Review Article

TRANSCRIPTION FACTOR 7 LIKE 2 (TCF7L2) VARIATIONCONTRIBUTES TO VEGF ALTERATIONS IN DIABETIC RETINOPATHY

ABSTRACT

Diabetic retinopathy (DR) is a multifactorial disease which causes blindness among peoplewith Diabetes worldwide. It has complex pathophysiology linked to various genetic variations. TCF7L2 (Transcription factor 7 like 2) is considered as one of the most important candidate genes which plays a major role in hyperglycemia and neovascularization.Neovascularization is one of the clinical symptoms of DR found to be associated with upregulation of vascular endothelial growth factor (VEGF) as established by numerous published articles. The purpose of this review is to highlight the role of TCF7L2 polymorphisms in the development of DRvia alterations in VEGF expression levels. We used available published data to explain the association of TCF7L2 polymorphisms with DR. We concluded that genetic studies reports revealed TCF7L2 polymorphisms might be associated with DR development.

Keywords:DM, DR, NPDR, PDR, TCF7L2, wnt, polymorphism

ABBREVIATIONS

DM: Diabetes Mellitus

DR: Diabetic Retinopathy

NPDR: Non-proliferative DR

PDR: Proliferative DR

TCF7L2: Transcription factor 7 like 2

VEGF: Vascular endothelial growth factor

1. INTRODUCTION

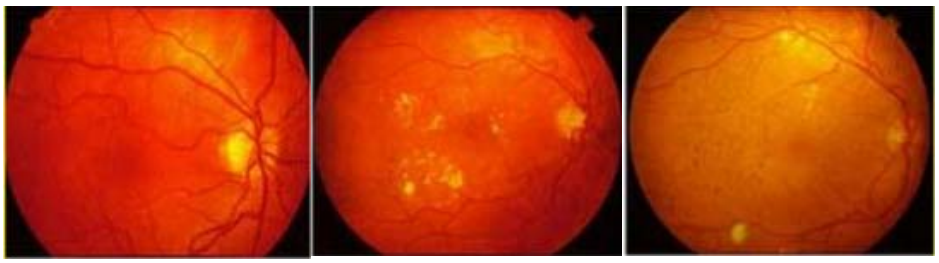
Diabetes mellitus (DM) is a metabolic disorder in which chronic hyperglycemia result to defect in insulin secretion or action leading to acute and chronic complications[1]. The complication usually manifest in the form of damage to vascular system of the body and are less common in DM patients with controlled hyperglycemia [2]. Uncontrolled hyperglycemia causes impaired metabolism which may result in oxidative stress, increased lipolysis (breakdown of lipids), elevated ketone bodies and increased gluconeogenesis[3, 4]. These factors affect the body tissues and subsequently they can cause both morphological and functional defects in organs such as the heart, kidneys, liver and eye[5].Diabetic Retinopathy (DR) is a diabetic complication which causes morphological damage to the eye leading to visual impairment and blindness[6].DR clinically leads to retinal ischemia accompanied by hemorrhages, destruction of the pericytes referred to as microaneuryms, hard exudates, cotton wool spots, intraretinal microvascular abnormalities and neovascularization[7–9]. The early stage of DR is characterized by vascular permeability; this condition is called non-proliferative diabetic retinopathy (NPDR) whereas progression of the NPDR results in abnormal growth of the retinal blood vessels leading to the

neovascularization that is a major symptom in the advanced stage of DR, which is known as proliferative diabetic retinopathy (PDR) [10] (Fig. 1). Recent researches have shown abnormalities in the expression of glucagon like peptide-1(GLP-1); an incretin hormone lead to hyperglycemia and vascular endothelial growth factor (VEGF), which subsequently lead to neovascularization that might be triggered as a result of variations in the gene of a transcription factor in the wnt signaling pathway referred to as transcription factor 7 like 2 (*TCF7L2*) [11–15].

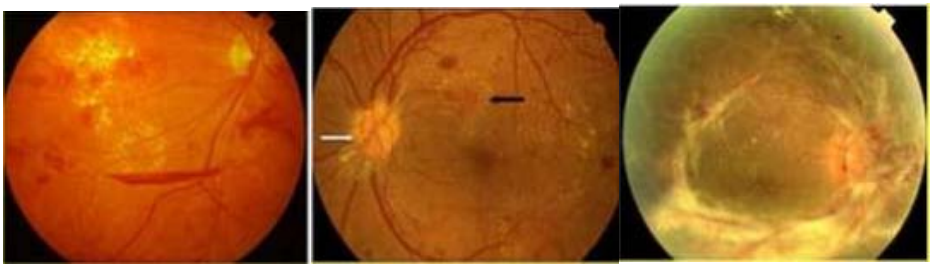
2. TRANSCRIPTION FACTOR 7 LIKE 2 (TCF7L2)

