Possible role of \textit{TCF7L2} in the pathogenesis of type 2 diabetes mellitus

Zhi-qiu Huang, Yao-qi Liao, Run-ze Huang, Jin-peng Chen and Hui-lin Sun

Department of Endocrinology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, PR China

\textbf{ABSTRACT}

With people’s changing life style and dietary habits, the prevalence of type 2 diabetes mellitus (T2DM) has become much more serious than ever before. T2DM is a polygenic metabolic disorder, resulting from the interaction of genetic and various environmental factors. Among all the T2DM related genes, the transcription factor 7 like 2 (\textit{TCF7L2}) gene is one of the most relevant risk-related genes for T2DM. However, the role of \textit{TCF7L2} in T2DM pathogenesis has not yet been interpreted thoroughly. Based on the experimental studies in recent years, this review discusses several possible mechanisms of T2DM pathogenesis induced by \textit{TCF7L2}.

\textbf{Introduction}

The prevalence of diabetes has increased significantly in recent years, with the development of social economy and the acceleration of the global ageing process. The first Chinese national diabetes prevalence survey showed that the diabetes prevalence was only 0.67% in 1980. In 2010, the estimated prevalence of diabetes among Chinese adults was 11.6% and the prevalence of prediabetes was 50.1% \cite{1}. Diabetes prevalence is rising across the globe, as the number of people with diabetes aged 20–79 years is predicted to rise to 642 million by 2040 globally \cite{2}. The healthcare costs related to diabetes could sum up to a considerable sum in the near future.

Type 2 diabetes mellitus (T2DM), characterized by hyperglycemia, impaired insulin secretion or insulin resistance, has accounted for more than 90% of the total diabetes cases. T2DM is a polygenic metabolic disorder, resulting from interaction of genetic and various environmental factors, including dietary intake. A study suggested that dietary fibre intake may modify the association between \textit{TCF7L2} rs7903146 and incidence of type 2 diabetes \cite{3}. The traditional treatments to T2DM, including oral antidiabetic drugs and insulin, used to achieve satisfactory therapeutic effects in controlling the progress of T2DM and preventing the occurrence of diabetic complications. However, these treatments did not prove competent for the incoming diabetic era. Thus, finding new treatment for T2DM was put on the agenda.

T2DM arises from the interplay of genetic and environmental factors, such as risk-related gene loci, obesity, lack of physical activity and high-calorie diet \cite{4}.

According to the genome-wide association study, there are around 100 variants at four loci associated with T2DM \cite{5}, which would provide a new way for people to understand the pathogenesis of T2DM at the gene level.

Among all the T2DM related genes, genetic variants in the transcription factor 7 like 2 (\textit{TCF7L2}) gene have been confirmed to be associated with T2DM among various ethnicities throughout the world \cite{6}. \textit{TCF7L2} is also known as \textit{TCF4} locus on chromosome 10q25.2–25.3 and encodes a high mobility group box-containing transcription factor, that is involved in the Wnt signaling pathway \cite{7}. In 2006, Grant et al. \cite{8} identified a microsatellite DG10S478 within intron 3 of \textit{TCF7L2} that was associated with type 2 diabetes in an Icelandic, Danish and US cohort. Further studies focused on five single nucleotide polymorphisms (SNPs) (rs12255372, rs7903146, rs7901695, rs11196205 and rs7895340) of \textit{TCF7L2} were conducted on different ethnicities \cite{9–15} and showed strong association between T2DM and \textit{TCF7L2} (Table 1).

Nevertheless, the exact mechanism for explaining the relationship between \textit{TCF7L2} and T2DM has not been interpreted thoroughly. In this paper, we aim to discuss the mechanisms underlying the involvement of \textit{TCF7L2} in the induction of T2DM by genetic mutation, Wnt signaling pathway and \(\beta\)-cell dysfunction.

