Interleukin 4 -590 C>T and Interleukin 13 -1112 C>T Gene Polymorphisms in Relation to the Susceptibility to Type 2 Diabetes Mellitus in Egypt

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ABSTRACT

Background*: Type 2 diabetes mellitus is the most frequent type of diabetes. It is caused by insulin resistance and often combined with symptoms of progressive defect in insulin secretion. Various factors have been implicated in the pathogenesis and complications of type 2 diabetes mellitus (T2DM), of which, immune response and inflammation were suggested to play a role.* ***Objective:*** *To investigate the association of IL-4-590 and IL-13 -1112 genetic polymorphisms with (T2DM) in Egyptian patients.* ***Subjects and Methods****: The study included 135 cases with type 2 DM (65 males and 70 females), with a median age of 56 years and 101 healthy unrelated controls from Nile Delta region, Egypt. DNA was extracted by purification Capture column kit supplied by Fermentas, K0721, USA. Polymorphisms of IL-4 -590(C>T) and IL-13 -1112(C>T) genes were characterized using ARMS-PCR technique.* ***Results:*** *The frequency of heterozygous (CT) genotype of IL-4-590 was significantly increased in type 2 diabetic patients compared to the control, CT genotype of IL-13-1112 was highly significantly increased in diabetic patients compared to control (85.2 vs.66.3, OR=2.9, p=0.001; 76.3 vs.51.5, OR=3' p= 0, respectively). The frequency of the homozygous (CC) genotypes of both IL-4 and IL-13 were significantly lower in type 2 diabetic patients than in the control group (10.4 vs. 26.7, OR=0.32, p=0.002; 20.7 vs 31.7, OR=0.6, p=0.04, respectively). The frequency of CT+TT genotypes of IL-4 gene were higher in patients compared to controls (89.6 vs. 73.3, OR =3.2, P= 0.002).Results did not show any significant difference between allele frequency in diabetic and healthy controls either.* ***Conclusion:*** *Polymorphisms related to IL-4-590 CT and IL-13-1112 CT genotypes may be considered as a risk factor for type 2 diabetes mellitus among Egyptian subjects.*

Key words*: IL4 polymorphism, IL13 polymorphism, type 2 diabetes mellitus, Egypt.*

INTRODUCTION

T2DM is believed to be a multi-factorial disease, it is influenced by both genetic and environmental factors such as increased calorie intake[(1)]. People with family history of the disease are at higher risk of developing T2DM since they share genetic background and likely share similar environments. Therefore, genetic factors were considered key determinants of the individual susceptibility to T2DM; it has been

estimated that 30- 70% of T2DM risk can be attributed to genetic factors [(1)].

Interleukin 4 (IL-4) was originally discovered as a low molecular weight T cell–derived polypeptide of 129 amino acids, which is encoded by the IL-4 gene on chromosome 5q23.31. It is secreted by helper T cells (CD4) type 2 (Th2) lymphocytes, and natural killer (NK) T cells, and by cells of the innate immune system, including mast cells, basophils, and esinophils [(2)]. Interleukin 4 regulates proliferation, apoptosis, gene expression, and differentiation in many hematopoietic cells; in particular, it directs the immunoglobulin (Ig) class switch to IgG1 and IgE, and down-regulates the production of Th1 cells [(3,4)].

Interleukin 13 is a 12 kDa protein product, produced by Th2 cells, and genetically implicated in the pathogenesis of inflammatory and immune systemic diseases, such as asthma and atopy. IL-13 shares several biological profiles with IL-4 including IgE production, CD23 and MHC class II expression, inhibition of antibody-dependent cell-mediated cytotoxicity with downregulation of IgG type I receptor and suppression of type I interferon [(5)].

Investigators of that field believe that T2DM is associated with immune system and in turn is related to the alteration of Th2 to Th1 immune response patterns[(6)]. It was reported that cytokine imbalance is involved in the pathogenesis of T2DM[(7)]. In addition, polymorphisms in the IL4R, IL-4, and the IL-13 loci have been reported to be associated with immune disorders and serum immunoglobulin levels [(8)].