Transcription factor 7 like 2 (*TCF7L2*) also called transcription factor 4 (Tcf4) is a member of T-cell factor (Tcf)/Lymphoid enhancer factor (Lef) transcription factor family[16]. *TCF7L2* gene spans 17 exons on chromosome 10q25.3 which encodes for a transcription factor involved in the Wnt signaling pathway [16, 17](Fig 2). Several single nucleotide polymorphisms (SNPs) including rs7903146 and rs12255372 in the intron region of the *TCF7L2* were identified and found to have association with metabolic disorders including T2DM. The rs7903146 is a nucleotide change from C to T at position 112998590 in the fourth intron of *TCF7L2*, whereas rs12255372 is a change in nucleotide at position 113049143 in the fifth intron from G to T (Fig 3).

Genome-wide association studies (GWAS)reported a relationship between a common micro-satellite region (DG10S478) in intron 3 of the TCF7L2 gene and T2DM [7, 8]. In addition, several studies identified other polymorphisms of TCF7L2 gene associated to T2DM, amongst which are rs7903146 (C/T) and rs12255372 (G/T) [21].



Normal **Background DR** **Moderate NPDR**



Severe NPDR **PDR neovascularization** **Fibrovascular membranes**

Figure 1. Fundus images of DR progression. This progression develops from background DR (mild DR) a form of NPDR to Fibrovascular membrane a form of PDR, as the DR progresses new vessels are formed. Gradual loss in the red colour and change in vein size occur with progression of DR. This image is adopted from El-bab et al. with modification[6].

A) Wnt ligand absent B) Wnt ligand present

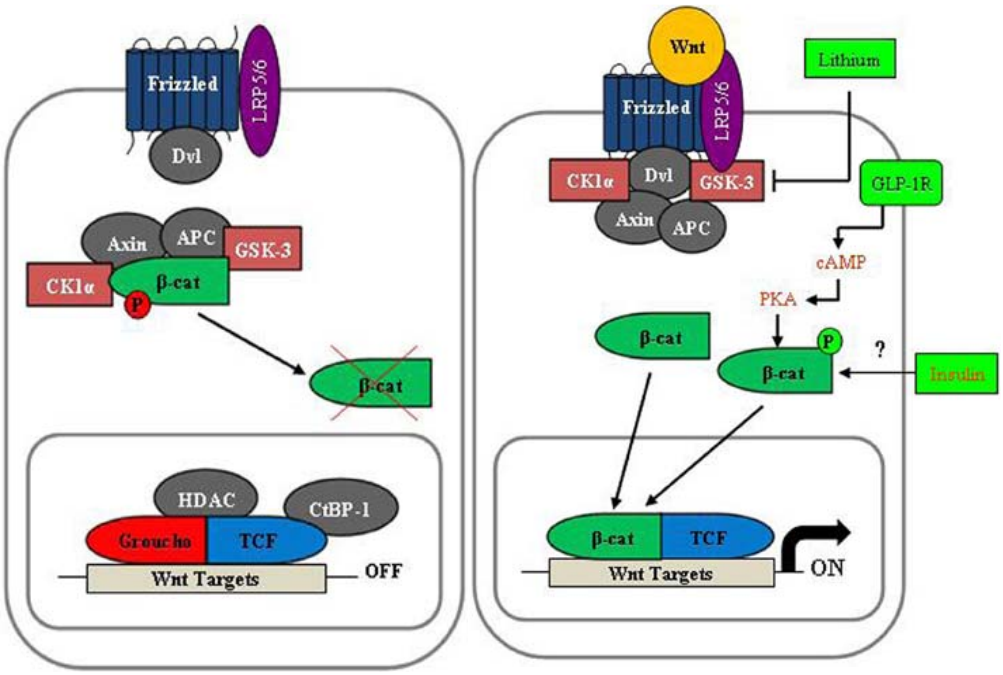


Figure 2.Canonical Wnt signaling pathway A) Shows β catenin regulation in the absence of wnt ligands. The destruction complex containing CK 1α, axin, APC, and GSK-3 phosphorylates β catenin and mark it for proteosomal degradation B) Shows the β catenin stimulation in presence of wnt ligands which prevents interaction between the destruction complex and β catenin and subsequently promote wnt targeted gene expression. This image is adopted from Chiang et al.[12].