\textbf{Possible role of \textit{TCF7L2} in the pathogenesis of T2DM}

\textbf{Genetic mutation in \textit{TCF7L2}}

As mentioned above, the most strongly associated T2DM locus resides within the \textit{TCF7L2} gene. The SNPs of the
**Table 1.** Significant TCF7L2 gene polymorphisms associated with T2DM in various ethnic groups.

| Polymorphism   | Ethnicity       | Significance | References                  |
|----------------|-----------------|--------------|-----------------------------|
| rs12255372     | European Caucasians | Y            | Wang et al. [9]             |
|                | Cameroonian     | Y            | Nanfa et al. [10]           |
| rs7903146      | French          | Y            | Cauchi et al. [11]          |
|                | South Indian    | Y            | Jyothi et al. [12]          |
| rs7901695      | African Americans | Y            | Sale et al. [13]            |
|                | Italian         | Y            | Cincia et al. [14]          |
| rs11196205     | Japanese        | Y            | Miyake et al. [15]          |
| rs7895340      | African Americans | Y            | Sale et al. [13]            |

**TCF7L2 gene confer T2DM risk to variant carriers.** Helgason et al. [16] refined the definition of the TCF7L2 type 2 diabetes risk variant to the ancestral T allele of a SNP, rs7903146, through replication in West African and Danish type 2 diabetes case-control studies and an expanded Icelandic study. Palmer et al. [17] evaluated 43 SNPs and the previously identified DG105478 microsatellite in African American and suggested that rs7903146 was the trait-defining polymorphism associated with type 2 diabetes risk. These studies interpret the intron 3 SNP rs7903146 as the causal variant within the TCF7L2 gene. However, the underlying functional mechanism to the association between variants and T2DM has remained elusive.

As the mutations in risk-related variants reside in an intronic region rather than an exon, it is reasonable to presume a regulatory process is involved in conferring T2DM risk [18]. Research indicates that the locus confers its T2DM risk by transcriptional protein complex binding across rs7903146 within TCF7L2 in a self-regulating manner [18]. Mondal et al. [19] suggested that intronic TCF7L2 variants might regulate alternative transcript isoforms, which in turn might have distinct physiologic roles in inducing T2DM. Acyl-CoA synthetases 5 (ACSL5) play an important role in lipid biosynthesis and fatty acid degradation, which could correlate with insulin resistance. Studies reported that better maintenance in glucose levels [20,21] and improvement in insulin sensitivity [20] in the whole-body ACSL5 knockout mice. Xia et al. [22] found that a causal variant within TCF7L2 resides in an element that controls the expression of ACSL5 and speculated that TCF7L2 regulates ACSL5 expression. Given the correlation between ACSL5 and insulin sensitivity, inhibiting ACSL5 enzyme activity to treat T2DM could be promising.

**Effector of Wnt signaling pathway**

TCF7L2 is a member of high-mobility group box-containing transcription factors and exerts its regulatory effect in the Wnt signaling pathway. The Wnt pathway plays an important role in pancreas islet cell proliferation and differentiation. In humans, T2DM may be related to a mutation in the TCF7L2 gene associated with the Wnt pathway [23]. The major effector of Wnt signaling is β-catenin/TCF, formed by free β-catenin and a member of the TCF family, including TCF7L2 [24].

TCF7L2 controls the transcription of the proglucagon gene (GCG) in gut endocrine L-cell lines through the Wnt signaling pathway. The proglucagon gene encodes the incretin hormone glucagon-like peptide-1 (GLP-1) [25]. GLP-1 sustains glucose homeostasis through the biological activities including stimulating insulin secretion, inhibiting glucagon secretion, slowing gastric emptying [26]. In addition, GLP-1 has other beneficial effects including promoting insulin gene transcription, stimulating pancreatic β-cell proliferation and neogenesis, inhibiting β-cell apoptosis [27]. The SNPs of TCF7L2 might induce T2DM by regulating the expression of GCG and the GLP-1 level in plasma. GLP-1 has attracted a great deal of attention for its promising therapeutic efficacy in T2DM.

A study indicated that β-catenin plays a critical role in modulating insulin secretion and that the overexpression of the transcriptional co-activator of β-catenin, TCF7L2, attenuates insulin secretion [28]. The mechanism of how the overexpression of β-catenin influences insulin secretion remains unclear. Elucidating it may provide a whole new approach to the treatment of T2DM.