The aim of the present work is to investigate the relationship of polymorphisms of IL-13-1112 C>T and IL-4-590 C>T genes to the susceptibility and severity of type 2 DM among Egyptian patients from the Nile Delta region of Egypt.

SUBJECTS & METHODS

This is a case controlled study that was conducted on 135 type 2 diabetic patients and 101 healthy controls recruited during the time period from May to December, 2011; Cases included 65 males and 70 females. Their age range was 28-80 years (median 56 years, mean ± SD was 56.11±9.1 years). Patients were recruited from the Outpatient Clinic and Inpatient Department of Diabetes and Endocrinology Unit, Specialized Medicine Hospital, Mansoura University, Egypt. All patients had a diagnosis of established type 2 DM, on the basis of medical history, clinical examination and laboratory tests as FBS, PPBS, HbA_{1c} and C-peptide. All cases were treated by hypoglycemic agents whether insulin or oral drugs.

Control group were 101 healthy unrelated blood donors taken from the same locality their age ranged 18-50 (median 30, mean ± SD=29.19±6.47 years; males=80, females=21), they were proved healthy and euglycemic by clinical and laboratory tests.

A written consent was taken from every participant in this study in addition to an approval from The Ethical and Scientific Committees of Mansoura University, Egypt.

Patients' data included age, sex, residence, parental consanguinity,

family history of DM, occupation, education, duration of DM, symptoms of presentation, type of diabetic treatment, hypertension and its relation to diabetes, history of neuropathy, retinopathy, and other diabetic complications and history of other drug therapy.

Physical examination included pulse, systolic and diastolic blood pressure and calculation of mean blood pressure which equals diastolic BP+ 1/3 pulse pressure[9]. Height, weight, and calculation of body mass index (BMI = weight (Kg)/ height $(m)^2$, Arterial pulsation, thyroid swelling, pallor, jaundice, and lower limb edema, diabetic skin affection and diabetic foot.

Biochemical analysis:

Sampling was done by withdrawing 8 ml of fasting venous blood from all patients and controls, 4ml on K_2EDTA, 3ml for analysis of cytokine gene polymorphisms by PCR and one ml for estimation of HbA_{1c}. The remaining 4 ml venous blood was pipette in plane tube (no anticoagulant), centrifuged and the separated serum, part was used immediately for estimation of glucose by the glucose oxidase method [10] (spin react kit, Madrid, Spain) . The remaining serum was stored at -70ºC till time of assay of insulin. Quantitative determination of insulin (Monobind Inc, 92630,USA). Glycosylated hemoglobin (HbA_{1c}) was measured by quantitative colorimetric method, determined as percent of glycohemoglobin in relation to total hemoglobin using kits produced by **Stanbio**, 0350, USA. Glycohemoglobin %= R of unknown/ R of standard× concentration of glycohemoglobin of standard (**Stanbio,** 0350, USA). Homeostasis Model of Assessment of Insulin Resistance (HOMA) was calculated as = Fasting glucose (mg/dl) × Fasting insulin (IU/ml)/ 405 [11].

DNA Extraction and Characterization of genetic polymorphisms using ARMS-PCR:

For all participants, DNA was isolated from whole blood according to the Generation DNA Purification Capture Column kit supplied by Fermentas, #K0721, USA.

Genotyping of IL-4-590 C>T:

For detection of the IL-4 gene polymorphism -590 C>T (rs2243250), the allele-specific PCR method (ARMS-PCR) was performed as described by **Howell** *et al*. [12]. In brief, for each person, two reactions were carried out with each of the forward primers: T primer: 5′-CTA AACTTGGGAGAACATTGTT-3′ or IL-4 F C primer: 5′-CTAAACTTGGGAGAACATTGTC-3′ Each of the two reactions contained the reverse primer IL-4 5′-AGTACAGGTGGCATCTTGGAAA-3′[12].

Reactions contained 5 µl of each primer, 10 µl of Dream Taq Green PCR Master Mix (2X) (Fermentas, K 1081, USA) to a final volume of 25 µl, amplification was performed on thermal cycler with 1 min at 96°C, followed by 10 cycles of 96° C for 15 s, 1st 10 cycle at 65.5° C for each SNP for 50 s, 72° C for 40 s; then 20 cycles of 96° C for 10 s, 60° C for 50 s, 72° C for 40 s. PCR products were loaded directly onto 2% agarose gels (containing 0.5 µg/ml ethidium bromide), electrophoresed and

visualized by photography under UV transillumination.

