methods utilized to delete *TCF7L2*. However, deletion in the β cells of adult mice using a tamoxifen-inducible rat insulin promoter 2-driven (RIP2.Cre-ERT2) also had no apparent effect on glucose homeostasis.³² These studies focused on relatively young (<12 weeks old) mice main-

tained on a normal diet. The time of gene deletion precluded examination of the effects on β cell proliferation during early postnatal growth. Recently, Sakhneny et al.³⁷ identified *TCF7L2*-dependent pericyte expression of secreted factors shown to promote β cell function, including bone morphogenetic protein 4 (BMP4). Since BMP4 can restore impaired glucose-stimulated insulin secretion in mice, this is a potential mechanism through which extra-islet *TCF7L2* activity could still affect β cell function. It is possible that *TCF7L2* plays key roles in glucose metabolism through actions beyond pancreatic β cells; mice overexpressing *TCF7L2* in peripheral tissues, but not in β cells, develop impaired insulin secretion due to loss of β cells.³⁸

At the present time, it is still unclear whether *TCF7L2* expression is increased or decreased in diabetes or in a diabetogenic environment (*e.g.*, high fat diet). The apparent discordance in animal models and the limitations of global deletion, targeted organ-specific deletion, or overexpression may not reproduce the effects of diabetes-associated variation in humans which likely produce subtle physiologic abnormalities given their relatively weak effects on disease predisposition. Accordingly, characterization of the diabetogenic effects of the T allele at rs7903146 are best served by detailed genotype-phenotype studies in humans.

The role of *TCF7L2* in the Wnt signaling pathway

Ni et al.³⁹ first reported that lithium [an inhibitory agent of glycogen synthase kinase-3 β (GSK-3 β)] and β -catenin/T cell factor (β -cat/TCF) selectively upregulates proglucagon gene transcription and GLP-1 synthesis in enteroendocrine cells, but not in α cells. This implies that proglucagon is differentially regulated in these two tissues. Subsequently, the same group demonstrated that *TCF7L2* is required for proglucagon expression in enteroendocrine cells, but not in pancreatic islets, in keeping with its expression patterns.⁴⁰ *TCF7L2* is part of the Wnt signaling pathway which regulates organogenesis.^{25,41,42} When a Wnt ligand binds to a frizzled receptor, it leads to the activation of either the canonical (β -catenin)-dependent or noncanonical (β -catenin-independent) Wnt signaling pathways.²⁵ For the purpose of this brief review we will be focusing on the role of *TCF7L2* in the canonical pathway. The key effector of this pathway is the complex formed by free β -catenin and one of the TCF family members [*TCF7L2*,^{32,40} *TCF7L1*, and Lymphoid Enhancer Binding Factor 1 (LEF-1)]. TCFs possess a high mobility group box DNA binding domain. β -catenin interacts with Forkhead box proteins (FoxOs), serving as a co-factor for FoxOs in mediating various signals—for example stimulating gluconeogenic gene expression.²⁵

In resting cells, the proteasome-mediated degradation process tightly controls the level of free β -catenin. This involves the actions of members of the β -catenin “destructive complex” (Fig. 1A), which includes two tumor suppressors known as adenomatous polyposis coli and Axin/conductin, as well as the serine/threonine kinases GSK-3 and casein kinase 1 α (CK-1 α).^{25,41,42}

Following Wnt ligand stimulation, an association is established between the Wnt receptor and *Dishevelled* (Dvl) that triggers the dissociation of the β -catenin “destructive complex.” Free β -catenin then accumulates and enters the nucleus, resulting in the formation of β -catenin/TCF complex and the activation of downstream target genes (Fig. 1B). The

FIG. 1. Summary of the canonical WNT pathway. (A) In the absence of WNT stimulation, β -cat is located within the “destructive complex”, phosphorylated by GSK-3, CK-1 α , and pERK, and subsequently destroyed by proteasome-mediated protein degradation. (B) Following WNT stimulation, the phosphorylation/destructive complex disassembles. This results in an accumulation of free β -cat, which enters the nucleus and forms the bipartite transcription factor β -cat/TCF7L2, leading to enhanced expression of the WNT target genes. CK-1 α , casein kinase 1 α ; GSK-3, glycogen synthase kinase-3; TCF7L2, transcription factor 7-like 2 locus.

proglucagon gene promoter is one of many downstream targets of the Wnt signaling pathway.

