

## ФАКТОР ТРАНСКРИПЦИИ 7 (TCF7L2): ФАКТОР РИСКА РАЗВИТИЯ САХАРНОГО ДИАБЕТА 2 ТИПА



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Влияние генетических факторов на развитие сахарного диабета 2 типа (СД2) крайне многогранно и до сих пор остается одним из главных вопросов диабетологии. В 2006 г. важным шагом в поиске генетических факторов развития СД2 стала идентификация гена *TCF7L2*, который является важным маркером предрасположенности к СД2 почти у всех этнических групп. Недавние генетические исследования выявили множество новых генов, ассоциированных с повышенным риском развития СД2. Среди этих генов *TCF7L2* оказался наиболее многообещающим, связанным с СД2. Генотипы *TCF7L2* оказывают влияние на развитие бета-клеток поджелудочной железы и секрецию инсулина, воздействуя на сигнальный путь Wnt. Определенные полиморфизмы гена *TCF7L2* увеличивают риск развития СД2, изменяя экспрессию фактора транскрипции (который играет ключевую роль в регуляции уровня глюкозы в крови) в поджелудочной железе. Цель данной статьи — представить всесторонний обзор исследований по ассоциации полиморфизма *TCF7L2* с СД2, проведенных в различных этнических группах во всем мире.

**КЛЮЧЕВЫЕ СЛОВА:** фактор транскрипции-7 (*TCF7L2*); сахарный диабет 2 типа; сигнальный путь Wnt; полногеномный поиск ассоциаций (GWAS)

## TRANSCRIPTION FACTOR 7-LIKE 2 (TCF7L2): A CULPRIT GENE IN TYPE 2 DIABETES MELLITUS

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The genetics of Type 2 diabetes a complex metabolic disorder, characterized by decreased insulin secretion and insulin resistance resulting in impaired blood glucose homeostasis remains enigma for geneticists. In 2006 an important step while finding genetic causes of diabetes type 2 was identification of transcription factor 7-like 2 (*TCF7L2*) gene an important marker in predisposition of type 2 diabetes in almost all ethnic population. Recent genetic research identifies numerous novel type 2 diabetes susceptible genes among these genes *TCF7L2* is considered as gang head and emerged as the most promising types 2 diabetes causing gene. Risk variants in *TCF7L2* effects pancreatic beta cell development and insulin secretion by influencing Wnt Signaling pathway. Genetic variants in *TCF7L2* confer risk for type 2 diabetes by altering expression of transcription factor (which has key role in blood glucose regulation) in pancreas. The purpose of this paper is to evaluate type 2 diabetes susceptible gene the *TCF7L2* and to present a comprehensive review of studies carried out worldwide in different ethnic population on association of *TCF7L2* polymorphism with type 2 diabetes.

**KEYWORDS:** Transcription factor-7- like 2 (*TCF7L2*); Type 2 diabetes; Wnt signaling pathways; Genome wise association studies (GWAS)

Non communicable diseases (NCDs) are rising as the main cause of death, disability, reduced quality of life and rising health care costs worldwide. The number of people dying worldwide due to Non communicable diseases (NCDs) is twice than that of the combined infectious diseases (like HIV/AIDS, tuberculosis and malaria), maternal and prenatal conditions and nutritional deficiencies [1]. Cardiovascular diseases (CVD) cancers and chronic respiratory diseases, diabetes mellitus (DM) are the commonly NCDs, diabetes a commonly occurring NCD ranked fourth among these NCDs. Diabetes mellitus occurred in low and middle income countries especially in south Asians[2,3]. Diabetes Mellitus (DM) is a metabolic syndrome (with increased blood glucose level as a hallmark) arising from endocrine disorder that affect around 6% of the world's population [4, 5]. Diabetes is accompanied by micro- and macro-vascular complica-

tions [6]. Diabetes causing 1.5 million global deaths each year. It has two main types namely Type 1 DM (T1D) and Type 2 DM (T2D), the latter being 90–95% of total cases globally [7, 8]. Poor lipid profile, lack of exercise, improper diet habits, socio-economic problems, central adiposity, inadequate health systems and environmental factors contributes to the development of T2D. Though lifestyle and environmental factors contribute to the development of DM but it does not completely explain its increased prevalence, and genetic has a significant role in its occurrence [9].