**β-Cell apoptosis, proinsulin conversion and β-cell responsivity**

The decrease in β-cell mass and function in pancreatic islets are the underlying mechanisms of the progress of T2DM. TCF7L2 influences β-cell functions by affecting β-cell survival in pancreatic islets. Yao et al. [29] identified a novel role of geniposide in promoting β-cell survival and regeneration by mechanisms involving the activation of β-catenin/TCF7L2 signaling. The carriers of an at-risk allele in TCF7L2 are thought to be more susceptible to T2DM, since active TCF7L2 might be essential for pancreatic β-cells proliferation. However, the molecular mechanism through which TCF7L2 influences β-cell survival remains elusive. Zhou et al. [30] suggested the p53-induced-nuclear-protein 1 (p53INP1) pathway was the molecular mechanism through which the risk-associated allele in TCF7L2 increased the expression of an inhibitory TCF7L2 isoform with lower transcriptional activity. Wang et al. [31] indicated that Wnt signaling is activated during adipose-derived stem cells (ADSCs) differentiation into islet β-cells, which suggested that TCF7L2 influences β-cell survival through the Wnt signaling pathway. The
β-cell apoptosis increased with the decrease of active TCF7L2, which influenced the insulin secretion eventually. Finding a way to prevent the apoptosis of β-cells may be a possible treatment for T2DM, like the use of geniposide [29].

The prohormone precursor to insulin, proinsulin, is produced in the β-cells of the islets, specialized regions of the pancreas. Increased levels of proinsulin relative to mature insulin concentrations can indicate impending insulin resistance and the development of T2DM [32]. Another hypothesis about TCF7L2 inducing β-cell apoptosis is the interference with proinsulin processing. It has been confirmed that silencing TCF7L2 would impair insulin vesicle trafficking [33]. Carriers of the risk alleles rs1225537 and rs7901346 in TCF7L2 have not only increased risk of T2DM, but also increased proinsulin and proinsulin-to-insulin ratio [34]. A meta-analysis revealed that the T-allele of the TCF7L2 rs7903146 is a significant risk factor for impaired proinsulin conversion [35]. Impaired proinsulin conversion may be one of the mechanisms of T2DM induction by TCF7L2.

The β-cells produce insulin when glucose starts to be released into the bloodstream from the digestion of carbohydrates in the diet. However, β-cells would likely fail to respond to the concentration of glucose in the blood in a timely manner in individuals with T2DM. Shah et al. [36] studied 120 individuals, of whom one-half were homozygous for TT at rs7903146 and one-half were homozygous for CC. In their study, β-cell responsiveness was slightly impaired in the TT genotype group and differed significantly between genotypes, implying that a genetic variant of TCF7L2 impairs glucose tolerance through effects on glucagon and insulin secretion [36].

In Alibegovic’s [37] study, a total of 38 healthy individuals were examined to identify the association between the T-allele of TCF7L2 rs7903146 and insulin compensatory secretion to compensate for insulin resistance induced by bed rest. Young healthy carriers of the risk T-allele exhibit a diminished compensatory increase in glucose-stimulated plasma insulin and plasma C-peptide secretion during nine days of bed rest, indicating a greater vulnerability to bed rest compared with carriers of the low-risk CC genotype [37]. The carriers of a risk-associated allele in the TCF7L2 gene may have impaired β-cell responsiveness to the regulation of glucose homeostasis, which is characteristic of T2DM.

New treatment emerged with better efficacy and safety when one mechanism was uncovered, such as the use of GLP-1 analogues or its agonists [38,39]. However, there are still other possible mechanisms by which TCF7L2 may be implicated in the induction of T2DM [40,41] that remain to be explored.

Conclusions

The variants in the TCF7L2 gene have been confirmed to be associated with T2DM, which is a polygenic metabolic disorder with a rapidly rising prevalence. This review summarized several potential mechanisms of T2DM pathogenesis associated with TCF7L2, including genetic mutations, Wnt signaling pathway and function, secretion and responsiveness of β-cells. A proper understanding of the mechanism will help the development of potential new therapeutics for T2DM.

Funding

This work was funded by Guangdong provincial research and development of public welfare project [grant number 2014A020212461].

Acknowledgement

The authors thank the funding from Guangdong provincial research and development of public welfare project [grant number 2014A020212461].