Genotyping of IL-13-1112 C>T:

For detection of the IL-13 gene polymorphism -1112C>T (rs1800925), the allele-specific PCR method (ARMS-PCR) was performed as described by **Hummelshoj *et al.*,**[13] In brief, for each person, two reactions were carried out with each of the forward primers: IL-13 -1046F C primer: 5′-TTCTGGAGGACTTCTAGGAAAA C-3′ or IL-13 -1046F T primer: 5′-TTCTGGAGGACTTCTAGGAAAA T-3′. Each of the two reactions contained the reverse primer IL-13 -740R: 5′-GGAGATGGGGTCTCACTATG-3′[13].

Reactions contained 5µl of each primer, 12 µl Dream Taq DNA Master Mix (2X, Fermentas, K1081, USA), to a final volume of 25 µl amplification was performed on thermal cycler with 2 min at 94°C, 15 cycles of 30 s at 94°C, 60 s at 63°C and 60 s at 72°C, 20 cycles of 30 s at 94°C, 60 s at 60°C and 60 s at 72°C, and finally 5 minutes at 72°C. The PCR products were separated on 2% agarose gel, band appears at 400 bp.

Statistical analysis:

Data were processed and analyzed using the Statistical Package of Social Science (SPSS, version 17). The frequency of studied allelic polymorphism among **patients** was compared to that of controls describing number and percent of each and tested for positive association using Fisher exact test and odds ratio (OR) with 95% confidence intervals (CI). A minimum level of $P < 0.05$ is considered significant.

RESULTS

Table 1: IL-4 -590 C>T and IL-13 -1112 C>T genetic variants among Egyptian cases with T2DM compared to controls

	Patients N (%)	**Controls N (%)**	***P*#**	**OR (95% CI)**
IL-4 -590 C>T				
CC	14 (10.4)	27 (26.7)	**0.002***	**0.32 (0.2- 0.6)**
CT	115 (85.2)	67 (66.3)	**0.001***	**2.9 (1.6-5.4)**
TT	6 (4.4)	7 (6.9)	0.566	0.6 (0.2-1.9)
CT+ TT vs. CC			**0.002***	**3.2 (1.6-6.4)**
C-allele	143 (52.9)	121 (59.9)	0.13	0.75 (0.52-1.09)
T-allele	127 (47)	81 (40)	0.13	1.3 (0.91-1.9)
IL-13 -1112 C>T				
CC	28 (20.7)	32 (31.7)	**0.04***	**0.6 (0.3-0.95)**
CT	103 (76.3)	52 (51.5)	**0.00****	**3 (1.74- 5.3)**
TT	4 (3.0)	17(16.8)	**0.00****	**0.2 (0.05- 0.5)**
CT+TT vs. CC			0.07	1.7 (0.98- 3.2)
C-allele	159 (58.9)	116 (57.4)	0.77	1.06 (0.7-1.5)
T-allele	111 (41.1)	86 (42.5)	0.77	0.9 (0.65-1.36)

** p significant <0.05 **p highly significant <0.001 # the value in each genotype is compared to other genotypes*
.i..e CC vs. CT+TT, CT vs. CC+TT and TT vs. CC+CT

The frequency of the homozygosity CC genotype was significantly lower in the diabetic than in the control. (10.4% vs. 26.7%, p=0.002), on the other hand the frequency at the heterozygosity (CT) at -590 of the IL-4 was significantly higher in patients than control (85.2% *vs* 66.3%, p=0.001). The frequency of the TT genotype was 4.4% in patients compared to 6.9% in the controls with non significant statistically difference (Table 1), there were a non significant difference as regard allelic frequency in patients compared to control (P>0.005) (Table 1).

Polymorphism at -1112 of IL-13 showed a highly significant increase of the frequency of CT genotype in diabetic patients compared to controls (76.3% *vs* 51.5%, p<0.001) (table 1).

