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RESEARCH ARTICLE

Association of TCF7L2 Gene with Familial Combined Hyperlipidemia in Diabetes Mellitus Type 2 Females Iraqi Patients

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Abstract

Genomic polymorphisms of transcription factor7 like 2 {TCF7L2} gene are scanned to be powerfully related to diabetes mellitus type 2 (DM2) in female Iraqi population. The point of this examination was to break down the relationship of TCF7L2 gene polymorphisms with DM2 in a very female populace of Iraq. Familial combined hyperlipidaemia (FCHL) is described by hypercholesterolaemia, hypertriacylglycerolaemia, or both. Also, instabilities in glucose metabolism are normally realized in FCHL. Thus, we guessed that TCF7L2 may add to the genetic defenselessness for this basic dyslipidaemia.. Techniques: 70 DM2 female patients and 60 healthy samples were chosen for the current study. Has been conducted designedly of one primer for amplification to scan the gene and using PCR technique with sequencing. We examined the impact of the TCF7L2 variations on FCHL and its segment characteristics triacylglycerol (TG), apolipoprotein B (ApoB) and total cholesterol (TC). The Results: For total participants, the (T/C *vs.* TG + GT) were significantly greater in samples with DM2 than in healthy controls, and FCHL, TC, ApoB or glucose for DM2 were associated with T>C and G>T .This result revealed that the risk of DM2 was raised by the existence of the T>C and G>T genotype of TCF7L2 gene in Iraqi female. The frequency of the T allele in TCF7L2 gene was greater in DM2 patients than in healthy samples. Conclusions: Our analysis proposed that the genetic polymorphisms of TCF7L2 were significantly related with high T>C and G>T in FCHL families with DM2 in the female populace of Iraq.

Keyword: *DM2 ;TCF7L2; FCHL; Hypertriacylglycerolaemia.*

Introduction

In the transcription factor 7-like 2 gene the intronic variants powered related with diabetes mellitus type two in cases from USA , Denmark and Iceland [1]. These conclusions have been replicated in various investigations of type two diabetes [2, 7]. The association evidence with DM2 appears in Europids [1, 4]. The great versatility assembles box-containing transcription component that has a job in the WNT signalling pathway was TCF7L2.

WNT proteins are amazing controllers of cell differentiation and proliferation, and that s signalling pathway includes proteins that straight contribute in cell adhesion and the transcription of gene [8]. WNT signalling pathway alterations have been located in diseases of human, embracing skeletons ,cancer, cardiovascular and neuronal disorders [9, 10]. Complex genetic disorder Familial combined hyperlipidaemia (FCHL) is related to coronary artery disorder. Influenced people with FCHL may give hypercholesterolaemia,hypertriacylglycerolaemia and blended hyperlipidaemia [11]. Additionally FCHL profiles have been related to medical highlights saw in DM2, for example impaired glucose tolerancem hyperinsulinaemia and hypertriacylglycerolaemia [12, 13].

Thinking about this phenotype cover, we conjectured that the TCF7L2 variations recently connected with DM2 may likewise add to the FCHL phenotype. In the blessing study, we will in general investigate the job of the TCF7L2 variants, recently connected DM2 [1] In FCHL and its part qualities apolipoprotein B, triacylglycerol and total cholesterol in females Iraqi FCHL families. What's more, we tried fasting glucose for relationship with these females Iraqi FCHL families.

The watched outcomes for triacylglycerol were tried for duplication in Finnish FCHL families.

Material and Methods

Samples

A complete of 130 females (age 25-45 years) were registered in this study, seventy patients with DM2 who have attended Specialist, Center for endocrinology and diabetes, Baghdad, from January 2017 to June 2018 and 60 healthy individuals with matches as a control group. Physicians diagnosed all patients, and therefore the study were approved by the Center Ethical Committee. Seventeen cases were categorized as DM2 utilizing the American Diabetes Association criteria [14].

Every member gave composed educated assent. The consideration criteria for FCHL were: total cholesterol (TC) as well as triacylglycerol (TG) (levels ≥age/sex-explicit 110th) families, Iraqi populace percent, we likewise utilized untimely CHD as a consideration rule for the cases [15, 16] to guarantee that families were influenced by the severe unique FCHL standards of Goldstein *et al.* [11] CHD was affirmed either by angiography having suffered from myocardial infarction.

