ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

# RS 290487 Variant of TCF7L2 Gene and Obesity in Egyptian Children.

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**ABSTRACT**

A large proportion of obesity-causing loci remain undiscovered. Researches on the biology of polygenic effects on obesity are needed. To study transcription factor 7-like 2 (TCF7L2) rs 290487 C allele as possible determinants of obesity and associated metabolic changes. The study included 43 obese children and 39 normal weight children. Clinical examination and fasting insulin, glycosylated Hb and lipid profile were measured. The homeostasis model (HOMA-IR) for insulin resistance was calculated. The ultrasonography was used to measure minimum subcutaneous fat thickness (SFT) and the maximum visceral fat thickness (VFT) .Genotyping of TCF7L2 rs 290487 was conducted. No significant difference in allele distributions of TCF7L2 rs 290487 polymorphism in obese and normal weight children. The results showed no associations of TCF7L2 rs 290487 polymorphism and obesity (OR 1.20, 95% CI 0.47 to 3.0; p=0.70). The study found that TCF7L2 rs 290487 polymorphism was not associated with metabolic syndrome (OR 1.36, 95% CI 0.38 to 4.8; p=0.62) or its features. Also, no association between the TCF7L2 rs 290487 C allele and measures of insulin secretion or HOMA-IR. Our study replicates the absence of association between the TCF7L2 rs290487 variant and obesity or associated metabolic changes, visceral fat thickness and metabolic syndrome.

**Keywords:** Obesity, TCF7L2 RS 290487, Metabolic Syndrome.

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ISSN: 0975-8585

## INTRODUCTION

The most risk-conferring allele for type 2 diabetes mellitus (T2DM) is rs 7903146 T allele of the TCF7L2 gene in European population **[1–7]** This allele is rare in other populations **[8]** . TheTCF7L2 rs 290487 C allele has been found to be associated with T2DM in East Asian populations**[8-10].** Their results indicate that TCF7L2 is involved in the pathogenesis of insulin resistance and insulin secretion. Also, TCF7L2 is expressed in some human tissues, including adipose tissue, liver, and heart **[7, 11, and 12].**

Wnts are family of secreted lapidated glycoproteins that might play important roles in adipogenesis and development of pancreatic islets **[13]** .The Wnt signaling pathway is mediated by catenin which is encoded on the TCFL2 gene **[13].**These data provide further support that TCF7L2 may have multiple effects as modulating adipogenesis, insulin sensitivity, and ß-cell functions **[14]** . TCF7L2 was not detected as a risk factor for obesity in European populations **[15]** . Another study revealed that the rs12255372 variant of TCF7L2 had a protective action for obesity in Mexican children **[16]** . So, further investigation to detect the role of TCF7L2 in obesity among different ethnic populations is needed.

We aim to assess the TCF7L2 rs290487 C allele and to show its contribution in obesity of Egyptian children. This TCF7L2 variant was therefore genotyped in obese children as well as in controls.

## MATERIAL AND METHODS

### Study Population

A case control study was conducted on 82 subjects (39 normal weight and 43 obese children).The study protocol was approved by the Human Ethics Committee of National Research Center, and written informed consent was obtained from all children and their parents. They were recruited from pediatrics Clinic at the National Research Centre (NRC). All non-obese volunteers were age-matched healthy subjects in good health and taking no medications. Exclusion criteria in our study were medical conditions associated with obesity such as hypothyroidism, Cushing syndrome or Turner syndrome or subjects taking anti- inflammatory drugs. All included cases and controls were subjected to full medical history taking, and clinical examination.Anthropometric indices: Body weight measured to the nearest 0.1 kg with a balance scale and height measured to the nearest 0.1 cm. Body mass index was calculated as weight divided by height squared (kg/m2). Waist circumference (WC) was measured at the level midway between the lowest rib margin and the iliac crest. Hip circumference (HIPC) was measured at the widest level over the greater trochanters in a standing position by the same examiner; then waist to hip ratio (WHR) and waist to height ratio (WHTR) were calculated **[17]** .

Blood pressure was measured according to American Heart Association guidelines; three times for patients and controls after 5-min rest in sitting position with the use of mercury sphygmomanometer. The mean value of 2nd and 3rd measurement was calculated. Metabolic syndrome is diagnosed by the occurrence of three or more of the following risk factors according to the 2007 International Diabetes Federation (IDF) **[19]** : obesity (particularly increased waist circumference (WC),serum Triglycerides (TG) ≥ 150 mg/dl, High Density Lipoprotiens (HDL) < 40 mg/dl, Blood Pressure (BP) ≥ 130/85, basal blood glucose ≥ 100 mg/dl .