### TYPE 2 DIABETES GENETIC ARCHITECTURE AND EARLY GENETICS

Inheritance no doubt has a key role in predisposition of diabetes type 2 [10]. Geneticist argued that genomics of T2D is

explored well to understand and manage the pathogenesis of T2D [11]. These claims are premature according to others [12]; in fact, a few have doubt in contribution of genetic predisposition to T2D pathogenesis [13]. In Sixteenth century Peter Frank a physician from Montpellier for the every first time suggest that heredity is playing a role in diabetes [14]. The Frank's view was supported by subsequent finding in 1950s and it was concluded that family history and genetics heterogeneity has a principal role in the predisposition of diabetes [15]. Earlier studies were mostly carried out on specific genes (i.e. those involved in glucose homeostasis) [16]. Considerable research by the end of 2005 was carried out throughout the world in spite of vast research only two genes polymorphism were found to be associated with type 2 diabetes: were E23K in KCNJ11 and P12A in PPARG [17, 18]. Mutation in these genes causes monogenic diabetes [19, 20]. In recent years genetics of diabetes type 2 is well explored due to advancement in molecular biology and also thanks to genome wide association study (GWAS) which facilitates the researcher in identifying various loci that is associated the diabetes [21, 22]. Number of risk loci associated with diabetes type 2 is climbed up from just 3 identified in 2006 to more approximately 70 today, nevertheless up-to-date 90 genetic loci involved in the pathogenesis of T2D is identified by GWAS [23, 24].

### TCF7L2; A GUILTY GENE IN TYPE 2 DIABETES

DECODE group of Iceland in the start of 2006 revealed the transcription factor-7-like 2 (TCF7L2) as an unexpected suspect gene for a diabetes type 2 [25]. After 2006 this gene drawn attention of geneticists and soon it was confirm that multiple polymorphisms in this gene has strong association with diabetes type 2 in multiple ethnic population. After the initial signals from DECODE group in Iceland wide-spread study is carried in white Europeans [26], Indians and Japanese [27–29], Mexican Americans [30], Chinese [31], and West Africans [32]. Studies in all racial population shows strong association of transcription factor-7-like 2 (TCF7L2) with diabetes type 2. Tracking of guilty genes nowadays is quite easy using new technologies. Due to technological advances, genetic variants in genes found guilty in diabetes can be assessed on a single chip. Recent advancement in genetic studies and genome wide association study has completely un-mask the complete genetic makeup of diabetes type 2 and identified number of variants in TCF7L2 associated with diabetes type 2, among other guilty genes it is the most promising gene in the development if type 2 diabetes [33–37].

### EXPLORING BIOCHEMISTRY OF TCF7L2

TCF7L2 gene (Alternate names (1) T-cell-specific transcription factor 4, (2) HMG box transcription factor 4) encodes a protein, the Transcription factor 7-like 2 (T-cell specific) containing a transcription factor which has key role in blood glucose regulation in humans [38]. Cytogenetic location of this polymorphic gene is 10q25.2-q25.3 [39]. It contains 18 exons, 619 amino acids and exists in helix-turn-helix structure [40]. Transcription factor 7-like 2 belongs to a family of transcription factors known as TCF/LEF family (containing TCF7 (TCF-1), TCF7L1 (TCF-3), TCF7L2 (TCF-4) and LEF1

these transcription factors binds to DNA via SOX-like high mobility group domain [41]. TCF/LEF family member specifically TCF7L2 regulate WNT pathway which has critical role in embryonic development of pancreas and islets, cell proliferation, Causation of several cancers, Regulation of adiposeness, and release of glucagon-like peptide-1 (GLP-1) from intestinal endocrine L-cells which effect two things mainly first it effect insulin secretion secondly the generation of new  $\beta$  stem cells from the ductal precursor cells and hence has critical role in controlling glucose homeostasis [42, 43]. The TCF7L2 is distributed and expressed in brain, pancreas, liver, intestine and fat cells [44].

### JOURNEY OF TCF7L2 ASSOCIATED STUDIES FROM 2006 (EARLIER GENETIC STUDIES) TO 2020 (RECENT GENETIC STUDIES)

Grant et.al and saxena et.al in 2006 for the first time correlate polymorphism in TCF7L2 with type 2 diabetes. Before that Pub-Med software was search for keyword TCF7L2 reveals 218 articles but none of that shared the term “diabetes” means the grant et al (2006) and saxena et.al (2006) are the pioneer in correlating TCF7L2 polymorphism with incidence of diabetes type 2. After that TCF7L2 replication studies were carried out word wide in different ethnic population each study conforming strong association of TCF7L2 with type 2 diabetes [45]. A comprehensive list of studies on Type 2 Diabetes Susceptibility Gene TCF7L2 rite from 2006, year of its discovery to 2019 is enlisted in the table 1.