In these people 70 females were delegated DM2. The examination configuration was affirmed by the morals panels of the taking an interest focuses. Samples with impaired malignancy, renal function, chronic inflammatory disease or connective-tissue disease were omitted from this analysis.

Biochemical Analysis

In the female Iraqi FCHL families, every one of the estimations were achieved by the Biotechnology Research/Molecular and Biotechnology laboratory/AL-Nahrain University. Serum glucose and lipid parameters were estimated as depicted before [15, 17].

Patients who utilized lipid-bringing down medications were considered after their lipid-bringing down treatment was pulled back for about a month, in light of the fact that dependent on the information of LDL kinetic and statin disposal rate, for statins four weeks has been clinically seen as a washout period.

DNA Extraction

Total blood samples were collected from vein of 70 Iraqi female patients with DM2 and 60 healthy samples as a control. Total blood was collected into 4ml EDTA tube, then stored in -20°C until farther used. DNA of these samples was extracted by using DNA extraction kit (Geneaid extraction kit, Korea).

Primers and Polymerase Chain Reaction

The (TCF7L2) gene has been conducted by the design of one primer for amplification to scan the gene. A fragment 498 bp was amplified by utilizing reverse primer R: 5′-AG AT GC AG CA AA GC CA AA GT-3′and forward primer F: 5′-TC TC TC CA TG GC TG AC AGTG-3′. The amplification reaction of PCR was approved in using a total volume of 20µl including of 5 µl of master mix (bioneer, USA) and 0.5 µl for each primer and 1.5 µl of DNA template than the mixture was completed to the total volume of 20µl with 12.5 µl of D.W.

The programmed of amplification was done by initial denaturation temperature for 5 min at (94 °C) succeed by 25 cycles of denaturation for 30sec at (94 °C), for 30sec at (60°C) and (72 °C) for 30sec with last incubation for 5 min at (72°C) using a thermal Cycler (Labnet). The products of PCR were detached by agarose gel electrophoresis(1.5%) then ethidium bromide staining and pictured by an introduction to (302nm) ultraviolet light.

Statistical Analysis

All analysis was achieved by utilizing Statistical Package for the Social Sciences (SPSS 20.0, Chicago, USA). Every single, consistent variable were communicated as the mean ± standard deviation (SD). The contrasts between the control and the DM2 patient members were surveyed utilizing independent samples t test. Contrasts in count information between DM2 patients and control members and downright factors, genotype and allele frequencies among patients with DM2 and controls were dissected utilizing the x^2 test.

Logistic regression examination with impact ratios (95% confidence interval (*CI*) and odds ratio (*OR*)) were utilized to evaluate the commitment of real hazard factors. Statistically significant reflected as p value ≤ 0.05.

Results

Table 1 illustrations Statistic and clinical attributes of healthy controls and DM2 patients in the female Iraqi patients. The glucose, TC, TG and Apo B serum concentrations were significantly greater for patients with DM2 than for control samples ($p \leq 0.05$).

Table 1: Statistic and clinical attributes of study members

Characteristics	DM2	Control	p value
Number (n)	70	60	
age (years)	31.24 ± 9.45	30.20 ± 9.45	0.075
TG (mmol/L)	2.06 ± 1.69	1.6±0.49	0.046*
TC (mmol/L)	6.44 ± 1.71	5.4±1.16	0.001 *
ApoB (g/l)	1.78 ± 0.64	1.0±0.29	0.002*
Glucose (mmol/l)	7.04 ± 0.99	4.6±0.38	0.001*

DM2: diabetes mellitus type 2; TC: total cholesterol; TG: triglyceride; ApoB: apolipoprotein B; Glucose values are fasting glucose * $p \leq 0.05$

Genetic Analysis

The results showed there are two fragments amplified of the (TCF7L2) gene has been detected in patients and normal samples 498 bp that represented in Figure 1.

