


# Association of ENPP1 (K121Q rs 1044498) and TCF7L2 (C/T rs7903146) Gene Polymorphisms with Type2 Diabetes in Zanjan Population (Northwest, Iran)

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## ABSTRACT

**Background & Objective:** Ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) is a class II membrane glycoprotein that binds to insulin  $\alpha$  receptor and can interfere in insulin signaling pathway. Transcription factor-7-like 2 (*TCF7L2*) is a transcription factor which plays a critical role in pancreatic  $\beta$  cell activity. ENPP1 and *TCF7L2* gene polymorphisms may have functional role in susceptibility to type2 diabetes (T2D). The aim of this study was to investigate the association of reported K121Q and C/T rs7903146 variants of *ENPP1* and *TCF7L2* genes with the risk of T2D in our population.

**Materials & Methods:** 240 T2D and 240 healthy subjects were recruited. Genotyping was carried out by PCR-RFLP method. T-test was used for association study.

**Results:** ENPP1 121Q (CC) genotype was significantly higher in T2D comparing to controls (OR;1.61, 95% CI;1.02-2.55,  $P=0.02$ ) and a significant association between the frequency of C allele and T2D was observed (OR;1.339, 95%CI;1.04-1.72,  $P=0.012$ ). TT genotype of *TCF7L2* C>T rs7903146 was significantly higher in T2D patients (OR;0.67, 95% CI;0.49-0.98,  $P=0.02$ ), but the T allele could not significantly affect the risk for T2D in our population.

**Conclusion:** The high frequency of Q allele of the ENPP1 K121Q and TT genotype of the *TCF7L2* might be considered as a predisposing factor for T2D.

**Keywords:** Diabetes Mellitus, Type 2, Ectonucleotide pyrophosphatase phosphodiesterase 1, Polymorphism, Transcription Factor 7-Like 2, PCR-RFLP



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## Introduction

Type 2 Diabetes (T2D) is a progressive multifactorial disease influenced by environmental and genetic factors and can be controlled or prevented if genetic factors are identified, and by changing the environment and lifestyle (1). T2D is a metabolic disease characterized by increase in blood glucose levels, but the cause of increased blood sugar is different in different patients. The main factor controlling and regulating blood sugar is the insulin hormone, which is secreted from pancreatic  $\beta$  cells and acts on cells in different tissues, helping to match the glucose uptake by them, and glucose increase is observed when glucose uptake by cells becomes difficult (2). T2D disease occurs if the levels of insulin secretion decrease for any reason or the cells do not respond properly to insulin secretion and show resistance to it (3). Changes in all genetic factors that play a role in regulating the function of the pancreatic  $\beta$  cells in the pathway for the production and secretion of insulin are good candidates for examination as a cause of diabetes (4). But the study of genetic and environmental factors that regulate the

response of cells to insulin are also important because they lead to insulin resistance and cause T2D (5). Several genes have been investigated in this regard. In some cases, T2D has been suggested as a single-gene disease, but it is believed to be polygenic. Presence of more than 50% T2D occurrence in the children of an affected parent, strengthens the importance of evaluating different candidate genes (6). Determining the genes involved in the onset of diabetes could help define the pathway of disorder leading to diabetes; in that case, appropriate and effective treatment strategies can be identified, and even preventive strategies can be developed (1).

Some genes polymorphisms are associated with impaired pancreatic  $\beta$  cell function in the secretion of insulin. The *TCF7L2* (Transcription factor 7-like 2) gene is located on the long arm of chromosome 10 (10q25.2-q25.3) and has 17 exons and 16 introns. Among the 17 exons of this gene, 4, 13, 15 and 16 can create different isoforms with alternative splicing, and

about 20 different isoforms have been isolated from different cells. In the process of splicing, the polymorphisms of intron IV (IVS IV) are of great importance (7). Studies have shown that the variants of TCF7L2 regulate the expression of various genes in the signaling of the Wnt path. In the intestine, it regulates the expression of the proglucagon gene and the GLP-1 hormone (glucagon like peptide-1). GLP-1 is an incretin hormone that stimulates the secretion of insulin by pancreatic cells after food intake (8).