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. JAMA. 2013;310(9):948–959.
[2] Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40–50.
[3] Hindy G, Sonesedt E, Ericson U, et al. Role of TCF7L2 risk variant and dietary fibre intake on incident type 2 diabetes. Diabetologia. 2012;55:2646–2654.
[4] Kwak SH, Park KS. Recent progress in genetic and epigenetic research on type 2 diabetes. Exp Mol Med. 2016[cited 2018 Feb 04];48(3):e220. DOI: 10.1038/emm.2016.7.
[5] Fuchsberger C, Flannick J, Teslovich TM, et al. The genetic architecture of type 2 diabetes. Nature. 2016;536(4):41–47.
[6] Acharya S, Al-Elq A, Al-Nafea A et al. Type 2 diabetes mellitus susceptibility gene TCF7L2 is strongly associated with hyperglycemia in the Saudi Arabia population of the eastern province of Saudi Arabia. Eur Rev Med Pharmacol Sci. 2015;19(16):3100–3106.
[7] Struwing J, Boyechko T, Barnett C, et al. The balance of TCF7L2 variants with differential activities in Wnt-signaling is regulated by lithium in a GSK3beta-independent manner. Biochem Biophys Res Commun. 2010;399(2):245–250.
[8] 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(3):320–323.

[9] Wang J, Zhang J, Li L, et al. Association of rs12255372 in the TCF7L2 gene with type 2 diabetes mellitus: a meta-analysis. Braz J Med Biol Res. 2013;46(4):382–393.

[10] Nanfa D, Sobngwi E, Atogho-Tiedeu B, et al. Association between the TCF7L2 rs12255372 (G/T) gene polymorphism and type 2 diabetes mellitus in a Cameroonian population: a pilot study. Clin Transl Med. 2015 [cited 2017 Jul 26];23(4):17. DOI: 10.1186/s40169-015-0058-1.

[11] Cauchi S, Meyre D, Dina C, et al. Transcription factor TCF7L2 genetic study in the French population: expression in human beta-cells and adipose tissue and strong association with type 2 diabetes. Diabetes. 2006;55(10):2903–2908.

[12] Jyothi KU, Jayaraj M, Subburaj KS, et al. Association of TCF7L2 gene polymorphisms with T2DM in the population of Hyderabad, Indiap. PLoS One. 2013 [cited 2017 Jul 26];8(4):e60212. DOI: 10.1371/journal.pone.0060212.

[13] Sale MM, Smith SG, Mychaleckyj JC, et al. Variants of the transcription factor 7-like 2 (TCF7L2) gene are associated with type 2 diabetes in an African-American population enriched for nephropathy. Diabetes. 2007;56(10):2638–2642.

[14] Cincia C, Fusco DD, Cacciotti L, et al. TCF7L2 gene polymorphisms and type 2 diabetes: association with diabetic retinopathy and cardiovascular autonomic neuropathy. Acta Diabetol. 2013;50(5):789–799.

[15] Miyake K, Horikawa Y, Hara K, et al. Association of TCF7L2 polymorphisms with susceptibility to type 2 diabetes in 4,087 Japanese subjects. J Hum Genet. 2008;53(2):174–180.

[16] Helgason A, Palsson 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.

[17] Palmer ND, Hester JM, An SS, et al. Resequencing and analysis of variation in the TCF7L2 gene in African Americans suggests that SNP rs7903146 is the causal diabetes susceptibility variant. Diabetes. 2011;60(2):662–668.

[18] Xia Q, Deliard S, Yuan C-X, et al. Characterization of the transcriptional machinery bound across the widely presumed type 2 diabetes causal variant, rs7903146, within TCF7L2. Eur J Hum Genet. 2014;48(1):103–109.

[19] Mondal AK, Das SG, Chu WS, et al. Genotype and tissue-specific effecton alternative splicing of the transcription factor 7-like 2 gene in humans. J Clin Endocrinol Metab. 2010;95(9):1450–1457.

[20] Bowman TA, O'Keeffe KR, D'Aquilla T, et al. Acyl CoA synthetase 5 (ACSL5) ablation in mice increases energy expenditure and insulin sensitivity and delays fat absorption. Mol Metab. 2016;5(3):210–220.

[21] Koscielný G, Yaikhom G, Iyer V, et al. The International Mouse Phenotyping Consortium Web Portal, a unified point of access for knockout mice and related phenotyping data. Nucleic Acids Res. 2014;42:D802–D809.

[22] Xia QH, Chesi A, Manduchi E, et al. The type 2 diabetes presumed causal variant within TCF7L2 resides in an element that controls the expression of ACSL5. Diabetologia. 2016;59(11):2360–2368.