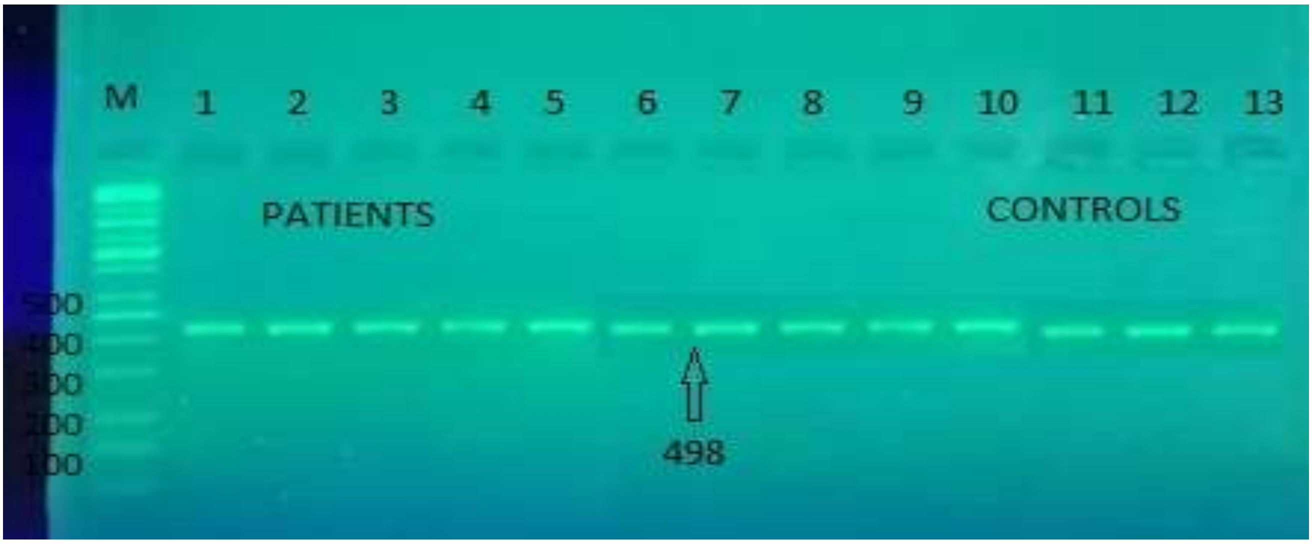
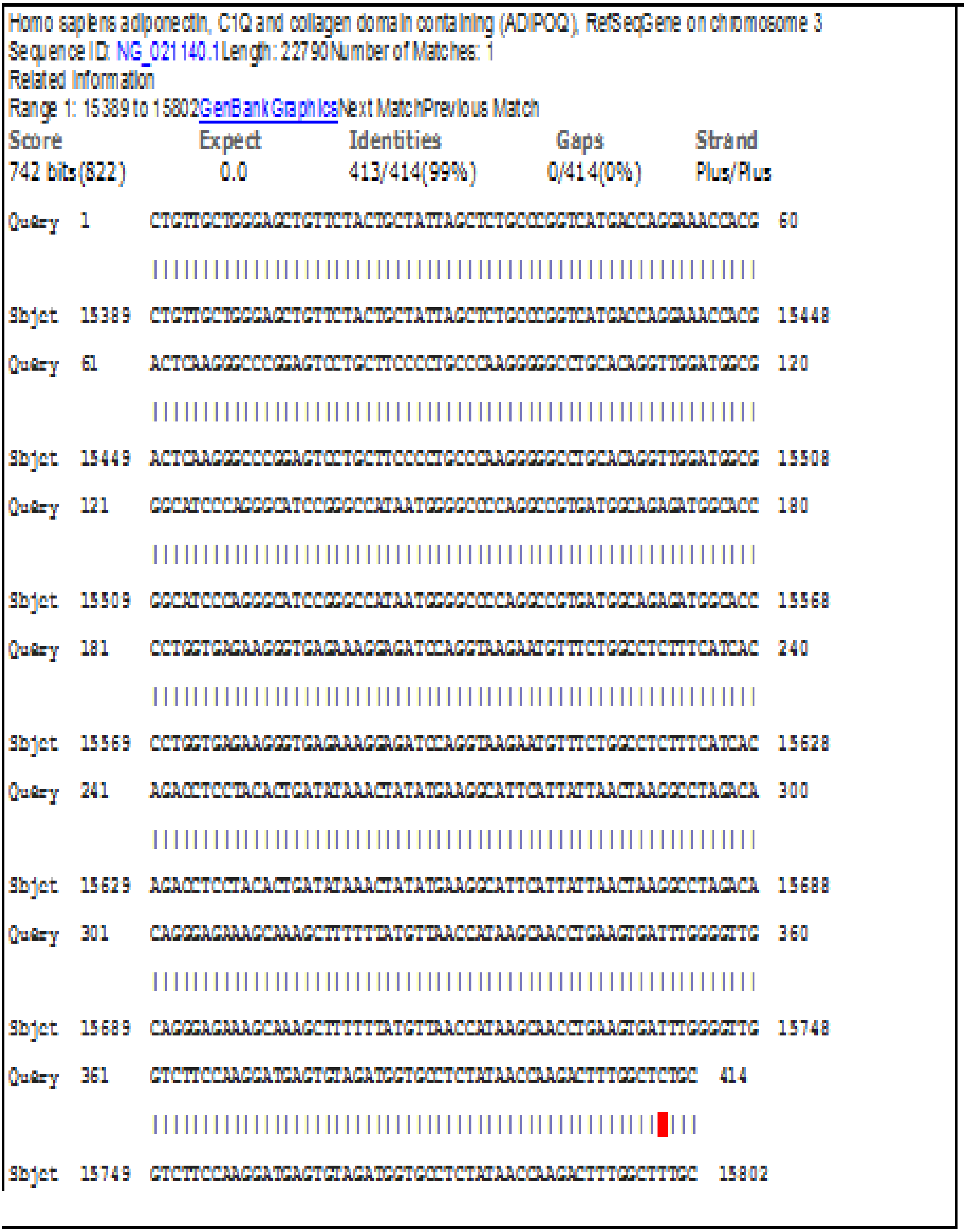