The frequency of the IL-13 promoter -1112 (C>T) polymorphism (genotype CC) was significantly lower in diabetic patients compared with control (20.7% *vs.* 31.7%, p=0.04), frequency of the IL-13 promoter-1112 (TT) polymorphism was lower in patients compared to control, with a highly significant difference (3% *vs.* 16.8%, p<0.001), Allele frequency, showed no significant difference between patients and controls (Table 1).

Table 2: Clinical parameters of Egyptian patients **with T2DM related to IL-4-590 C>T and IL-13-1112 C>T polymorphic variants.**

	IL-13(-1112 C/T)				**IL-4(-590 C/T)**			
	CCN(%)	**CT**	**TT**	***p***	**CC**	**CT**	**TT**	***p***
Family history								
Positive	18 (23.1)	59 (75.6)	1 (1.3)	>0.05	5 (6.4)	70 (89.7)	3 (3.8)	>0.05
Negative	10 (17.5)	44 (77.2)	3 (5.3)		9 (15.8)	45 (78.9)	3 (5.3)	
Consanguinity								
Positive	3 (20.0)	12 (80.0)	0 (0.0)	>0.05	2 (13.3)	11 (73.3)	2 (13.3)	>0.05
Negative	25 (20.8)	91 (75.8)	4 (3.3)		12 (10.0)	104(86.7)	4 (3.3)	
Gender								
Male	15 (23.1)	50 (76.9)	0 (.0)	>0.05	8 (12.3)	53 (81.5)	4 (6.2)	>0.05
Female	13 (18.6)	53 (75.7)	4 (5.7)		6 (8.6)	62 (88.6)	2 (2.9)	

p >0.05 non-significant

It was noted that 78 patients (57.7%) had a positive family history of the diabetes type 2, while 15 of the patients (11.1%) had positive parental consanguinity. Comparing cases-subgroups in terms of gender, family history and consanguinity in relation to their genotype frequencies of IL-4-590 C/T or IL-13-1112 C/T polymorphic variants were found to be statistically non-significant (p>0.05) (Table 2).

Table 3: Demographic and clinical parameters of studied Egyptian cases with T2DM related to genotypic variants of IL-13-1112 C>T and IL-4-590 C>T

	IL-13 -1112 C>T			**IL-4 -590 C>T**		
	CC	**CT**	**TT**	**CC**	**CT**	**TT**
F Insulin	87.5 ± 79.2	57.3 ± 43.1	49.9 ± 54.8	67.9±60.3	63.6±53.1	45.± 52.5
P#	0.008*	*0.02**	*0.6*	*0.7*	*0.9*	*0.4*
HOMA	32.4 ± 29.5	27.7 ± 25	20.2 ± 17.6	36.2±37	27.7±24	23.70 ± 30.4
P	0.4	*0.6*	*0.5*	*0.2*	*0.4*	*0.6*
FBS	159.7± 63.9	201.1±76.9	207.50± 4.1	212.0 ± 88.8	191.± 73.9	184.2 ± 86.7
P	0.01*	*0.02**	*0.7*	*0.3*	*0.5*	*0.8*
HbA1c	7.5 ± 1.9	7.6 ± 1.6	7.8 ± 1.9	7.6±2.	7.6 ±1.6	7.0 ±1.5
P	0.8	*0.9*	*0.8*	*0.9*	*0.7*	*0.4*

*p significant <0.05 **p highly significant <0.001 # the value in each genotype is compared to other genotypes i.e CC vs. CT+TT, CT vs. CC+TT and TT vs. CC+CT*

There was a significant increase in fasting insulin level in patients with CC genotype of IL-13 compared to those with CT and TT genotypes (87.5 ± 79.2 *vs.* 57.3 ± 43.1 and 49.9 ± 54.8 IU/ml respectively; *p*= 0.008). Also, there was a significant increase in fasting insulin level in patients with CT genotype compared to those with CC and TT genotypes (57.3 ± 43.1 *vs.* 87.5 ± 79.2 and 49.9 ± 54.8 IU/ml respectively; p = 0.02). On the other hand there was no statistically significant differences regarding genotypes of IL-4-590 CT, p>0.05 (table 3).