Murtaugh et al.⁴³ showed that pancreatic β -catenin deletion did not perturb pancreatic islet endocrine cell mass or function, although β -catenin is essential for acinar cell differentiation. On the other hand, β -catenin deletion impairs pancreatic development by affected cells.⁴⁴ However, although the number of islets in early embryonic development was reduced, later developmental stages exhibited normal pancreata developed from cells without β -catenin deletion.⁴⁴ Functional studies using a β -catenin mutant confirm a role of Wnt signaling in pancreatic growth and development,⁴⁵ including that of β cells.

These effects are not confined to islet cells. Ross et al.⁴⁶ showed that when Wnt signaling in preadipocytes is inhibited, these cells differentiate into adipocytes. Disruption of Wnt signaling also causes trans-differentiation of myoblasts into adipocytes *in vitro*, highlighting the importance of this pathway to mesodermal cell fate. The role of the Wnt

signaling pathway in adipogenesis and osteogenesis have been extensively reviewed elsewhere.^{25,41}

TCF7L2 genotype–phenotype experiments in humans

The association of the *TCF7L2* locus with type 2 diabetes was first validated independently in the Diabetes Prevention Program, where data from an oral glucose tolerance test suggested that the diabetes-associated alleles were associated with decreased insulin secretion.¹³ Unfortunately, the methodology used to measure insulin secretion was qualitative—the investigators used the difference in insulin concentrations measured during fasting and at (presumed) peak (30 min) concentrations after an oral glucose challenge. The change in insulin concentrations was then divided by the equivalent change in glucose concentrations. Unfortunately, these measures do not necessarily reflect insulin secretion: insulin

FIG. 2. Schematic representing various factors that affect glucose tolerance. S_g represents the action of glucose effectiveness. Elements affected by risk allele of *TCF7L2* represented by asterisk (*).

concentrations are the result of three processes—insulin secretion into the portal vein, hepatic extraction of insulin, and clearance of insulin from the peripheral circulation.

Hepatic extraction is unlikely to be passive, and in fact there is evidence to suggest that it changes with alterations in β cell function.^{47,48} In addition, to truly quantify β cell function, it is necessary to express insulin secretion as a function of the prevailing insulin action.⁴⁹ Accordingly, although these observations have been independently replicated, caution is required before blanket acceptance that *TCF7L2* confers diabetes risk (solely) by impairing insulin secretion.²³

What are the factors driving glucose tolerance? Stimulation of insulin secretion and suppression of glucagon secretion are important and known to be defective in T2DM.⁵⁰ Additionally, the ability of insulin to stimulate glucose uptake and suppress endogenous glucose production (EGP)

(insulin action or insulin sensitivity) is also impaired in T2DM. Glucose effectiveness is the ability of glucose to stimulate its own uptake and suppress its own release. This is also impaired in diabetes.⁵¹ The other parameter determining glucose tolerance is the rate of gastric emptying and intestinal absorption (of calories) (Fig. 2). We shall therefore consider the known effects (if any) of diabetes-associated variation in *TCF7L2* on these individual parameters in turn (Table 1).