Figure 1: Shows agarose gel electrophoresis for amplified TCl2F7 with fragment 498 bp of children diastases belonging to healthy. Bands were fractionated by electrophoresis on 1.5 % agarose gel (2h, 5v/cm,1x tris-ac;2etoc buffer staining with red safe stain) and visualized under U.V. lane (1,2,3,4,5) represented patients sample and lane (7,8,9,10,11) represented healthy sample

Table 2 :Description of Mutations in region of TCl2F7 by using primer for 498 pb

Sample	No. Of sample	Type of substitution	Location	Nucleotide	Nucleotide change	Amino acid change	Predicted effect	Range of nucleotide
Patients	18	Transition	15799	T>C	INTRON			15389 to 15802
	17	Trinsvertion	15799	T>G	INTRON			15389 to 15802
	17	Trinsvertion	15661	G>T	INTRON			15388 to 15797
	18	Trinsvertion	15430	T>G	GTC>GGC	Glycine ;8 > Glycine	nonsense	15389 to 15801
Control	60	Trinsvertion	15430	T>G	GTC>GGC	Glycine > Glycine	nonsense	15389 to 15798

Figure(2-5) illustrations the alignment of gene bank of TCF7L2 gene in sample controls and patients with DM2 , the sequence done by. In intron the (T>C) variation absorbed in eighteen patients in location 15799 , (T>G) variation absorbed in seventeen patients in location 15799 while in (18) patients were shown the (G>T) variation with glycine amino acid change in location 15661. The (T>G) variation with glycine amino acid change appeared in (60) healthy controls in location 15430.



Figures 2: Alignment of 18 patients sample(T>C) of TCF7L2 gene with standard TCl2F7 from Gene Bank

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Homo sapiens adiponectin, C1Q and collagen domain containing (ADIPOQ), RefSeqGene on chromosome 3
Sequence ID: NG_021140.1Length: 22790Number of Matches: 1
Related Information
Range 1: 15389 to 15802GenBankGraphicsNext MatchPrevious Match
Score            Expect      Identities       Gaps          Strand
742 bits(822)    0.0         413/414(99%)     0/414(0%)     Plus/Plus

Query  1      CTGTTGCTGGGAGCTGTTCTACTGCTATTAGCTCTGCCCGGTCATGACCAGGAAACCACG  60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  15389  CTGTTGCTGGGAGCTGTTCTACTGCTATTAGCTCTGCCCGGTCATGACCAGGAAACCACG  15448