The ENPP1 gene (Ectonucleotide Pyrophosphatase/Phosphodiesterase) is located on the long arm of chromosome 6 (6q22–q23), which has 25 exons and 24 introns. The product of this gene is an endogenous transmembrane glycoprotein that can inhibit the signaling of the insulin receptor (9). ENPP1 disrupts insulin signaling in various peripheral tissues such as the liver, muscle, fat, and pancreas by inhibiting tyrosine kinase activity of the insulin receptor and somehow causing insulin resistance (10). The ENPP1 protein contains 925 amino acids. Various studies have shown that the amino acid 121 of this protein, coded by the gene's exon 4, is important for its binding to the insulin receptor and the inhibition of its function. If the amino acid 121 is gln (Q), its inhibitory power will be greater than when the lys (K) amino acid is in this position (11). Therefore, K121Q polymorphism can be a predisposing factor for insulin resistance and T2D.

Considering the evidence of the importance of rs7903146 C/T polymorphisms of TCF7L2 gene and rs1044498 K121Q of ENPP1 gene, this study investigated these two polymorphisms in patients with T2D in Zanjan.

## Materials and Methods

In this case-control study, 240 T2D patient and 240 healthy control subjects referred to the Diabetes Clinic entered the study after evaluation by an endocrinologist and necessary ethical clearances.

The diabetic index was considered in accordance with the WHO criteria for fasting blood glucose above 126 mg/dL and HbA1C higher than 6.5. All the selected subjects were over 35 years of age, and 1 mL of blood sample was taken after obtaining an informed written consent from patients.

DNA extraction was performed from all blood samples containing EDTA at the genetic laboratory of Zanjan Islamic Azad University Research Center with the Cinna Pure DNA extraction kit (Sina Clone Iran). In all the samples, an exon region of the ENPP1 gene and an intron region of TCF7L2 were amplified by the PCR method by using specific primer pairs (Table 1).

A 30  $\mu$ L PCR mixture containing 50 ng genomic DNA, 1.5 mmol/L MgCl<sub>2</sub>, 0.5 mmol/L of each dNTPs, and 0.5 pmol of each primer were prepared.

The PCR cycles consisted of an initial denaturation at 95°C for 5 min., followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 1 min s and elongation at 72°C for 30 s. The final extension step occurred at 72°C for 5 min.

PCR-RFLPs were performed for genotype analysis—238bp PCR products of the ENPP1 exon 4 fragment for the analysis of K121Q (A/C) polymorphism was digested with AvaII (Thermo Fisher Scientific). A allele was not digested and gave 238bp fragment and C allele cleaved to 148bp and 90bp fragments (Table 1).

A 266bp PCR product of the TCF7L2 IVS IV fragment for rs7903146 C/T polymorphism detection was digested with RsaI (Thermo Fisher Scientific). RsaI cleaved C allele and gave 233 and 33bp fragments. T allele was not digested (Table 1).

Genotype and allele frequencies for the studied polymorphisms were compared by Fischer's exact test. The agreement of genotype frequencies with the Hardy-Weinberg equilibrium expectation was tested using the X<sup>2</sup> test. Continuous variables were presented as mean  $\pm$  SD and compared by T test. Statistical tests were performed by Statistical Package for Social Sciences (SPSS 18 for Windows; SPSS Inc. Chicago, IL, USA). The results were considered statistically significant when the P-value was less or equal to 0.05.

## Ethics

This study was approved by Tabriz Islamic Azad University medical ethics group (IR.IAU.TABRIZ.REC.1395.37)

**Table 1.** The Specific Primers and Restriction Enzymes for rs1044498 A>C ENPP1 and rs7903146 C>T TCF7L2 Polymorphisms

Polymorphism	Sequence (5'-3')	Annealing TM	Restriction Enzyme	Product Size	Parts of Cutting (bp)	
ENPP1 K121Q rs1044498 A>C	GCAATTCTGTGTTCACTTTGGA	58 °C	AvaII	238	A	238
	TTTCACTATGTATTGTTGCCAGT CAGCAAACAC				C	148 90
TCF7L2 Rs7903146 C>T	CTGAACAATTAGAGACTAAGCA CTTTTTAGGTA	58 °C	RsaI	226	A	266
	TTTCACTATGTATTGTTGCCAGT CAGCAAACAC				C	233 33

**Table 2. Description of Anthropometric, clinical, and metabolic data for all volunteers**

Characteristics	T2D Subjects (N=240)	Control (N=240)	P-value
Men	116	118	-
Women	124	122	-
Age	58.3± 12.7	54.1±11.3	0.169
HbA1C %	8.1±1.5	4.8±0.5	<0.001
FBS mg/dl	157.3±60.2	81.2±13.7	<0.001
Triglycerides mg/dl	188.8±12.9	139.8±38.9	<0.001
Cholesterol mg/dl	181±50.4	167.1±19.6	<0.001
HDL mg/dl	43±8.6	48.7±7.2	0.037
LDL mg/dl	126.3±31.8	96.8±16.9	<0.001

\*Significance ( $P<0.05$ ). Values are expressed as mean + standard deviation (SD), and were compared by t-test.