Several studies have examined insulin secretion using an intravenous glucose tolerance test (IVGTT) and, subsequently, using the minimal model to estimate insulin secretion and action. The minimal model applied to IVGTT data enables assessment of insulin sensitivity,² which has been validated against the hyperinsulinemic clamp.⁵² Damcott et al.⁵³ was one of the first to observe an association between

TABLE 1. THE EFFECT OF DIABETES-ASSOCIATED VARIATION IN *TCF7L2* ON THE VARIOUS PARAMETERS AFFECTING GLUCOSE TOLERANCE AS STUDIED IN HUMAN SUBJECTS

	Citation	Model	Conclusions ^a
Insulin secretion	Florez et al. ¹³	OGTT	T allele at rs7903146 associated with ↓ insulin concentrations
	Damcott et al. ⁵³	OGTT; IVGTT	OGTT ↔; IVGTT: ↓ β cell function
	Munoz et al. ⁵⁴	IVGTT	T allele at rs7903146 associated with ↓ AIRg
	Wegner et al. ⁵⁶	OGTT; IVGTT	OGTT: ↓ β cell function; IVGTT: ↓ β cell function
	Schafer et al. ⁵⁷	OGTT, IVGTT, Hyperglycemic clamp	OGTT: ↓ insulin concentrations; IVGTT/clamp: ↔
	Pilgaard et al. ⁶²	OGTT, IVGTT, Hyperglycemic clamp, MMTT	OGTT: ↔; Clamp ↔; MMTT: ↓ insulin concentrations
	Lyssenko et al. ³¹	OGTT, IVGTT	OGTT: ↓ insulin concentrations; IVGTT: ↓ insulin concentrations
GLP-1 secretion	Shah et al. ¹²	OGTT	OGTT: ↓ β cell responsivity to glucose
	Ingelsson et al. ⁶⁸	OGTT, euglycemic clamp, IVGTT	T allele at rs7903146 associated with ↓ insulin concentrations
	Schafer et al. ⁵⁷	OGTT	No effect of genotype on postprandial GLP-1 concentrations
	Smushkin et al. ⁵⁸	OGTT	
	Daniele et al. ⁵⁹	MMTT	
	Gjesing et al. ⁶⁰	MMTT	
GLP-1 response	Silbernagel et al. ⁶¹	OGTT	T allele at rs7903146 associated with ↓ ISR during GLP-1 infusion
	Pilgaard et al. ⁶²	Hyperglycemic clamp ± GLP-1	
	Schafer et al. ⁵⁷		
	Smushkin et al. ⁵⁸		
Insulin action	Rasmussen-Torvik et al. ⁶³	Euglycemic clamp	No association between insulin action and rs7903146
	Pilgaard et al. ⁶²	Euglycemic clamp	↑ EGP in subjects with T allele at rs7903146
	Lyssenko et al. ³¹	OGTT, euglycemic clamp	
	Elbein et al. ²³	IVGTT	OGTT, no differences in HOMA-IR; Clamp, ↑ EGP in subjects with TT genotype at rs7903146
	Shah et al. ¹²	OGTT, Glycerol, FFA	Reduced S_i in subjects with TT genotype at rs7903146
	Ingelsson et al. ⁶⁸	OGTT, euglycemic clamp, IVGTT	No effect on S_i
			No association between rs7903146 and insulin action
Glucagon suppression	Smushkin et al. ⁵⁸	Hyperglycemic clamp ± GLP-1	Impaired suppression of glucagon by glucose in subjects with TT genotype at rs7903146
	Shah et al. ¹²	OGTT	Impaired glucagon suppression in subjects with TT genotype at rs7903146

^a ↓ = reduced; ↑ = increased; ↔ = no effect.

AIR_g, acute insulin response to glucose; EGP, endogenous glucose production; HOMA-IR, homeostasis model assessment—insulin resistance; ISR, insulin secretion rate; IVGTT, intravenous glucose tolerance test; MMTT, mixed meal tolerance test; OGTT, oral glucose tolerance test; S_i , insulin action; *TCF7LC2*, transcription factor 7-like 2 locus.

rs7901695 and rs7903146 and insulin sensitivity and disposition index (DI) using this methodology. Munoz et al.⁵⁴ reported a 31% reduction in DI values for the TT allele in European Americans and African Americans using a similar model. The at-risk allele was also associated with lower acute insulin response to glucose when adjusted for insulin action (S_i) in both ethnic groups. This has also been observed in other studies using IVGTT, where associations between the risk allele and glucose-stimulated insulin secretion are observed.^{55,56}

These studies suggest that progressive loss of insulin secretion might be the essential component of the phenotype that predisposes carriers of the *TCF7L2* variant to develop T2DM, although the ultimate mechanism by which insulin secretion is impaired by diabetes-associated variation in *TCF7L2* is as yet unknown.