Query  61     ACTCAAGGCCCCGGAGTCCTGCTTCCCCTGCCCAAGGGGGCCTGCACAGGTTGGATGGCG  120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  15449  ACTCAAGGCCCCGGAGTCCTGCTTCCCCTGCCCAAGGGGGCCTGCACAGGTTGGATGGCG  15508

Query  121    GGCATCCCAGGGCATCCGGGCCCATAATGGGCCCCAGGCCGTGATGGCAGAGATGGCACC  180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  15509  GGCATCCCAGGGCATCCGGGCCCATAATGGGCCCCAGGCCGTGATGGCAGAGATGGCACC  15568

Query  181    CCTGGTGAGAAGGGTGAGAAAGGAGATCCAGGTAAGAATGTTTCTGGCCTCTTTCATCAC  240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  15569  CCTGGTGAGAAGGGTGAGAAAGGAGATCCAGGTAAGAATGTTTCTGGCCTCTTTCATCAC  15628

Query  241    AGACCTCCTACACTGATATAAACTATATGAAGGCATTCATTATTAACTAAGGCCTAGACA  300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  15629  AGACCTCCTACACTGATATAAACTATATGAAGGCATTCATTATTAACTAAGGCCTAGACA  15688

Query  301    CAGGGAGAAAGCAAAGCTTTTTTATGTTAACCATAAGCAACCTGAAGTGATTTGGGGTTG  360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  15689  CAGGGAGAAAGCAAAGCTTTTTTATGTTAACCATAAGCAACCTGAAGTGATTTGGGGTTG  15748