### Method

### Abdominal Ultrasonography

In addition to the routine abdominal ultrasound examination based on the clinical indication, ultrasonography (US) distinctively quantifies visceral fat and subcutaneous fat. We measured the maximum preperitoneal visceral fat thickness (VFT) and the minimum subcutaneous fat thickness (SFT) by US. The visceral fat thickness (VFT) was measured by 3.5 - 5 MHz convex-array probe **[20]**.

**The Laboratory Measurements**

Ten millimeters of venous blood were withdrawn under complete aseptic precautions from fasting subjects (12 - 14 hrs). Samples were labeled and left to clot at room temperature for 15 min then centrifuged; sera were collected and a liquated for evaluation of the following :

1) Determination of complete lipid profile (serum TG, HDL, LDL cholesterol)and fasting blood glucose levels were done using Olympus AU 400 supplied from Olympus Life and Material Science (Europe GmbH, Wendenstraße, Hamburg, Germany) **[21]** .
2) Insulin levels were estimated by Enzyme immunoassay (ELISA).
3) Insulin resistance was calculated by the homeostasis model (HOMA-IR) using the following formula: HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmoL/L)/ 22.5 **[22]** .
4) Glycosylated Hb (HbA1c) was measured using STANBIO Kit.

**DNA Genotyping**

Genomic DNA was extracted using a commercial DNA extraction kit according to manufacture's protocol (QIAamp DNA BLOOD Mini kit ,QIAGEN ,USA ) CAT NO.51104 using automated nucleic acid extractor QIAcube (QIAGEN) . DNA yield was measured by Nano-dropper . The purified genomic DNA showed A *260/280* ratio between 1.7 to 1.9.

Rs 290487 polymorphism was determined by a predesignedTaqman SNP genotyping assay (Applied Biosystems ).Oligonucleotides used for allelic discrimination assays for Rs 290487 as following:context sequences for Rs 290487([VIC/FAM]) CCAGTACAAATCATGGTGACACCA[C/T]GCAAAATTGAAAATGAGAAAGGTGT .The reaction was performed in 25 ul final volume with real time polymerase chain reaction via QuantStudio 12 KFlex Real Time PCR System (Applied Biosystems).For genotyping quality control ,duplicate samples and negative controls were included to insure accuracy .

**Statistical Analysis**

The standard computer program Statistical Package for the Social Sciences (SPSS) for Windows, release 12.0 (SPSS Inc., USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD). Comparison between groups wasmade using Student t test for continuous variables and Chi-Square tests for categorical variables.While the comparison between more than two groups were done by using One Way Analysis of Variance (ANOVA).Odds ratios (ORs) with 95% confidence intervals (CI) were calculated. P values < 0.05 were considered as statistically significant.

**RESULTS**

The study included 43 obese children, and 39 normal weight children, 57.3% females and 42.7% males with no statistical significant difference between groups. Table 1 shows anthropometric, ultrasonography characteristics and laboratory parameters of the obese children and controls. The mean age was 10.8 ±3.3 years in control children, and was 12.0±2.5 years in obese group with no statistical significant difference. The study revealed significant differences between obese children and controls for BMI, subcutaneous fat and visceral fat and liver size (P=0.00).

The genotype and allele distributions of TCF7L2 rs 290487 polymorphism in the study participants are shown in Table 2. No significant difference in allele distributions of TCF7L2 rs 290487 polymorphism in obese and normal weight children.

Regarding the role of gender in allele distributions of TCF7L2 rs 290487 polymorphism, the study showed that it has no roles (Table3).

No significant obesity associations with of TCF7L2 rs 290487 polymorphism(OR 1.20, 95% CI 0.47 to 3.0; p=0.70).We studied the association of metabolic phenotypes with TCF7L2 rs290487 polymorphism .We found thatTCF7L2 rs290487 polymorphism was not associated with metabolic syndrome (OR 1.36, 95% CI 0.38 to 4.8;

p=0.62) or its features. Also, we did not observe any association between the TCF7L2 rs 290487 C allele and measures of insulin secretion (Tables 4&5).

Genotype–phenotype correlations were performed to investigate the association of TCF7L2 rs 290487 C allele and metabolic parameters in obese and control children. Our study revealed that the gene was not correlated with any parameter (Table 6) .

