Association of Cytotoxic T Lymphocyte Antigen 4 Gene Polymorphism with Type 1 Diabetes in Children

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ABSTRACT

Background: Type-1 diabetes mellitus (T1DM) is a progressive complex autoimmune disease in which combinations of environmental as well as genetic factors contribute to T-cell mediated destruction of insulin-secreting β-cells of the pancreas. The (CTLA-4) encodes of the T cell receptor involved in the control of T cell proliferation and mediates T cell apoptosis. The contribution of CTLA-4 gene variants to type 1 diabetes has been analyzed in several ethnic groups.

The aim of this Cross sectional, case-control study was to investigate the association of CTLA-4 gene exon 1 49 A/G polymorphism, with T1DM in children and its relation to diabetic complications.

Subjects and methods: A total of 100 subjects were included in the study, those subjects were classified into two groups. Fifty children with T1DM aged 10-18 years (12.5±2.0 years), and fifty healthy age and sex matched children as a control group. All candidates were subjected to full clinical evaluation and anthropometric measurements. All the patients had the following laboratory investigation been done (RBG, average HbA1c, Quantitative determination of urinary microalbumin). CTLA-4 gene polymorphism PCR-RFLP was done for all the subjects included in the study.

Results: In the current study, CTLA-4 genotyping among the diabetic group was: the mutant homozygous genotype GG in 15(30%), the mutant heterozygous genotype AG in 29(58%) and wild homozygous genotype AA in 6(12%). However, among the control group: it was 3(6%) with GG genotype, 19(38%) with AG genotype and 28(56%) with AA genotype with P value < 0.001 which denoting a higher prevalence of AG and GG genotype in diabetic group with highly statistical significance. There was a significant association between CTLA-4 mutant genotypes and patients with younger age of onset of diabetes (P=0.011) and higher dose of insulin (P=0.002). CTLA-4 +49 mutant genes did not have any impact on complications of type 1 diabetes. Neither has it shown an impact on HbA1c.

Conclusion: The results of the present study shows that the CTLA-4 A/G +49 polymorphism was associated with type 1 diabetes in Egyptian children with a significant association between CTLA-4 mutant genotypes and patients with younger age of onset of diabetes and higher dose of insulin. However, this polymorphism did not have any impact on complications of type 1 diabetes.

Key Word: T1DM, CTLA- 4, Antigen, Polymorphism

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List of Abbreviations

2-h PG	2-houres Post Glucose
ACE	Angiotensin Converting enzyme
ADA	American Diabetes Association
AIRE	The autoimmune regulator
AP2	Adapter protein
APC	Antigen Presenting Cells
ARF-1	ADP ribolysation factor-1
BG	Blood glucose
BMI	Body mass index
BP	Blood Pressure
CD	Cluster of differentiation
cdk4	Cyclin Dependent Kinase 4
CNS	Central nervous system
CSII	Continuous subcutaneous insulin infusion
CTLA-4	Cytotoxic T lymphocyte Antigen- 4
CVD	Cardiovascular disease
DC	Dendritic Cells
DCCT	Diabetes Control and Complications Trial
DCs	Dendritic cells
DKA	Diabetic ketoacidosis
DM	Diabetes Mellitus
DR	Diabetic retinopathy
flC1LA-4	Full length form of CTLA-4
FOXP3	The transcription factor forkhead box P3
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GDM	Gestational Diabetes Mellitus
GFR	Glomerular filtration rate
GI	Glycemic inde
GL	Glycemic load
HbA1C	Glycosylated hemoglobin (Hemoglobin A1c)
HHS	Hyperglycemic hyperosmolar state
HLA	Human Leukocyte Antigen
HNF	Hepatocyte nuclear factor
IA	Islet antigen
IAAs	Insulin autoantibodies
ICA	Including islet cell
ICOS	Inducible co-stimulator

IDDM12	Insulin Dependent Diabetes Mellitus 12
IDF	International Diabetes Federation
IDO	Indoeamine 2,3 Dioxygenase
Ig	Immunoglobulin
IL	Interleukin
INF-γ	Interferon gamma
INS	Insulin gene
ISPAD	International Society for Pediatric and Adolescent Diabetes
IT AMs	Immunoreceptor tyrosine-based activation motifs
IZS	Insulin Zinc Suspension
LAT	Linker of activation in T cells
LAX	Linker for activation of X cells
LCK	Lymphocyte-specific protein tyrosine kinase
liCTLA-4	ligand- independent CTLA-4
LYP	Lymphoid tyrosine phosphatase
MDI	Multiple Daily Injections
MHC	Major Histocompatibility Complex
MODY	Maturity onset diabetes of the young.
NAFLD	Non-alcoholic fatty liver disease
NKT	Natural Killer T cells
NOD	Non-obese diabetic
NPH	Neutral Protamine Hagedorn insulin
NSGP	National Glycohemoglobin Standardization Program
OGTT	Oral Glucose Tolerance Test
PLD	Phospholipase D
PP2A	Protein phosphatase 2A
PTK	Protein tyrosine kinase
PTPN22	Protein tyrosine phosphatase, non-receptor type 22
PVD	Peripheral vascular disease
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
sCTLA-4	Soluble CTLA-4
SIT	SHP2 interacting TRAP
SLE	Systemic Lupus Erythematosus
SNPs	Single nucleotide polymorphisms
T1DM	Type 1 Diabetes Mellitus
Tconv	Conventional T-cells
TCR	T-cell receptor
TCRζ	TCRzeta
TDD	Total Daily Dose

TDEI	Total daily energy intake
TGF-β	Transforming growth factor beta
TGN	Trans-Golgi network
Th	T helper
TNF	Tumor necrosis factor
TRAPs	Transmembrane adaptor proteins
Treg	Regulatory T-cells
TRIM	T-cell receptor-interacting molecule
USDA	The United States Department of Agriculture

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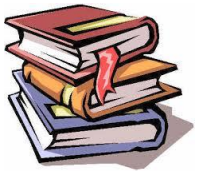

INTRODUCTION