Query  361    GTCTTCCAAGGATGAGTGTAGATGGTGCCTCTATAACCAAGACTTTGGCTTGGC  414
              ||||||||||||||||||||||||||||||||||||||||||||||||||| ||
Sbjct  15749  GTCTTCCAAGGATGAGTGTAGATGGTGCCTCTATAACCAAGACTTTGGCTTTGC  15802
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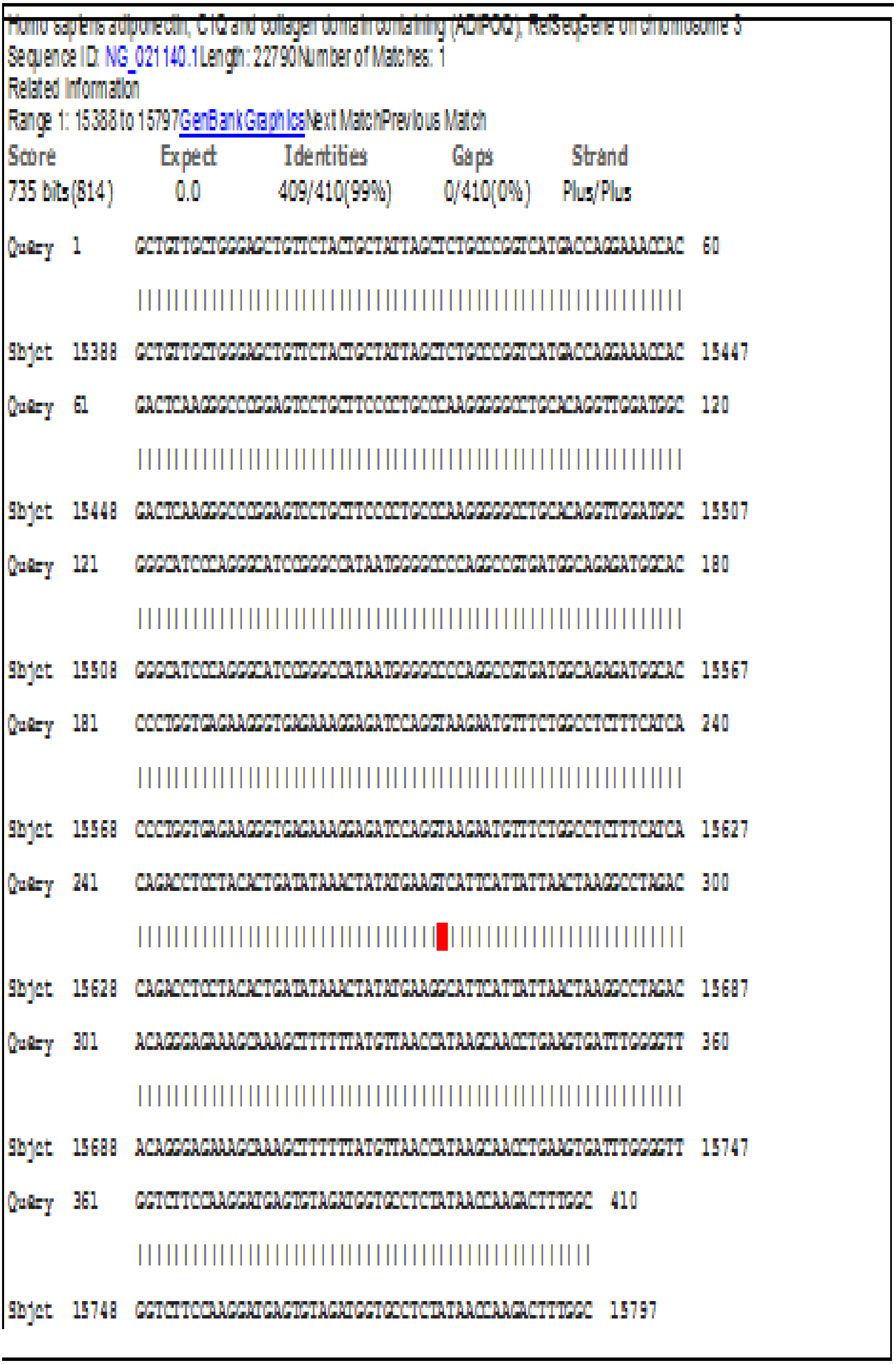
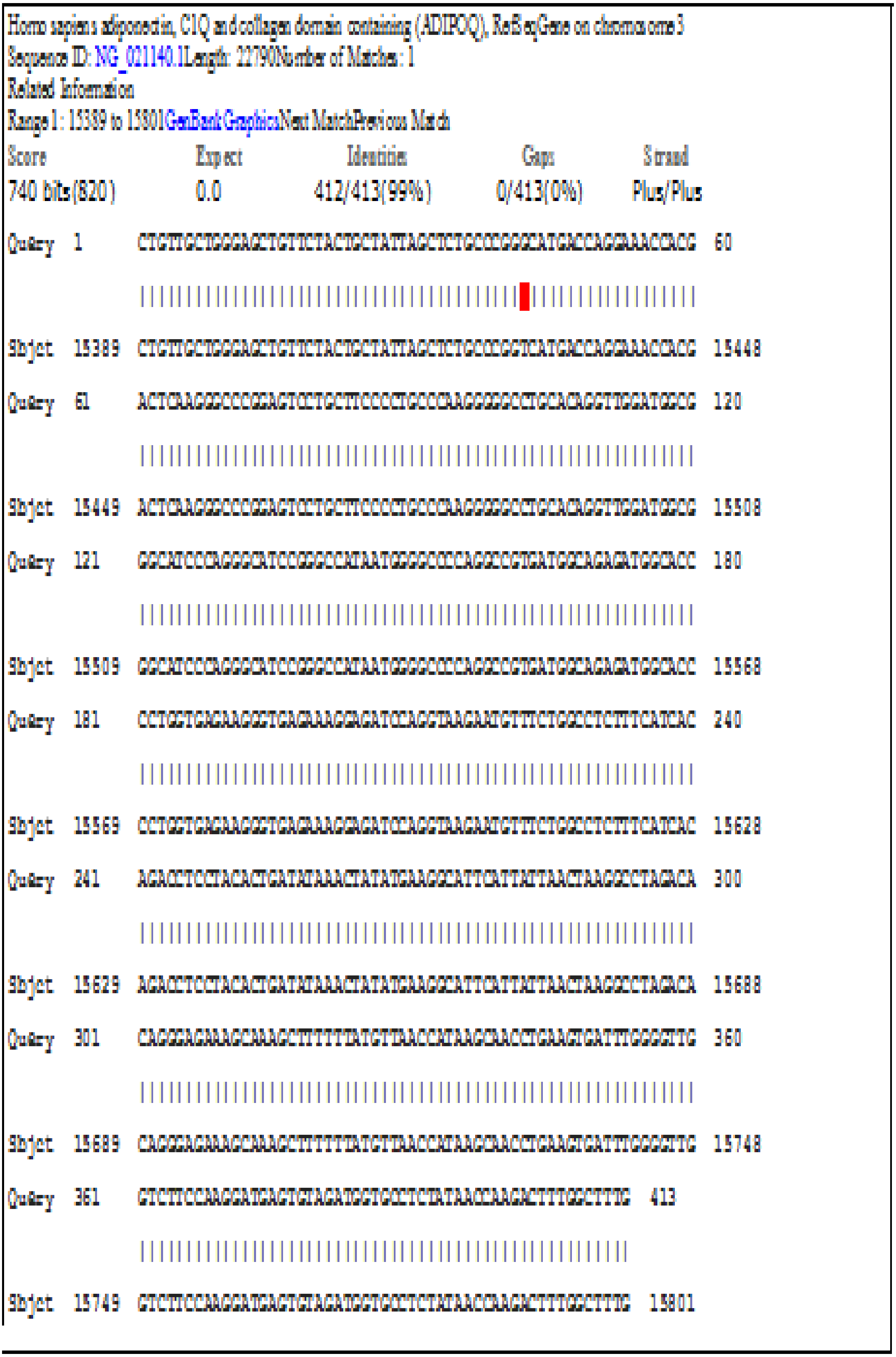
Figures 3: Alignment of 17 patients sample(T>G) of TCF7L2 gene with standard TCl2F7 from Gene Bank



