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MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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Transcription Factor 7-Like-2 (TCF7L2) rs7903146 (C/T) Polymorphism in Patients with Type 2 Diabetes Mellitus

Thesis

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous group of metabolic disorders usually characterized by the incapability of pancreatic beta (β) cells to increase insulin secretion to compensate for insulin resistance in the peripheral tissues ***(Alexandra et al., 2017).***

Type 2 diabetes mellitus (T2DM) represents a global major healthcare burden. According to the International Diabetes Federation (IDF), Egypt is in the World's ninth place in terms of diabetes incidence, affecting up to 8.9 million people. By the year 2045, Egypt is expected to be in the seventh place, with about 16.9 million diabetic patients, due to the rapidly increasing and aging population, which will be considered one of the highest incidence rates in the Middle East and North Africa region. Therefore, it is crucial to understand the mechanisms that contribute to the pathogenesis of DM ***(International Diabetes Federation, 2019)***.

T2DM is a multi-factorial disease, the susceptibility of which is determined by several genetic and environmental factors. However, it is supposed that the environmental factors and life style changes may lead to T2DM only in the presence of predisposing genetic factors to the disease. Great efforts have

been made to identify the different genes associated with the risk of development of T2DM ***(Prabhanjan et al., 2016)***.

The Transcription factor 7-like-2 gene (TCF7L2) gene encodes a transcription factor involved in the Wnt signaling pathway, which plays an important role in pancreatic islet development and adipogenesis. TCF7L2 protein forms heterodimers with β -catenin, inducing the expression of various genes, including the insulinotropic hormone glucagon-like peptide 1 (GLP-1) gene, the insulin gene and other genes that encode proteins involved in processing and exocytose of insulin granules ***(Jin, 2016)***.

There are a number of single nucleotide polymorphisms (SNPs) in the TCF7L2 gene were found to be strongly associated with T2DM, one of them is the TCF7L2 rs7903146 (C/T), in which there is a substitution of the (C) to (T) nucleotide at the position (112998590) within intron (3) chromosome (10). It was hypothesized that this SNP may modify T2DM susceptibility by indirectly reducing GLP-1 secretion from entero-endocrinal cells or through a primary effect in the pancreatic islets ***(Oskolkov et al., 2016)***.

Aim of the Work

The aim of this work is to investigate the potential association of the Transcription factor 7 like-2 (TCF7L2) rs7903146 (C/T) gene polymorphism in patients with type 2 diabetes mellitus.

According to the World Health Organization (WHO), diabetes mellitus (DM) is described as a group of metabolic disorders characterized and identified by the presence of hyperglycaemia. The heterogeneous aetio-pathology includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs ***(WHO, 2019)***.

There have been recent calls to review and update the classification system for diabetes. This is because many people with diabetes do not fit into any single category. There have been recent advances in knowledge of pathophysiological pathways and emerging technologies to examine pathology and treatments that act on specific pathways. The recent classification system of the WHO in 2019 (table 1) can be internationally applicable and use easy and readily available clinical parameters and resources is based on clinical parameters to identify diabetes subtypes ***(WHO, 2019)***.

Table (1): WHO Classification of Diabetes Mellitus.

Type of diabetes	Brief description
Type 1 diabetes	β-cell destruction (mostly immune mediated) and absolute insulin deficiency; onset commonly occurs in childhood and early adulthood.
Type 2 diabetes	Most common type, various degrees of β-cell dysfunction and insulin resistance; commonly associated with overweight and obesity.
Hybrid forms of diabetes	
1.Slowly evolving, immune mediated diabetes of adults	-Previously known as latent autoimmune diabetes of adults (LADA), Similar to slowly evolving type 1 in adults but more often has features of the metabolic syndrome, a single autoantibody and retains greater β-cell function.
2. Ketosis-prone type 2 diabetes	- Presented with ketosis and insulin deficiency but later does not require insulin; common episodes of ketosis, not immune-mediated.
Other specific types	
1. Monogenic diabetes	
-Monogenic defects of β-cell function	- Caused by specific gene mutations, has several clinical manifestations requiring different treatment, some occur in the neonatal period, others by early adulthood.
- Monogenic defects in insulin action	- Caused by specific gene mutations; has features of insulin resistance without obesity; diabetes develops when β-cells do not compensate for insulin resistance.
2. Diseases of the exocrine pancreas	- Various conditions that affect the pancreas can result in hyperglycemia (trauma, tumour, inflamation, etc.)
3. Endocrine disorders	- Occurs in diseases with excess secretion of insulin antagonist hormones as cortisol, epinephrine growth hormone