**Table 1: Anthropometric, ultrasonography characteristics and laboratory parameters of the study participants**

| Items | Controls N = 39 | | Obese Children N = 43 | | Sig. (2-tailed) |
|---|---|---|---|---|---|
| | Mean | Std. Deviation | Mean | Std. Deviation | |
| Age Years | 10.8 | 3.3 | 12.0 | 2.5 | NS |
| BMI | 19.63 | 4.34 | 34.65 | 6.37 | 0.00 |
| Subcutaneous Fat [cm] | 1.17 | 0.45 | 2.40 | 0.66 | 0.00 |
| Visceral Fat[cm] | 2.71 | 1.06 | 4.78 | 1.29 | 0.00 |
| Liver size[cm] | 12.01 | 1.66 | 14.80 | 1.64 | 0.00 |
| HOMA-IR | 2.19 | 1.52 | 3.59 | 1.90 | 0.00 |
| FBS mg/dl | 83.82 | 29.47 | 79.47 | 12.23 | 0.38 |
| Cholesterol mg/dl | 161.47 | 31.62 | 167.28 | 36.55 | 0.45 |
| Triglyceride mg/dl | 84.24 | 28.21 | 103.67 | 35.47 | 0.01 |
| HDL-C mg/dl | 54.24 | 14.43 | 43.15 | 12.00 | 0.00 |
| LDL-C mg/dl | 89.29 | 33.90 | 101.72 | 34.24 | 0.11 |
| Fasting insulin uIU/mL | 12.80 | 11.54 | 18.38 | 8.91 | 0.02 |

BMI : Body mass index
HOMA IR : Homeostatic model assessment of insulin resistance
FBS : Fasting blood sugar
HDL-C: High density lipoprotein
LDL-C : Low density lipoprotein

**Table 2: Genotype and allele distributions of TCF7L2 rs 290487 polymorphism In the study participants**

| Study Participants | | TCF7L2 rs 290487 polymorphism | | | Total | Asymp. Sig. (2-sided) |
|---|---|---|---|---|---|---|
| | | CC | CT | TT | | |
| Controls | N | 24 | 13 | 2 | 39 | NS |
| | % | 61.5% | 33.3% | 5.1% | 100.0% | |
| Obese Children | N | 30 | 10 | 3 | 43 | |
| | % | 69.8% | 23.3% | 7.0% | 100.0% | |
| Total | N | 54 | 23 | 5 | 82 | |
| | % | 65.9% | 28.0% | 6.1% | 100.0% | |

ISSN: 0975-8585

**Table 3: Genotype and allele distributions of TCF7L2 rs 290487 polymorphismIn relation to gender**

| GENDER | | TCF7L2 rs 290487 polymorphism | | | Total | SIG |
|---|---|---|---|---|---|---|
| | | TT | CT | TT | | |
| Female | Count | 30 | 13 | 3 | 46 | |
| | % within GENDER | 65.2% | 28.2% | 6.6% | 100.0% | |
| Male | Count | 25 | 9 | 2 | 36 | NS |
| | % within GENDER | 69.4% | 25.0% | 5.6% | 100.0% | |
| TOTAL | Count | 55 | 22 | 5 | 82 | |
| | % within GENDER | 66.3% | 27.7% | 6.0% | 100.0% | |

**Table 4: The association of metabolic phenotypes with TCF7L2 rs290487 polymorphism in the studied parameters**

| TCF7L2 rs 290487 polymorphism / Items | CC N= 54 Mean | CC N= 54 Std. Deviation | CT N= 23 Mean | CT N= 23 Std. Deviation | TT N= 5 Mean | TT N= 5 Std. Deviation | Sig. |
|---|---|---|---|---|---|---|---|
| BMI | 27.40 | 8.81 | 27.66 | 11.27 | 25.56 | 6.79 | 0.90 |
| Subcutaneous Fat [cm] | 1.84 | 0.90 | 1.76 | 0.72 | 1.61 | 0.80 | 0.82 |
| Visceral Fat[cm] | 4.01 | 1.68 | 3.43 | 1.39 | 3.16 | 0.78 | 0.30 |
| Liver size[cm] | 13.65 | 2.03 | 13.31 | 2.43 | 12.12 | 2.02 | 0.82 |
| FBS mg/dl | 81.56 | 24.77 | 82.17 | 16.37 | 76.40 | 8.62 | 0.87 |
| HBA1C% | 5.78 | 0.59 | 5.47 | 0.76 | 5.76 | 1.13 | 0.19 |
| HOMA-IR | 2.89 | 1.70 | 2.92 | 2.17 | 2.98 | 2.40 | 0.99 |
| Fasting insulin uIU/mL | 15.35 | 8.61 | 16.25 | 14.52 | 15.30 | 10.97 | 0.64 |
| Cholesterol mg/dl | 162.72 | 32.57 | 165.35 | 37.83 | 177.60 | 36.32 | 0.64 |
| Triglyceride mg/dl | 93.07 | 33.98 | 95.52 | 34.75 | 102.80 | 22.12 | 0.81 |
| HDL-C mg/dl | 47.92 | 13.86 | 49.34 | 16.18 | 54.86 | 16.21 | 0.59 |
| LDL-C mg/dl | 94.02 | 33.03 | 97.04 | 38.59 | 102.20 | 37.82 | 0.85 |