### TCF7L2 A CANDIDATE GENE FOR TYPE 2 DIABETES, CONFORMATION VIA GENOME WIDE ASSOCIATION STUDY:

Genome-wide association studies are well-powered, systemic, organized and comprehensive survey to explore and identify the link of various genetic variation (SNPs) and disease predisposition on large genomic scale [46]. Genome wide association studies as laid down spectacular advances in finding genetic cause of the diseases like cancer, diabetes, kidney failure, depression, asthma and many more. Promising Genome wide association studies also found TCF7L2 gene culprit in diabetes Type 2 [47]. In earlier genetic study era (start of 2007), two stage genome wide associations was conducted to identify different risk loci in TCF7L2. At stage first a meta analysis was conducted in 2367 French patients a consent form was signed from all patients and studied was approved by ethics committee of French general health hospital and Imperial College London, the study results show strong association of TCF7L2 with diabetes type 2 [48]. Second stage (late in year 2007) a huge genomic study was conducted in UK white population. In this study geneticist included a new parameter of association of TCF7L2 with diabetes type 1 as some geneticist in that time predict that type 1 diabetes is nothing but severe case of type 2 diabetes. All identified SNPs of TCF7L2 in this study shows strong association with type 2 diabetes but no association with type 1 diabetes confirming type 1 diabetes as an autoimmune disease [49]. Later further genome wide association studies carried out in different ethnic population stamped TCF7L2 as a guilty gene in type 2 diabetes [50, 51].

**Table 1.** List of studies on Type 2 Diabetes associated Gene TCF7L2 from 2006-2020

S.No	Selected population	Design	Aim of study and SNPs Explored	Reference and year of publication
1	American population	Association study	SNP rs12255372 in the TCF7L2 gene was associated with betacell function.	Munoz et al. (2006)
2	Italic population	Association study	TCF7L2 variant rs7903146 shows significant association with diabetes type 2	Melzer et al. (2006)
3	Scotland U.K	Association study. Case-control design.	rs790314 variant of TCF7L2 shows strong association with diabetes type 2.	Kimber et al. (2007)
4	Finnish population	Association study	A TCF7L2 SNP rs12255372, is strongly associated with diabetes type 2	Scot et al. (2007)
5	European Population	Association study	The presence of the TCF7L2 rs7903146 risk allele increases risk for diabetes.	Stéphane et al. (2008)
6	North India	Association study	Four TCF7L2 SNPs (rs7903146, rs11196205, rs10885409) associated with T2D	Sanghera et al. (2008)
7	Multiple ethnic group	Meta Analysis	TCF7L2 four SNPs in various ethnicities, containing rs7903146 rs7901695, rs12255372 and rs11196205 is linked with diabetes type 2	Tong et al. (2009)
8	East Asian population	Meta-analysis	rs7903146 T, rs12255372 T, rs11196205 and rs290487 of TCF7L2 confer risk of type 2 diabetes.	Luo et al. (2009)
9	Iranian population	Association study	In Iranian population TCF7L2 variant rs7903146 is associated with type 2 diabetes	Amoli et al. (2010)
10	German population	Case control study	The following SNPs rs7903146, rs12255372, rs11196205, and rs7895340 in TCF7L2 confer risk for T2D	Haupt et al. (2010)
11	Polish population	Case control study	Risk variant rs7903146 in the TCF7L2 gene show increase risk for diabetes type 2	Buraczynska et al. (2011)
12	Austria population	Association study	TCF7L2 variants rs7903146 rs12255372, and rs11196205 are associated with coronary artery disease specifically in patients with T2DM	Muendlein et al. (2011)
13	Multi ethnic population	Meta analysis	TCF7L2 SNPs rs7903146, rs12255372, rs7895340 and rs4506565 confer risk of type 2 diabetes	Peng et al. (2012)
14	Northern Chinese population	Case control study	Northern Chinese population having rs290487 in TCF7L2 is associated with type 2 diabetes	Qiao et al. (2012)
15	Southern Chinese population	Case control study	The rs7903146 SNP of the TCF7L2 gene increases susceptibility to T2DM in Chinese population	Wang et al. (2012)
16	Chinese Han population	Meta analysis	This study concluded rs7903146C/T polymorphism of the TCF7L2 gene is associated in Chinese Han population	Dou et al. (2013)
17	Southern-Brazil population	Case control study	The TCF7L2 SNP rs7903146 (C/T) Confer risk of type 2 diabetes mellitus in Southern-Brazil	Assmann et al. (2013)
18	Indian populations.	Case control study	rs7903146 variant of TCF7L2 is found guilty in Indian populations.	Hussain et al. (2014)
19	Iranian Kurdish Ethnic Group	Case control study	rs7903146, rs12255372, and rs290487 SNPs of TCF7L2 are associated with T2DM	Shokouhi et al. (2014)
18	Uyger Population china	Case control study	rs12255372, rs7901695 variants in TCF7L2 is associated with diabetes type 2.	Yao et al. (2015)
19	Chinese Hui population	Case control study	TCF7L2 varaint rs12255372 (G>T) polymorphism is genetic factors associated with Type 2 diabetes.	Yang et al. (2015)