4- Drug or chemical induced	- Some medications and chemicals impair insulin secretion or action and can also destroy β-cells such as thiazides, glucocorticoids, alpha and beta adrenergic agonists, Dilantin, Pentamidine, Nicotinic acid and Interferon-alpha.
5-Infection-related diabetes	- Some viruses have been associated with direct β-cell destruction such as congenital rubella, Coxsackie B, Cytomegalovirus, Adenovirus and Mumps.
6- Uncommon specific forms of immune-mediated diabetes	-Insulin receptor autoantibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases. In the past, this syndrome was termed Type B insulin resistance.
7- Genetic syndromes associated with diabetes	- Genetic syndromes associated with diabetes include; Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Prader–Willi syndrome, Alstrom syndrome, Bardet-Biedl syndrome, Friedreich's ataxia, Huntington's chorea, and myotonic dystrophy.
Hyperglycemia first detected during pregnancy	
1-Diabetes mellitus in pregnancy	-Type 1 or type 2 diabetes first diagnosed during pregnancy and defined by the same criteria as in non-pregnant.
2-Gestational diabetes mellitus	- Hyperglycaemia below diagnostic thresholds for diabetes in pregnancy including one or more of the following; fasting plasma glucose of 92-125 mg/dL or a 1-hour plasma glucose ≥ 180 mg/dL following a 75g oral glucose or 2-hour plasma glucose 153-199 mg/dL following a 75g oral glucose

(WHO, 2019)

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of inadequate insulin secretion, excessive or inappropriate glucagon secretion and inability of the body to respond fully to insulin, defined as insulin resistance ***(Clare et al., 2019).***

A. Epidemiology of T2DM :

According to the International Diabetes Federation (IDF), the estimated number of diabetes mellitus cases in 2017 was about 424.9 million, with a global prevalence of 8.8% of adults 20-79 years old. In high income countries, approximately 87% to 91% of all diabetic patients are estimated to have T2DM, 7% to 12% are estimated to have T1DM and 1% to 3% to have other types of diabetes ***(IDF,2017).***

Egypt is in the world's ninth place in terms of diabetes incidence, affecting up to 8.9 million people in 2019. By the year 2045, Egypt is expected to be in the seventh place, with about 16.9 million diabetic patients, due to the rapidly increasing and aging population, which will be one of the highest incidence rates in the Middle East and North Africa regions. It was estimated that there were about 4.8 million undiagnosed diabetic cases in Egypt.

DM represents a huge economic burden, in 2019; the IDF estimated the total healthcare expenditure worldwide on diabetes to reach 760 billion USD, meanwhile in Egypt, the healthcare expenditure was estimated to be about 7 billion USD ***(International Diabetes Federation, 2019).***

B. Risk Factors for T2DM :

1. Genetic Factors:

Type 2 diabetes mellitus, as a complex disease, arises due to interaction between different environmental factors in the presence of genetic predisposition. To locate genes and loci that are responsible for the risk of type 2 diabetes, genome wide association studies (GWAS) were utilized to compare the genomes of diabetic patient group and the non-diabetic control group. GWAS has revealed many loci and genes associated with type 2 diabetes such as TCF7L2 (transcription factor 7-like 2), PPARG (peroxisome proliferator-activated receptor-gamma), CDKAL1 (cyclin dependent kinase 5 regulatory subunit associated protein 1- like 1), PROX1 (prospero homeobox 1), MTNR1B (melatonin receptor 1b) and many other loci (Table 2) ***(Gaulton et al., 2015).***

Table (2): Examples of Genetic Loci Associated with T2DM and their Mechanisms

Gene Locus	***Mechanism involved in Diabetes Mellitus***
TCF7L2 *(rs7903146)*	Involved in Wnt-signalling pathway, influencing pancreatic beta cells development and function.
PPARG *(rs1801282)*	Involved in adipocyte differentiation, acts as a receptor for insulin sensitizing drugs (as thiazolidinediones) and has a role in insulin resistance.
CDKLA1 (rs7754840)	Cyclin Kinase (CDK5) inhibitor involved in the cell cycle of the beta cells and insulin response.
PROX1 (rs340874)	Implicated in pancreas development, insulin sensitivity and elevated fasting blood glucose levels.
MTNR1B (rs10830963)	Involved in glucose homeostasis and associated with increased blood glucose levels and reduced Beta cell function.

(Gaulton et al., 2015)

2. Age:

The prevalence of glucose intolerance (pre-diabetes and T2DM) increases with advancing age. The main factors are that aging induces a decrease in insulin sensitivity and insufficient compensation of beta cell function, in addition to the decrease in beta cell proliferation capacity and enhanced sensitivity to apoptosis. It was found that the first and second phase of insulin secretion normally decreases at the rate of approximately 0.7% per year with aging, this decrease in β cell function is accelerated about two-fold in people with impaired glucose tolerance. Decline

in lean body mass and visceral adiposity i.e., central obesity that accompanies aging may contribute to insulin resistance. Those conditions contribute to the development of glucose intolerance and T2DM ***(Seo et al., 2010).***

3. Obesity, Lifestyle and Dietary Factors:

There is a close association between obesity, physical inactivity and T2DM. The likelihood and severity of T2DM are closely linked with the body mass index (BMI), obesity being defined as BMI more than or equal 30 kg/m2; whereas BMI ranging from 25 to 29.9 kg/m^2 is classified as overweight. There is a seven times greater risk of diabetes in obese people and a threefold increase in risk for overweight people compared to those with healthy weight ***(Kodama et al., 2014).***

It is known that body fat distribution is an important determinant of increased risk of diabetes; in addition, duration of obesity was found to increase risk of developing T2DM, with greater risk among people who have been obese for longer periods of time ***(Abdullah et al., 2011).***

Dietary factors also influence the risk of developing T2DM, the type of fats in diet are important, where saturated fatty acids increase the risk, while polyunsaturated and monounsaturated fatty acids decrease the risk .Recent evidence has also suggested