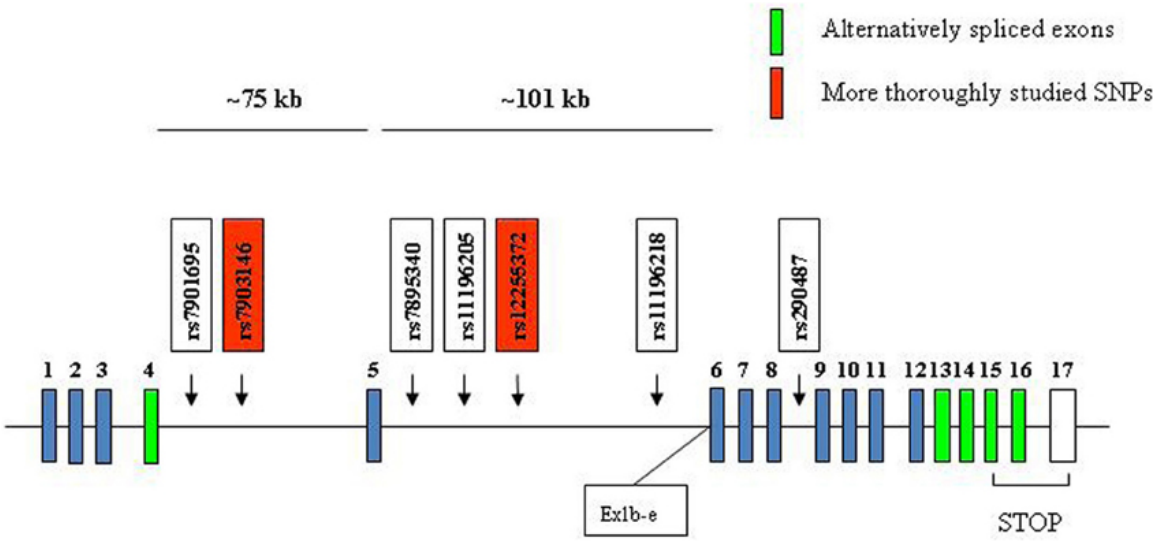


Figure 3.*TCF7L2* gene structure. The *TCF7L2* is located in chromosome 10q25.3. The blue coloured bar-shape are exons whereas the green coloured bar-shape indicate exons that undergo alternative splicing, STOP is the region where transcription of TCF7L2 gene terminate, whereas The two single nucleotide polymorphisms (SNPs) in red are the most studied. This image is adopted from Ip et al.[22].

3. ROLE OF *TCF7L2*POLYMORPHISMS IN UPREGULATION OF VEGF LINKED DR

Genetic variation of rs7903146 (c.382-41435C>T) and rs12255372 (c.482+9017G>T) were successfully linked to T2DM in various ethnic groups [1, 13, 18, 20, 22–25]. But it is still not clear if *TCF7L2* genetic variant is related to DR [26, 27].

Although the exact mechanism of *TCF7L2* in DRdevelopment is not clearly established. However,polymorphisms in the *TCF7L2* might be associated with DR via Wnt targeted genes, several studies have reported the association of these genes with DR in different cohorts i.e. Chinese, Japanese, Indian and American population VEGF [15, 28, 29], ICAM-1 [30, 31] and eNOS[28, 32].VEGF is a vasoactive factor and a mediator of vascular leakage; it is partly responsible for the collapse of the inner blood retinal barrier. which is upregulated in the retina in DR[29]. VEGF expression is increased in the neovascular membranes of diabetic patients with DR [33]. VEGF antagonists have been found useful in the treatment of DR[34].The VEGF family is part of the platelet-derived growth factor (PDGF) supergene family members which consist of VEGFα, VEGFβ, VEGFγ, VEGFδ, VEGFε and PlGF (placental growth factor)[6, 35, 36].VEGFα has been studied extensively and reported to play critical role in both vasculogenesis and neovascularization [37-42].Investigation on PDR shows the relationship between *TCF7L2* and *VEGFα*[28].

The expression of *VEGFα* increases with increase in expression of *TCF7L2;* which might be as a result of rs7903146 (c.382-41435C>T), several studies have reported rs7903146 and rs12255372 (c.482+9017G>T) to be in linkage disequilibrium[19, 34, 35], thus showing that both rs7903146 and rs12255372 might play crucial role in the upregulation of VEGFα. There are two binding sites in the VEGFα promoter region linked to TCF7L2, which may implicate in increased expression of VEGFα transcription through TCF7L2 binding, therefore, genetic polymorphism may lead toelevated *TCF7L2 levels* which result in over expression of *VEGFα*; related to derangement of retinal vessels and neovascularization [28]**.**We believe the mechanism revealing the association of TCF7L2 polymorphism to *VEGFα* is applicable to other genes expressed by TCF7L2 in the wnt signaling pathway.

CONCLUSION

In addition to confirming the association of TCF7L2 gene variants to DM, TCF7L2 SNPs might play a role in the development of DM complications including DRvia upregulation of VEGF.Studies are required to establish the relationship between TCF7L2 polymorphisms with other diseases associated with neovascularization such as Age related macular degeneration, diabetic macular edema, and corneal neovascularizationetc.

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