## Results

Descriptive statistics of the metabolic characteristics of the study population are presented in Table 2. There were no significant differences between the mean age of both T2D and control subjects. Additionally, plasma glucose, HbA1C, total cholesterol, triglycerides, and LDL levels were significantly higher in T2D subjects ( $P<0.001$ ) but the T2D patients had a significantly lower mean HDL ( $P=0.037$ ) levels.

The genotype distribution and allelic frequencies in T2D patients and healthy controls for the ENPP1 A>C K121Q polymorphism are presented in Table 3. The studied genotype and allelic frequencies were in the Hardy-Weinberg equilibrium in both T2D patients ( $X^2=0.026$ ,  $P=0.98$ ) and healthy control groups ( $X^2=0.097$ ,  $P=0.95$ ). The CC and AC genotypes, and C

allele frequencies were significantly higher in T2D patients when compared with controls (Table 3).

The genotype distribution and allelic frequencies in T2D patients and healthy controls for the TCF7L2 IVS IV C>T polymorphism are presented in Table 4. The studied genotype and allelic frequencies were in the Hardy-Weinberg equilibrium in both T2D patients ( $X^2=0.59$ ,  $P=0.97$ ) and healthy control groups ( $X^2=0.043$ ,  $P=0.98$ ). The CC genotype was significantly higher in normal control subjects compared to T2D patients (Table 4). TC heterozygote genotype frequency was not significantly different in T2D and normal subjects ( $P>0.05$ ). We did not observe any significant difference in T and C alleles' frequency among control and T2D patients (Table 4).

**Table 3: Genotypic and allelic distribution of ENPP1 K121Q polymorphism in relation to T2D**

Genotypes	Study groups			
	T2D	Control	P value	OR (CI95%)
AA (Lys/Lys)	60(25%)	86(36%)		Reff*
AC (Lys/Glu)	100(42%)	83(34%)	0.058	1.433(0.92-2.24)
CC (Glu/Glu)	80 (33%)	71(30%)	0.02	1.615(1.02-2.55)
Allele				
A	0.458	0.531		Reff
C	0.542	0.469	0.012	1.339(1.04-1.73)

\*P-value=0.005, OR (CI95%)= 1.68(1.13-2.48)

**Table 4: Genotypic and allelic distribution of TCF7L2 rs7903146 polymorphism in relation to T2D**

Genotypes	Study Groups			P-value	OR (CI95%)
	T2D	Control			
CC	62(26%)	79(33%)		Reff*	
TC	89(37%)	93(39%)	9	0.08	0.731(0.47-1.12)
TT	89(37%)	68(28%)		0.02	0.67(0.45-0.98)
Allele					
C	0.444	0.523		Reff	
T	0.556	0.477		0.34	0.95(0.74-1.21)

\*P-value=0.01, OR (CI95%)= 0.59(0.37-0.94))

## Discussion

In this study, T2D was associated with high levels of triglycerides, cholesterol, and LDL and low HDL. Dyslipidemia could be a side effect of T2D and insulin resistance but because of its importance in terms of cardiovascular disease evaluation and the controlling of lipid profiles, it is suggested for T2D patients. Diabetes is associated with a greater risk of mortality from cardiovascular diseases (CVD) (12).

Increased hepatic secretion of large triglyceride-rich VLDL and impaired clearance of VLDL appears to be of central importance in the pathophysiology of diabetic dyslipidemia (13).

T2D is a metabolic disorder characterized by increased blood glucose levels resulting from problems in insulin secretion, insulin action, or both. Cell insulin resistance plays a major role in T2D and various genetic factors, too, could cause insulin resistance (11).

Ecto-nucleotide pyrophosphatase phosphodiesterase-1 (ENPP1) is an endogenous transmembrane glycoprotein that inhibits insulin receptor signaling and could be related to insulin resistance (9). Glu (Q allele) on 121aa position of ENPP1 is more effective in reducing insulin stimulation of IR autophosphorylation, insulin receptor substrate-1 phosphorylation, phosphatidylinositol 3-kinase activity, glycogen synthesis, and cell proliferation (11).

