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REVIEW PAPER

The gateway to Genetic pathogenesis in Diabetes mellitus: TCF7L2

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ABSTRACT

Undoubtedly, Diabetes is procuring the status of a potential rampant in India with more than 60 million diabetic individuals diagnosed with the disease currently. With the lifestyle and dietary habits of people changing the health risk of type 2 diabetes mellitus has become more serious than it was ever before. One of the most risk related genes of T2DM is transcription factor 7 like 2 (TCF7L2). It is very well known that diabetes has become the most threatening pandemic in public health. Due to an inclination in ageing population, thereby burdening existing healthcare workers it has become an epidemic in some of the countries, especially in poorly developed countries. The cure is unknown but; however, prevention includes major lifestyle changes, control obesity and oral hypoglycemic changes.

Keywords: - Type 2 diabetes mellitus, TCF7L2, Genetic mutations, SNP.

INTRODUCTION

Diabetes is notably one of the oldest known diseases to mankind and was proclaimed first in Egyptian manuscript 3 millennia ago [1]. Type 1 and type 2 diabetes were initially distinguished in 1936 and in 1988, type 2 diabetes mellitus was set out as a component of metabolic syndrome [2,3]. Defects in insulin secretion, functioning or both cause a set of metabolic disorders characterized by hyperglycemia resulting in Diabetes mellitus [4]. Diabetes is amongst the major reasons of morbidities in non-communicable disease category around the world. World Health Organization (WHO) has reported that type 2 diabetes (T2DM) has increased tremendously all around the world irrespective of the income levels in the countries. People surviving T2DM are more susceptible to both long-term and short-term health issues leading to early fatalities especially in cases with its stealthy onset and late recognition [5]. The incidence of diabetes diagnosed in adults was increased by 49% from 1990-2000 according to the Centers for disease control and Prevention. Unless the Disease is battled effectively in its early stages, the chances of an irreversible damage increases. More than 62 million Indians have been diagnosed with the disease Diabetes, procuring status of a potential epidemic in India. India (31.7 million) was leading the charts in the world with highest number of people with diabetes mellitus in 2000 followed by China (20.8 million) with the United

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States (17.7 million) in second and third place respectively [6,7].

Diabetes surrounds a range of heterogeneous metabolic disorders characterized by inability of the body to generate glucose and keep glucose homeostasis in check. Despite being two distinct disorders, they are rather considered as two ends of a diabetic range with maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA) and other subtypes [8]. Juvenile diabetes or Type 1 diabetes is also known as insulin-dependent diabetes due to the patient's complete dependence on insulin injections. It is an autoimmune condition destructing pancreatic beta cells and distinguished by complete absence of insulin secretion. Often diagnosed in children and youth of age <35 years [8].

Type 2 diabetes is the most dominant form of diabetes with 90% of all reported cases. The health risk of incidence of T2DM is maximally attributed to changes in lifestyle and dietary habits of people [9]. There are many research studies on Diabetes reporting it as the most threatening health pandemic. The pathophysiology of diabetes has been studied extensively for many years. In the last two decades, many findings in relation to T2DM and underlying molecular mechanisms with associated genes have been reported. Genome wide studies as GWAS have appallingly mentioned the role of different SNPs in correlation to T2DM and glycemic traits. It mentioned that SNP assays could be used to study the association of different genes and diseases [10,11]. In earlier literature, GWAS studies have mentioned 38 SNPs to be related with T2DM directly and many others were found to be associated with glycemic traits [11,12].

The main suspect: TCF7L2 gene

The gene mainly responsible for the early incidence of T2DM in adults is reported to be transcription factor 7 like 2 (TCF7L2). It has been found to be strongly associated and is also the most studied genes for T2DM. TCF7L2 encodes a transcriptional factor playing an important role in WNT signaling pathway, a key cell developmental and growth regulatory mechanism.

Mutations found in risk-related variants reside in an intronic region rather an exon, it becomes easy to presume a regulatory process is involved in conferring T2DM risk. The risk allele is associated with decreased insulinogenic index and lower disposition index, suggesting a reduced capacity for insulin secretion in relation to insulin sensitivity. It is being identified as a diabetes gene, has also been found to be important for several vital functions in the pancreatic islet, including pancreas development, determination of beta-cell mass, maintenance of secretory function of mature beta cells, regulation of insulin production and processing. There was a contradiction noted in TCF7L2 working mechanism, when an anomaly was observed within the β cells, the expression was increased 5-fold instead of being reduced [13]. B-cat/ TCF, formed by free β-catenin and a member of TCF family, is the major effector of WNT signaling including TCF7L2 [14].