BMI : Body mass index
FBS : Fasting blood sugar
HBA1C: Glycosylated haemoglobin
HOMA IR : Homeostatic model assessment of insulin resistance
HDL-C: High density lipoprotein
LDL-C : Low density lipoprotein

**Table 5: Odds Ratio results of CC alleles on studied Items**

| ITEM | Obesity | HBA1C% | High Fasting Insulin | High HOMA-IR | Fatty Liver | High Visceral Fat | Metabolic syndrome |
|---|---|---|---|---|---|---|---|
| **Odds ratio** | 1.20 | 1.72 | 1.11 | 0.93 | 0.83 | 2.30 | 1.36 |
| **95 % CI** | 0.47 to 3.0 | 0.68 to 4.3 | 0.43 to 2.81 | 0.34 to 2.57 | 0.33 to 2.07 | 0.68 to 7.77 | 0.38 to 4.8 |
| **P** | P = 0.70 | 0.24 | 0.82 | 0.90 | 0.69 | 0.17 | 0.62 |

HBA1C: Glycosylated haemoglobin
HOMA IR : Homeostatic model assessment of insulin resistance

ISSN: 0975-8585

**Table6: Genotype–phenotype correlations**

| Genotype | | FBS | Cholesterol | TG | HDL-C | LDL-C | HBA1C | Fasting Insulin | HOMA-IR | BMI | SFT | VFT | Liver Size |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TCF7L2 | r | -.005 | .076 | .087 | .092 | .079 | -.147 | -.081 | -.041 | -.050 | -.029 | -.178 | -.137 |
| | P | .966 | .498 | .439 | .409 | .478 | .188 | .464 | .5 | .656 | .803 | .127 | .234 |

BMI : Body mass index
FBS : Fasting blood sugar
TG : Triglycerides
HBA1C: Glycosylated haemoglobin
HDL-C: High density lipoprotein
HOMA IR : Homeostatic model assessment of insulin resistance
SFT : Subcutaneous fat thickness
VFT : Visceral fat thickness

## DISCUSSION

TCF7L2 has been associated with adipogenesis **[23]** and with BMI **[1, 15, 24].** Data on genetic susceptibility of Egyptian populations to obesity and associated inflammatory diseases are very scarce. The aim of this study was to assess the possible association of the TCF7L2 rs 290487polymorphism with obesity in Egypt.

Evaluating BMI and visceral fat thickness showed that no association between both and the TCF7L2 rs 290487polymorphism. This study replicates the absence of association between the TCF7L2 rs 290487 C allele and obesity as observed in Egyptian population. Also TCF7L2 was not identified as a risk factor for obesity in a study involving European populations **[15].** Additionally, another study showed that the rs12255372 variant of TCF7L2 was protective for obesity in Mexican children **[16].**

We did not observe any association between the rs 290487 C allele and metabolic syndrome, or with fasting insulin and glucose levels or HOMA-IR. Other study showed no association of clinical and metabolic characteristics and the distribution of the allele C and CC genotype of the single nucleotide polymorphism rs290487 in non-diabetic patients in Henan province in China **[25].** But an association of T2DM and theTCF7L2 rs 290487 C allele was found in Han Chinese in Henan province in China **[25].**

## CONCLUSION

TCF7L2 rs 290487 C allele was not associated with obesity in our Egyptian children. Also, it was not associated with higher level of metabolic syndrome in obese children.

**Conflict of Interest :** None

All authors have contributed significantly and are in agreement with the content of the manuscript, all authors declare no conflict of interest and no any financial support or relationships that may pose conflict of interest relevant to this work . Authors have full control of all primary data and that they agree to allow the journal to review their data if requested .

## ACKNOWLEDGEMENT

The study was a part of a project supported financially by National Research Centre Fund Egypt , grant no.10010324.

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