In this study, we investigated the significant association of Q allele in K121Q polymorphism of ENPP1 gene with T2D. QQ and KQ genotypes frequencies were significantly higher in T2D patients (Table 3).

Fajar *et al.*, in a meta-analysis showed that 121Q allele of ENPP1 is associated with T2D risk in American, European, and African populations (10). In the Chinese population, Li *et al.* investigated Q allele of K121Q polymorphism associated with T2D susceptibility (14). Bhatti *et al.* reported that ENPP1 K121Q polymorphism was not associated with T2D in the north Indian Punjabi population. According to their results, there was no QQ

genotype in their studied population and the frequency of Q allele was low (15).

Over expression of ENPP1 could be a factor that led to insulin resistance and T2D. Instead of over-expression, ENPP1 K121Q polymorphism, with the replacement of Lys 121 with Glu, could influence ENPP1 interaction with insulin receptor on the muscle, fat, and other cells (11). Kang *et al.*, results showed K121 allele carriers were responsive to insulin resistance diminution by BMI (body mass index) reduction. Q121 allele carriers could adopt a different lifestyle and control blood glucose level to prevent T2D (16). Q 121 allele carriers were mostly lean and this variant was not associated with obesity (17). Obesity could be associated with insulin resistance by induction of some cytokines and hormones or augmentation of some metabolites. The ENPP1 Q121 variant affected insulin resistance by the insulin receptor influence and did not seem to be associated with risk of obesity (18).

Sortica *et al.* in a meta-analysis detected a significant association between ENPP1 K121Q polymorphism and increased susceptibility to Diabetic Kidney Disease (DKD) in European and Asian populations (19). Sumi *et al.* reported the association of the ENPP1 Q121 variant with the coronary artery disease. Most of the factors that cause insulin resistance could be a risk factor for coronary atherosclerosis (20). Then, if we evaluate ENPP1 polymorphism in T2D patients or their normal relatives, by suggesting a suitable lifestyle, diabetes can be prevented or delayed and diabetic patients screened for the possibility of other related diseases can improve the quality of life of individuals.

Transcription factor7-like2 (TCF7L2) gene polymorphisms could cause variants of TCF7L2 that are strongly associated with T2D. TCF7L2 is an important factor in pancreatic island function regulation (8). TCF7L2 as a transcription factor regulates glucagon and glucagon like peptide1 (GLP1) with a set-out proglucagon gene

(GCG). It is transcribed in pancreas alpha cells, intestinal L cells, and the colon. GLP1 has potent effects on glucose mediated insulin secretion (GSIS), insulin gene expression, beta cell growth, and differentiation. Therefore, TCF7L2 could be a potential agent for T2D treatment (21).

TCF7L2 intron 4 (IVS IV) sequence variants are important to produce some functional transcript variants of TCF7L2 mRNA that exon 4 involves in it, like C>T rs7903146 (8). In the study of this variant, we did not find any significant allelic frequency difference between T2D and normal subjects but the TT homozygote genotype was significantly associated with T2D. Shokouhi *et al.* reported a significant susceptibility of T allele with T2D in the Iranian Kurdish ethnic group (22). Palizban *et al.* introduced TCF7L2 gene rs7903149 polymorphism as an important risk factor behind the development of T2D (23). Different studies reported that the risk of T2D development in homozygote carriers of TCF7L2 mutant variants was twice higher (24–26).

## Conclusion

A functional study of TCF7L variants showed that some variations like T rs7903146 are associated with decreased insulin secretion (26, 27). Pharmacogenomics analysis reports showed that, in TCF7L2 T rs7903146 variant carriers with T2D, sulfonylurea treatment was not effective (26). The ENPP1 K121Q polymorphism is associated with insulin resistance and modulated the efficacy of lifestyle intervention on the incidence of T2DM (16). In conclusion, detection of genetic factors associated with T2D could help suggest a proper lifestyle and effective treatment. It was good for recognition of diabetes related disorders and controlling them.

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## Conflict of Interest

Authors declare no conflict of interests.

## Author Contributions

S.M. and A.E. designed the study, P.G. and S.M. performed molecular genetic experiments and analyzed data, S.M., and P.G. wrote the paper.

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