[23] Maschio DA, Oliveira RB, Santos MR, et al. Activation of the Wnt/β-catenin pathway in pancreatic beta cells during the compensatory islet hyperplasia in prediabetic mice. Biochem Biophys Res Commun. 2016;478(4):1534–1540.

[24] 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(4):379–383.

[25] Weijuan S, Dingyan W, Yu-Ting C, et al. The Wnt signaling pathway effector TCF7L2 controls gut and brain proglucagon gene expression and glucose homeostasis. Diabetes. 2013;62(3):789–800.

[26] Nadkarni P, Chepuruy OG, Holz GG, et al. Regulation of glucose homeostasis by GLP-1. Prog Mol Biol Transl Sci. 2014;121:23–65.

[27] Manandhar B, Ahn J-M. Glucagon-like Peptide-1 (GLP-1) analogs: recent advances, new possibilities, and therapeutic implications. J Med Chem. 2015;58(3):1020–1037.

[28] Sørensen B, Cognard E, Lee KL, et al. A critical role for β-catenin in modulating levels of insulin secretion from β-cells by regulating actin cytoskeleton and insulin vesicle localization. J Biol Chem. 2016;291(50):25888–25900.

[29] Yao DD, Yang L, Wang Y, et al. Geniposide promotes beta-cell regeneration and survival through regulating β-catenin/TCF7L2 pathway. Cell Death Dis. 2015 [cited 2017 Jul 26];6:e1746. DOI: 10.1038/cddis.2015.107.

[30] Zhou Y, Zhang E, Berggreen C, et al. Survival of pancreatic beta cells is partly controlled by a TCF7L2-p53-p53INP1-dependent pathway. Hum Mol Genet. 2012;21(1):196–207.

[31] Wang H, Ren W, Hu X, et al. Effect of Wnt signaling on the differentiation of islet β-cells from adipose-derived stem cells. Biomed Res Int. 2017 [cited 2017 Jul 26];2017:2501578. DOI: 10.1155/2017/2501578.

[32] Mykkänen L, Haffner SM, Hales CN, et al. The relation of proinsulin, insulin, and proinsulin-to-insulin ratio to insulin sensitivity and acute insulin response in normoglycemic subjects. Diabetes. 1997;46(12):1990–1995.

[33] 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(4):894–905.

[34] Silbernaugel G, Renner W, Grammer TB, et al. Association of TCF7L2 SNPs with age at onset of type 2 diabetes and proinsulin/insulin ratio but not with glucagon-like peptide 1. Diabetes Metab Res Rev. 2011;27(5):499–505.

[35] Shen J, Fang Y, Ge W. Polymorphism in the transcription factor 7-like 2 (TCF7L2) gene is associated with impaired proinsulin conversion—a meta-analysis. Diabetes Res Clin Pract. 2015;109(1):117–123.

[36] Shah M, Varghese RT, Miles JM, et al. TCF7L2 genotype and α-cell function in humans without diabetes. Diabetes. 2016;65(2):371–380.

[37] Alibegovic AC, Sonne MP, Hojbjerre L, et al. The T-allele of TCF7L2 rs7903146 associates with a reduced compensation of insulin secretion for insulin resistance induced by 9 days of bed rest. Diabetes. 2010;59(4):836–843.

[38] Dharmalingam M. Efficacy and tolerability of GLP-1 agonists in patients with type 2 diabetes mellitus: an Indian perspective. Ther Adv Endocrinol Metab. 2014;5(6):159–165.

[39] St Onge E, Miller S, Clements E, et al. The role of glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes. J Transl Int Med. 2017;5(2):79–89.
[40] Oh KJ, Park JY, Kim SS, et al. TCF7L2 modulates glucose homeostasis by regulating CREB- and FoxO1-dependent transcriptional pathway in the liver. PLoS Genet. 2012 [cited 2017 Jul 26];8(9):e1002986. DOI: 10.1371/journal.pgen.1002986.

[41] Frietze S, Wang R, Yao L, et al. Cell type-specific binding patterns reveal that TCF7L2 can be tethered to the genome by association with GATA3. Genome Biol. 2012 [cited 2017 Jul 26];13(9):R52. DOI: 10.1186/gb-2012-13-9-r52.