S.No	Selected population	Design	Aim of study and SNPs Explored	Reference and year of publication
20	Tianjin Population China	Meta analysis	Transcription factor 7-like 2 (TCF7L2) SNP rs7903146 is associated with T2D	Guan et al. (2016)
22	Venezuela population	Pilot case control study	We find strong association of the rs7903146 SNP of TCF7L2 with T2DM	Moran et al. (2016)
23	Caucasians population	Multi ethnic Cohort study	TCF7L2 rs7903146 risk allele was associated with diabetes type 2 in Caucasians	Cropano et al. (2017)
24	Turkish population	Case control study	TCF7L2 variants rs7903146 ,rs12255372 is found culprit in T2D	Kaya et al. (2017)
25	Chinese population	Case control study	TCF7L2 variant rs7903146 increases susceptibility to DN (diabetic neuropathy) in Chinese population.	Zhuang et al. (2018)
26	Nanjing population of china	Meta analysis	TCF7L2 variant rs12255372 strongly associated with Type 2 diabetes in the Chinese population	Yan li et al. (2018)
27	Pakistani population	Case control study	TCF7L2 variant rs12255372 had strong association in regulating fasting plasma glucose	Shahzadi et al. (2019)
28	Iranians population	GWAS (genome wide association study)	TCF7L2 variants rs7903146, rs12255372 and rs11255372 is found to have promising role in the incidence of type 2 diabetes.	Kalantari et al. (2019)
29	Puerto Ricans population	Case control study	TCF7L2 –rs7903146 shows significant interaction with BMI, weight and waist circumference hence leading to Type 2 diabetes.	Mercedes et al. (2020)

#### PUZZLED MECHANISM OF TCF7L2 ALLELES CAUSING TYPE 2 DIABETES

The Wnt signaling pathways is greatly important in regulating carcinogenesis and embryonic development (stem cell differentiation, amplification and migration) also involved in the development of the body parts [52, 53]. Wnt signaling pathway (the canonical pathway or beta-catenin/TCF7L2-dependent pathway) is expressed in liver, pancreas, brain and adipose tissues [54]. In pancreas it helps in the development of pancreas, islet function, insulin production and secretion. In beta cells of pancreas canonical wnt signaling is modulated by two hormones namely glucagon-like peptide-1 and the chemokine stromal cell-derived factor-1, furthermore glucagon-like peptide-1 and its agonist exendin-4 restore the pancreatic beta cells mass by switching on Wnt signaling which then start proliferation to restore mass of beta cell [55]. Genome-wide association studies (GWAS) have identified several risk variants in TCF7L2 that is found culprit in type 2 diabetes. Interestingly most of these risk variants encode proteins that are involved in islet growth and functioning. Seven of them are part of genes that regulate Wnt signaling. Thus canonical Wnt signaling and beta-cell function is greatly influenced by TCF7L2 mutation. Polymorphism in TCF7L2 leads to loss in function of pancreas; impair insulin secretion, perturbations in the Wnt signaling pathway that leads to type 2 diabetes [56, 57].

#### CONCLUSION

Candidate gene association studies (CGAS) and genome wide association studies (GWAS) identified multiple genes associated with diabetes type 2, transcription factor 7-like 2 (TCF7L2) is gang head of type 2 diabetes susceptible genes [58]. Risk variants leads to over-expression of TCF7L2 gene in beta cells of pancreas but the mechanism is not fully understood and it is a question which is still need to be answered by geneticists, resulting in reducing secretion of insulin from beta cells and hence increasing blood sugar level [59, 60]. Comprehensive knowledge about TCF7L2 have significant role in controlling diabetes, separating and identifying the prospective diabetes individuals with high risk diabetes associated loci in a population so that preventive measures can be initiated [61, 62].

#### ADDITIONAL INFORMATION

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