Fasting blood sugar at presentation was significantly lower in patients with CC genotype of IL-13-1112 compared to those of CT and TT genotype (159.7± 63.9 Vs. 201.1 ± 76.9 and 207.50 ± 74.1 mg/dl respectively; p=0.01). Also, FBS was significantly lower in patients with CT genotype compared to other genotypes, (201.1 ± 76.9 versus 159.7± 63.9 and 49.9 ± 54.8 mg/dl respectively; p= 0.02) (table 3).

Regarding insulin resistance, HOMA level, in IL-13-1112 was 32.4±29.5 in CC genotype patients, with marked insulin resistance versus 27.7±25 in CT genotype and 20.2 ± 17.6 in TT genotype which showed less insulin resistance, but these figures did not reach statistical significance (p>0.05) (table 3). Patients of IL-4-590 CC genotype also, was higher in insulin resistance than patients of CT and TT genotypes (36.2±37, 27.7±24, 23.70 ± 30.4 respectively), also still statistically insignificant (p>0.05) (table 3).

No statistically significant difference was noted comparing the frequencies of IL-13-1112 C/T and IL-4-590 C/T genotypes when comparing patient subgroups as regard HBA_{1c}, p> 0.05 (table 3). CT genotype of IL-13-1112 showed lower frequency of patients with retinopathy compared to CC and TT genotype (33.3 *versus* 78.3%) (data not shown).

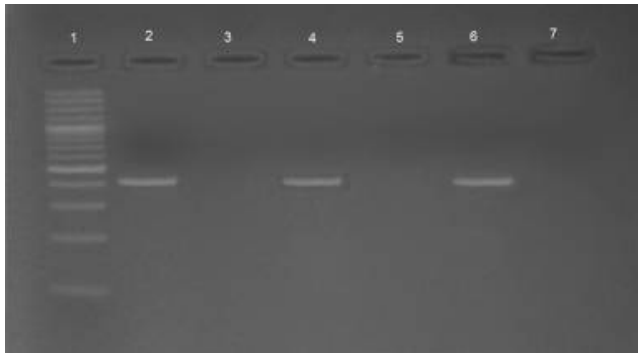

Figure (1): IL-13, Lane 1 DNA ladder 100 bp (fermentas), Lane 2 normal allele band at 400 bp, lane 3 mutant allele no band at 400 bp, this polymorphism (CC).

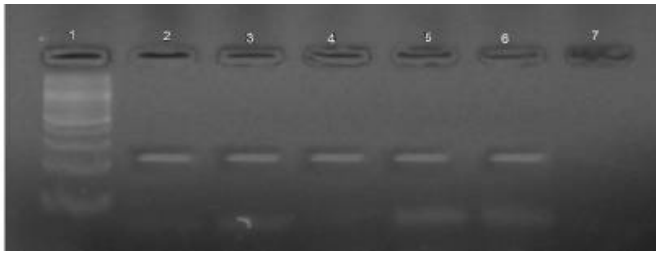

Figure (2): IL-4, Lane 1 DNA ladder 100 bp (fermentas). Lane 2 normal allele band at 215 bp, lane 3 normal allele band at 215 bp this patient (CT) polymorphism. Lane 6 normal allele band at 215 bp and lane 7 mutant allele no band at 215 bp this polymorphism (CC).

DISCUSSION

Immune system plays key roles in the pathogenesis of type 2 diabetes[7]. Cytokines are key mediators which regulate immune response and it is well established that expression of cytokines by immune cells depends on several factors such as infection, inflammation, hormonal condition and also cytokines gene polymorphisms[14].

IL-4 and IL-13 located to a region on chromosome 5q31-q33, this region contains a cluster of proinflammatory cytokines important in immune regulation. IL-4 and IL-13 share a receptor component, IL-4Rα, which has been shown to be an important factor in the development or expression of atopy and asthma[8].