Figures 4: Alignment of 17 patients sample(G>T) of TCF7L2 gene with standard TCl2F7 from Gene Bank



Figures 5: Alignment of 60 controls and 18 patients sample(T>G) of TCl2F7 with standard TCl2F7 from Gene Bank

Table 3 illustrations the distribution of the alleles and genotypes for the variations of TCF7L2 gene in the female Iraqi populace. The distribution of genotypes (T/C *vs*. TG + GT) and allele frequency presented significant difference between DM2 and healthy control samples .For female members, T allele was statically significantly greater in patients with DM2 than in healthy controls.

Table 3: Distributions of variants in DM2 patients and control subjects

Variants	DM2 *n* (%)	Control *n* (%)	*p* value
T/C	**18(25.7%)**	**0(0%)**	**0.022 ***
T/G	**18(25.7%)**	**60(100%)**	
G/T	**17(24.3%)**	**0(0%)**	
Allele			
T	**70(50%)**	**60(50%)**	**0.002***
G	**52(37.15%)**	**60(50%)**	
C	**18(12.85%)**		

Table 4 illustrations the mean of the alleles and genotypes for the variations of TCF7L2 gene in the female Iraqi populace. The T/C and G/T genotypes no found in controls while T/G genotype appear in both subjects, the FCHL and its part qualities apolipoprotein B (ApoB), total cholesterol (TC) and triacylglycerol (TG) were higher significant in patients with diabetets than healthy controls (*p-value* = 0.001).

Table 4: Mean by genotype of the analyzed characteristics for TCF7L2 variants in the patients and controls FCHL families

Samples	Parameters	Variants		
		T/C	T/G	G/T
DM2	**TG**	2.2±0.58	2.8±0.75	2.0±0.63
	TC	5.2±1.08	5.8±1.59	5.2±1.17
	ApoB	1.0±0.30	1.2±0.35	1.0±0.30
	Glucose	5.0±0.51	4.8±0.29	4.8±0.48
Controls	**TG**	0	2.0±0.60	0
	TC	0	5.5±1.52	0
	ApoB	0	1.1±0.36	0
	Glucose	0	4.7±0.40	0

Table 5 illustrations multivariable logistic regression examination consolidating genotypes with following factors: TG, TC and ApoB serum concentrations which were the major frustrating variables for DM2. In the present examination, for all our members, after multivariate change, remain altogether related withDM2 (*OR* = 1.002, 95% confidence interval (*CI*): 1.020–1.760, *p* = 0.021).