Schafer et al.⁵⁷ suggested that diabetes-associated variation in *TCF7L2* impairs GLP-1 but not glucose-induced insulin secretion. In contrast, Smushkin et al.,⁵⁸ using a similar design, failed to demonstrate impaired responsiveness to GLP-1 infusion that is attributable to *TCF7L2*. Most,^{59–61} but not all,⁶² studies well-powered to detect small effects on GLP-1 concentrations have failed to demonstrate an association between *TCF7L2* and GLP-1 secretion in response to an oral challenge.

Previous investigators^{54,63} have reported that variation in *TCF7L2* does not alter insulin action. However, Rasmussen-Torvik et al.⁶³ used insulin concentrations (1 mU/kg/min) during a euglycemic clamp that result in maximum suppression of EGP, thereby precluding assessment of hepatic insulin action. Pilgaard et al.⁶² reported increased fasting EGP in a cohort of 37 males heterozygous or homozygous for the T allele at rs7903146. In this experiment, low-dose insulin infusion (0.3 mU/kg/min) suppressed EGP equally regardless of the presence or absence of the diabetes-associated allele at *TCF7L2*, whereas the effects of high-dose insulin (1 mU/kg/min) were impaired in people with diabetes-associated variation in *TCF7L2*. Lyssenko et al.³¹ studied a larger cohort composed of subjects with diabetes, impaired glucose tolerance, or normal glucose tolerance and reported higher basal EGP in individuals with one or two copies of the T allele.

Shah et al.¹² reported that insulin action was unaffected by genotype during an oral glucose challenge, alone or in combination with free fatty acid elevation to induce insulin resistance. Since *TCF7L2* may alter the relative contributions of gluconeogenesis and glycogenolysis to EGP⁶⁴ through its regulation of multiple genes associated with hepatic glucose metabolism, we used the deuterated water technique to measure gluconeogenesis and glycogenolysis. The diabetes-associated variant at rs7903146 was not associated with changes in fasting EGP, gluconeogenesis, and glycogenolysis.⁶⁵ Similarly, there was no effect on insulin-induced suppression of these parameters.

There has been limited examination of the effects of *TCF7L2* on glucose effectiveness (S_g).⁵¹ Elbein et al.²³ reported no effect of the diabetes-associated allele in *TCF7L2* on S_g using the minimal model to analyze IVGTT data. In one study, the T allele was associated with fasting gastric volume and emptying of liquids from the stomach.⁶⁶ However, this has not been independently validated and at present its significance is uncertain.

People with T2DM exhibit impaired postprandial suppression of glucagon.^{3,4} Smushkin et al. first demonstrated

that despite no differences in fasting glucagon values between genotype groups, in the presence of hyperglycemia, glucagon suppression was impaired in subjects homozygous for the T allele.⁵⁸ A subsequent study using an oral challenge demonstrated similar findings¹²; although fasting and nadir glucagon did not differ between genotypes, post-challenge suppression of glucagon was impaired in the subjects with a TT genotype at rs7903146. In the presence of acute insulin resistance, induced by free fatty acid elevation, fasting glucagon concentrations increased to a greater extent in the TT group than in those with the CC genotype. These observations are supported by the report that in islets from nondiabetic TT donors, the relative α cell population is increased compared with matched CC donors, whereas the relative β cell population is reduced.⁶⁷

Conclusions

Within the last decade, our understanding of the genetic basis of T2DM has grown significantly; however, much remains to be elucidated. Of the possible SNPs that have been associated with T2DM, *TCF7L2* confers the greatest risk for development of the disease. The data to date have suggested that its effects are mainly mediated through changes in β cell function. However, there is some evidence to suggest that diabetes predisposition may also be mediated through effects on α cell function raising the possibility that α cell dysfunction contributes to the early development of T2DM.

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