بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سامية زكى يوسف

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Association Between *GLIS3* rs7020673 Polymorphism and Type 2 Diabetes Mellitus among Egyptian Population

Thesis

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Lubna Ezz Eldin Mohamed

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List of Abbreviations

Abb.	Full term
2-h PG	2-h Plasma Glucose
ADA	American Diabetes Association
ALL	Acute Lymphoblastic Leukaemia
AMKL	Acute Megakaryoblastic Leukaemia
BCAR1	Breast cancer antiestrogen resistance 1
BIM	Bcl-2 interacting mediator of cell death
BIM S	Bcl-2 interacting mediator of cell death Short isoform
BMI	Body Mass Index
C2H2	Cys2His2
CBD	C-terminal Binding Protein
CCND2	Cyclin D2
CDK5	Cyclin Kinase 5
CDKAL1	CDK5 regulatory subunit associated protein 1-like 1
CI	Confidence interval
CKD	Chronic kidney disease
CLIA	Chemiluminescence immunoassay
COBL	Cordon-Bleu WH2 Repeat Protein
CVD	Cardiovascular disease
DBD	DNA-binding Domain
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
E1	Ubiquitin-activating enzyme
E2	Ubiquitin-conjugating enzyme
E3	Ubiquitin–protein ligase
ELISA	Enzyme-linked immunosorbent assay
ER	Endoplasmic reticulum
ESRD	End-stage renal disease
FAM	Fluorescein amidites
FPG	Fasting Plasma Glucose
FGF18	Fibroblast growth factor 18
FOXA2	Forkhead box A2
FT4	Free thyroxine

List of Abbreviations cont...

Abb.	Full term
GA	Glycated albumin
GDM	Gestational diabetes mellitus
GLIS3	Gli similar 3
GLIS3-REs	GLIS3-response elements
GLISBS	GLIS-binding sites
GWAS	Genome-wide association studies
H	Kruskal-Wallis Test
Hb A1c	Glycated hemoglobin A1c
HCC	Hepatocellular carcinoma
Hh	Hedgehog
HLA	Human Leukocyte Antigen
HNF1β	Hepatocyte nuclear factor 1β
HNF6	Hepatocyte nuclear factor 6
HOMA	Homeostatic model assessment
HPLC	High-performance liquid chromatography
HPLC-UV	High performance liquid chromatography coupled with ultraviolet detection
HRP	Streptavidin-horse radish peroxidase
HS	Highly-significant difference
HTN	Hypertension
IA	Islet autoimmunity
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
Ins2	Insulin gene
IR	Insulin resistance
KDIGO	Kidney Disease: Improving Global Outcomes
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MTNR1B	Melatonin receptor 1B
NDH	Neonatal diabetes and congenital hypothyroidism
NFQ	Non-fluorescent quencher
NGN3	Neurogenin 3

List of Abbreviations cont...

Abb.	Full term
NGS	Next generation sequencing
NGSP	National Glycohemoglobin Standardization Program
NRD	N-terminal Repressive Domain
NS	Non-significant difference
OGTT	Oral glucose tolerance test
OR	Odds ratio
P –value	Probability
PCR-RFLP	Polymerase chain reaction-restriction fragment length polymorphism
PDX1	Pancreatic duodenal homeobox 1
PIAS4	Protein Inhibitor of Activated STAT 4
PKC	Protein Kinase C
PPARG	Peroxisome proliferator-activated receptor-gamma
PPxY	Proline- Proline-x-Tyrosin
Prox1	Prospero homeobox protein 1
Ptch	Protein patched homolog
qPCR	Quantitative polymerase chain reaction
RCC	Renal cell carcinoma
real-time PCR	Real-time polymerase chain reaction
RIA	Radioimmunoassay
ROS	Reactive oxygen species
S	Significant difference
Shh	Sonic Hedgehog
SMAD2	Suppressor of Mothers against Decapentaplegic
Smo	Smoothened
SNP	Single nucleotide polymorphism
SNPs	Single nucleotide polymorphisms
SRP55	Splicing factor protein 55
SUFU	Suppressor of Fused
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

List of Abbreviations cont...

Abb.	Full term
TAD	Transactivation Domain
TCF7L2	Transcription factor 7-like 2
TGFβ	Transforming growth factor β
TMB	Tetra methyl benzidine
TSH	Thyroid-stimulating hormone
VIC	Victoria blue dye 2`-chloro-7`phenyl-1, 4-dichloro-6- carboxy- fluorescein
WFS1	Wolfram syndrome 1
WHO	World Health Organization
WNT	Wingless related integration site
WWTR1	WW domain containing transcription regulator 1
X^2	Chi-Square Test
Z	Wilcoxon`s Rank-Sum Test
ZF	Zinc finger

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous metabolic disease characterized by glucose intolerance, which seems to result from the combined effects of insulin resistance and a failure of the pancreatic β-cells to compensate for the increased demand of insulin ***(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 8th place in terms of diabetes incidence, affecting up to 8.2 million people. By the year 2045, Egypt is expected to be in the 6th place, with about 16.7 million diabetic patients and will represent the highest incidence 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, 2017)***.

Type 2 diabetes mellitus (T2DM) is a multi-factorial disease, genetic and environmental factors as well as life style have been considered as major risk factors in the development of T2DM ***(Hasan et al., 2018).*** 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 GLI-similar 3 (*GLIS3*) gene codes for a Krüppel-like zinc finger transcription factor that is located in a nuclear compartment of the cell and in the Golgi complex and is highly expressed in beta cells. It controls gene transcription through Glis3-binding sites (GLISBS) in regulatory regions of the target genes ***(Guilherme et al., 2017).***

Growing evidence indicates that GLIS3 plays a critical role in pancreatic cell lineage specification, particularly in the development of mature beta cells. GLIS3 is also important to beta cell mass maintenance and regulation of insulin expression in adults ***(Guilherme et al., 2017)***. GLIS3 may function as a cell-type-dependent trans activator or repressor and may protect pancreatic β cells against apoptosis ***(Wen and Yang, 2017).***

Single nucleotide polymorphism (SNP) is a variation at a single position in a DNA sequence among individuals ***(Matsuda, 2017).*** *GLIS3* (rs7020763) which shows reduced GLIS3 expression was found to modulate the alternative splicing of the pro-apoptotic protein, promoting the expression of apoptosis of the β cell and β cell death. These data suggest that proper GLIS3 expression could be required for β cell survival ***(Wen and Yang, 2017).***

AIM OF THE WORK

The aim of the present study is to investigate the potential association between the *GLIS3* (rs7020763) gene polymorphism and type 2 diabetes mellitus and its impact on glycemic control among Egyptian population.

Type 2 Diabetes Mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both ***(Goyal and Jialal, 2022)***.

A. Epidemiology of T2DM:

According to the International Diabetes Federation (IDF), in 2021, diabetes caused 6.7 million deaths; and 537 million adults aged between 20 and 79 years old were living with diabetes, a number that will likely rise up to 783 million by 2045. ***(International Diabetes Federation, 2021).*** The World Health Organization (WHO) Global report on diabetes shows that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults ***(WHO, 2019)***.

Egypt is in the world's tenth place in terms of diabetes incidence, affecting up to 10.9 million people in 2021. By the year 2045, Egypt is expected to be in the ninth place, with about 20 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 6.8 million undiagnosed diabetic cases in Egypt. DM represents a huge economic burden, in 2021; the IDF estimated the total healthcare expenditure worldwide on diabetes to reach 966 billion dollars, meanwhile in Egypt, the healthcare