The present study showed that type 2 diabetes mellitus is associated with certain polymorphic genotypes pertaining to Il-4-590 CT and IL-13-1112 CT genes. Homozygosity CC of IL-4-590 gene showed significantly lower frequency in patients when compared to the control group. Heterozygosity CT of IL-4-590 gene showed significantly higher frequency in patients compared to control group. These finding are in agreement with **Ho et al.**[15] who found significant

increase in IL-4-590 CT genotype in Taiwanese with type 2 diabetes mellitus. Similarly, **Achyut et al.**[16] demonstrated a significant association of VNTR polymorphism of IL-4 with increased risk of T2DM, as well as its associated complications in the north Indian population. Also, in contrast to our findings, Maier **et al.**[17] reported lack of association of IL-4 with type 1 diabetes mellitus in white British population. **Jahromi et al.,** [18] have reported no significant differences were found in the frequency of the IL-4-590 C>T polymorphism between T2DM patients and controls in Caucasoid patients.

Nonetheless, these results are in contrast to results of **Arababadi et al.,**[19] who concluded that there was no significant differences between genotype frequencies of IL-4-590 CT genotypes in diabetic and healthy controls in Iranian population.

In addition, insulin levels and blood glucose varied in accordance with patients genotypes. So, there was a significant increase in fasting insulin level in patients with CC genotype of IL-13 compared to those with CT and TT genotypes, fasting blood sugar at presentation was significantly lower in patients with CC genotype of IL-13-1112 compared to those of CT and TT genotype.

Regarding IL-13-1112 C>T genetic polymorphisms, to our knowledge, this is the first report studying the relation between IL-13-1112 (C>T) polymorphism and T2DM. Our results showed a highly significant increase in IL-13 CT genotype in diabetic cases when compared to control group. There is no significant difference in IL-13-1112 allelic frequencies between the diabetic and control group. On the other hand, IL-13-1112 (CC+ TT) was higher in control non-diabetic group versus type 2 diabetic group. For other immune disorders these findings go in hand with the finding of **Cui et al.,** [20] who reported that IL-13-1112 C/T polymorphisms were significantly associated with asthma. **Kim et al., (2003)**[21] found that two IL-13 promoter polymorphisms A-1512C and C-1112T were significantly associated with total IgE levels in Korean children with asthma. These results are in contrast to result of **Maier et al.**[17] who concluded that IL-13 variants are not associated with type 1 diabetes in British patients.

Taking into consideration the fact that genetic polymorphisms are population specific, we can come to the conclusion that IL-4-590 CT and IL-13-1112 CT gene polymorphisms are associated with type 2 DM among Egyptian population. In this respect, we recommend further larger studies in multiplex families.

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التعدد الشكلى لجينات الانترليوكين ٤-٥٩٠ والانترليوكين ١٣-١١١٢ فى مرضى النوع الثانى للسكرى فى مصر

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ملخص البحث ، والهلدف منه: يعتبر النوع الثانى لمرض البوال السكرى الاكثر انتشارا، حيث يحدث ارتفاع لنسبه الجلوكوز فى الدم نتيجه لعدم استجابه خلايا الجسم للانسولين المفرز من البنكرياس. أثبتت الدراسات وجود عده عوامل تؤدى لحدوث النوع الثانى من مرض البوال السكرى منها عوامل بيئيه وعوامل وراثيه واخرى التهابيه. ولذلك كان الهدف من هذا البحث هو دراسه العلاقه بين بعض الجينات المتحكمه فى افراز الانترليوكين وظهور النوع الثانى من مرض البوال السكرى فى منطقه الدلتا – مصر

طرق البحث والمواد المستخدمه : شملت الدراسه ١٣٥ مريضابالنوع الثانى من مرض البوال السكرى منهم ٦٥ ذكور، ٧٠ اناث بمتوسط عمر ٥٦ سنه بالاضافه الى ١٠١ من الاصحاء المتبرعين بالدم كمجموعة ضابطة، حيث تم استخلاص الحامض النووى لجميع الحالات ثم عمل تفاعل البلمره المتسلسل باستخدام البادىء الخاص بجينات الانترليوكين ٤-٥٩٠ والانترليوكين ١٣-١١١٢ .

نتائج البحث: بالتحليل الاحصائى للنتائج تبين وجود اختلافات ذات دلاله احصائيه تفسر ظهور المرض فى الاشخاص الغير متماثلين جينيا وذلك فى الجينات محل الدراسه (الانترليوكين ٤-٥٩٠، الانترليوكين ١٣-١١١٢). وقد نوقشت التفسيرات المحتمله لهذه النتائج - وامكانية الاستفادة منها.