The major role of TCF7L2 is to control the transcription of Proglucagon gene in gut endocrine L-cell lines through the WNT signaling pathway. The Proglucagon gene encodes the incretin hormone Glucagon-like peptide-1 [15]. Glucagon-like peptide-1 sustains glucose homeostasis through biological activities including other important

functions like stimulating insulin secretion, inhibiting glucagon secretion, slowing gastric emptying, promoting insulin gene transcription, stimulating pancreatic β-cell proliferation and neogenesis, inhibiting β-cell apoptosis [16,17]. By regulating expression of GCG and GLP-1 levels in plasma, the SNPs of TCF7L2 might include T2DM. Also, from all the SNPs reported for T2DM, those present of TCF7L2 have been widely studied and found to be having significant associations with T2DM among different ethnicities throughout the world having a wide prognostic potential [18]. The TCF7L2, SNPs investigated in different parts of the world were also found to be correlated with many other diseases such as gestational diabetes, PCOS, prostate cancer, schizophrenia and others [19,20,21].

Genetic mutations in TCF7L2

Genome Wide Association Studies (GWAS) have been making a terrific number of attempts and approaches on the studies of Diabetes and other genetic diseases. Since the last decade, they have shown 38 SNPs involved with T2DM and in addition to that two dozen SNPs are involved with Glycemic traits. Grant *et al.* investigated 5 major SNPs associated with TCF7L2 [22,23]. The locus for these SNPs resides within the TCF7L2 gene and has been established to be strongly associated with T2DM. The major SNPs (rs12255372, rs7903146, rs7901695, rs11196205 and rs7895340) of TCF7L2 gene confer T2DM risk to variant carriers [24]. The research on these SNPs also reflected strong associations in different ethnicities as well. GWAS have reported more than 240 loci for T2DM, after years of extensive international research distinguishing more genetic components. A specific set of variants in TCF7L2 have correlation with T2DM. Research studies have been carried out explicating the clarity regarding pathogenesis of T2DM as well. A research on 7061 Scandinavian subjects followed up to 22 years reported three SNPs (rs7903146, rs12255372, and rs10885406) in TCF7L2, and a subset of them underwent extensive metabolic studies [24]. There are different research studies from around the world reporting significant associations of TCF7L2 genetic SNPs and incidence of T2DM in varied populations of South Asian ethnicities residing in their country of origin and/ or other parts of the world [24-27].

Major SNPs of TCF7L2 associated with T2DM

rs7903146

This SNP has been found majorly associated with the incidence of diabetes and poor disease management in populations of varied ethnicities. A study of 1038 normal glucose-tolerant and 1031 T2DM subjects selected from the Chennai Urban Rural Epidemiology (CURE) study from Chennai, India, reported that the prevalence of T allele of rs7903146 was significantly higher in diabetic subjects as compared to the normal population group included in the study [28]. Another such research of the UK-resident South Asian population inclusive of 831 T2DM subjects and 437 control subjects, mentioned the odds of developing T2DM to be 1.31 times higher than the normal population. This high risk was conferred to rs7903146 mutation [25]. TCF7L2 intron SNP rs7903146 was strongly found to be associated with T2DM in a case-control research study of African-Americans reporting an odds ratio of 1.51 [29]. This SNP has been referenced numerous times by researchers around the world as being substantially involved in the

incidence of T2DM in multiethnic populations [30-34].

rs12255372

rs12255372 has also majorly been associated with diabetes in Indian population. An Asian Indian study of put on a conclusion of rs12255372 (G/T) being significantly higher in diabetics (33%) exhibiting an adjusted Odds ratio of 1.56 for TT genotype and 1.29 for TG genotype when compared with the GG genotype **[28]**. A research study on African-American population specified the highest association of rs12255372 SNP of TCF7L2 as ~70% **[29]**, which was found lower compared to other SNPs of TCF7L2 where the prevalence was reported to be as high as 80% **[35]** The association between rs12255372 (G/T) polymorphism in the TCF7L2 gene and T2DM in an Iranian population, 236 unrelated patients with T2DM, and 255 normoglycemic controls without diabetes were studied. The PCR-RFLP method was used for genotyping rs12255372 (G/T) polymorphism. The minor T allele of TCF7L2 rs12255372 was found to significantly increase the risk of T2DM, with an allelic odds ratio. A significant difference in TT genotype was observed between T2DM patients and normoglycemic controls. On assuming dominant and recessive models, ORs of 1.52 [95% CI (1.05-2.21) p = 0.026)] and 1.74 [95% CI (1.01-3.00) p = 0.043] were obtained, respectively, thereby implying that the co-dominant model would best fit the susceptible gene effect.

rs11196205 and rs3792267

Association of TCF7L2 rs11196205 and rs3792267 polymorphisms with T2DM has also been studied. The allelic distribution and genotypic frequencies between patients and healthy controls for both SNPs were analyzed. There was a non-significant differences for allele and genotype frequencies between subjects with T2DM and don-diabetics, which doubts the direct association of these two SNPs in the incidence and management of T2DM **[35]**.

Conclusion

Many research studies around the world confirmed that the SNP mutations in the TCF7L2 gene as enhancing susceptibility to the development of T2DM and furthermore the poor management of the disease. These SNP mutations have also found to be significantly associated with other metabolic disorders. The data generated from research studies on the SNP mutations of TCF7L2 gene might be utilized further to develop prognostic tools, for timely diagnosis of T2DM to overcome the irreversible harm caused by the co morbidities related to T2DM.

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