Table 5. Numerous logistic regression analysis for control and DM2 patient samples

Risk Factors	*OR*	95% *CI*	*P-value*
T/C *vs.* TG + GT	1.002	1.020–1.760	0.021 *
TG	0.981	0.721–0.922	0.002 *
TC	1.61	1.427–1.603	0.003 *
ApoB	0.029	0.018–0.045	0.006 *

Discussion

We realized that TCF7L2 gene variations were related to DM2 in an Iraqi female populace. Considering multivariate change, the relationship between the polymorphisms of TCF7L2 gene with DM2 were not altered. To the greatest of our insight, this was the principal concentrate to examine the relationship of the polymorphisms of TCF7L2 gene with DM2 in a female populace of Iraqi. Ongoing examinations have reliably demonstrated that TCF7L2 is a strong helplessness gene for DM2 [2, 7]. The past investigations have concentrated on the vital job in malignancy movement and oncogenesis [18, 20].

Utilitarian investigations are needed to recognize the job of TCF7L2 in DM2 and to decide how variations of this gene influence powerlessness to DM2. DM2 is described by weakening insulin emission in light of expanded metabolic interest. This can be credited to faulty ß cell mass and additionally weakened ß cell work [21]. This imperfection in ß cell pay appears to outcome from the association between ecological variables and hereditary inclination. Albeit a few investigations bolster the relationship between DM2 and TCF7L2 variations [1, 6] the hidden pathophysiological components of the related TC7L2 variance are not recognized.

In the current examination, we explored the TCF7L2 variations, beforehand unequivocally connected with DM5, likewise add to the FCHL segment attributes and glucose serum levels in an Iraqi female FCHL family. Our information demonstrates that TCF7L2 variations show huge proof for relationship with great TG for a similar hazard allele in both examination tests.

In the examination test, the frequencies of allele of the T alleles of TCF7L2 variants were lesser than the comparing esteems detailed in African/American and European countries for DM2 [1, 5]. The frequencies of allele for the T alleles of TCF7L2 variants saw in this investigation were, be that as it may, in a decent concurrence with a past TCF7L2 analysis for DM2 in Mexicans [22]. As to the frequencies of allele of this examination relate with the frequencies of allele announced already in Finns people in DM2 [23].

The information exhibited in this investigation give solid proof of a relationship between TCF7L2 gene variations and great TG levels in FCHL families. Although we watched contrasts in the allele frequencies for these variations among patients and controls populaces, we recognized huge proof of relationship with high TG for similar SNPs. The TCF7L2function in adipose tissue is not acknowledged. Curiously, expression of TCF7L2 in adipose tissue is diminished in corpulent subjects with DM2 [24]. The transcription factor of the canonical Wnt signaling pathway encodes by TCF7L2 gene , which is one of the key growth regulatory mechanisms and development of the cell. Wnt signaling assumes a considerable role in insulin secretion and ß cell proliferation [25,26] and impacts synthesis of glucagon-like peptide 1 (GLP-1) in intestinal cells [27].

The GLP-1, working together with insulin, assumes an imperative job in homeostasis of blood glucose, and it has been hypothesized that TCF7L2 gene variations may impact the weakness to DM2 by in a roundabout way adjusting GLP-1 levels [27]. TCF7L2 has been recognized in homeostasis of glucose through the control expression of pro-glucagon gene, that s in intestinal cell was encoded GLP-1 [28].

We conjecture that TCF7L2 and it up 'til now obscure variations might be engaged in adipose function or adipogenesis by adjusting genes transcriptional regulation prompting to deposition TG. In this investigation, we exhibit for the initial time that TCF7L2 a third transcription factor, , recently connected with DM2 is additionally connected with an essential FCHL part attribute, TG, in female Iraqi FCHL families.

These transcription factors manage a course of downstream genes, it is enticing to estimate that moderately secondary variations in transregulation of various objective genes of TCF7L2, HNF4A and USF1 add to the complex FCHL phenotype [16]. Further examinations to investigate the job of TCF7L2 in FCHL could incorporate TCF7L2 resequencing and territorial linkage imbalance investigation into Iraqi FCHL members. This should help distinguish extra variations to be tried for contrasts in functional significance and gene expression in FCHL.

Conclusions

Taking everything into account, to the greatest of our insight, these information is the major to exhibit that the T alleles in TCF7L2 quality are altogether connected with great TG levels in Iraqi female FCHL families. The watched significant difference of TCF7L2 between Iraqi FCHL-and TG-influenced members and normolipidaemic healthy control people gives utilitarian proof that TCF7L2 is in reality engaged with the pathogenesis of FCHL.

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