# The effect of calpain-10 gene polymorphism on the development of type 2 diabetes mellitus in a Turkish population

Wpływ polimorfizmu genu kalpainy-10 na rozwój cukrzycy typu 2 w populacji tureckiej

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## Abstract

**Introduction:** The variations in the Calpain-10 gene have been suggested to be related to susceptibility to type 2 diabetes mellitus (T2DM) in different populations. In this study, we investigated the relationship between single nucleotide polymorphism (SNP)-19, -44 and -63 in the Calpain-10 gene and the development of T2DM in a Turkish population.
**Material and methods:** A total of 211 subjects were recruited: 118 patients with a diagnosis of T2DM and 93 unrelated healthy subjects.
**Results:** There were no significant differences in the genotype and allele distribution of SNPs studied between the patients with T2DM and controls ($p > 0.05$), whereas the frequencies of 121 haplotype and 122/121 haplotype combination were found to be higher in patients with T2DM than in controls ($p < 0.05$). No association was observed between the variations in the Calpain-10 gene and glycaemic control and lipid parameters ($p > 0.05$). The SNP-19 insertion/insertion was significantly related to increased body mass index (BMI) in male diabetic patients ($p < 0.05$).
**Conclusions:** The present study indicates that 121 haplotype and 122/121 haplotype combination of SNP-19, -44 and -63 in the Calpain-10 gene are associated with the development of T2DM in Turkish patients. **(Endokrynol Pol 2014; 65 (2): 90–95)**

**Key words:** *Calpain-10; haplotype; SNP; type 2 diabetes*

## Streszczenie

**Wstęp:** Zmienność w genie kodującym kalpainę-10 wydaje się być związana z podatnością na cukrzycę typu 2 (T2DM) w różnych populacjach. Autorzy przeprowadzili badanie, w którym ocenili związek między polimorfizmem pojedynczego nukleotydu (SNP)-19, -44 i -63 genu kodującego kalpainę-10 a rozwojem T2DM w tureckiej populacji.
**Materiał i metody:** Do badania zrekrutowano 211 osób: 118 pacjentów z rozpoznaniem T2DM i 93 niespokrewnionych zdrowych osobników.
**Wyniki:** Nie stwierdzono żadnych istotnych różnic w genotypie ani dystrybucji alleli badanych SNP między pacjentami z T2DM a osobnikami kontrolnymi ($p > 0{,}05$), choć częstości występowania haplotypu 121 i kombinacji haplotypów 122/121 była większa u pacjentów z T2DM niż osobników kontrolnych ($p < 0{,}05$). Nie stwierdzono powiązania między zmiennością genu kodującego kalpainę-10 a stopniem wyrównania glikemii i wartościami parametrów gospodarki lipidowej ($p > 0{,}05$). SNP-19 typu insercja/insercja wykazywał znamienny związek ze zwiększonym wskaźnikiem masy ciała (BMI) u mężczyzn z T2DM ($p < 0{,}05$).
**Wnioski:** W przeprowadzonym badaniu wykazano, że haplotyp 121 oraz kombinacja haplotypów 122/121 SNP-19, -44 i -63 w genie kodującym kalpainę-10 wiążą się z rozwojem T2DM w populacji tureckiej. **(Endokrynol Pol 2014; 65 (2): 90–95)**

**Słowa kluczowe:** *kalpaina-10;haplotyp; SNP;cukrzyca typu 2*

## Introduction

Type 2 diabetes mellitus (T2DM) is an important metabolic disease. The number of subjects with diabetes worldwide is expected to be 438 million in 2030 [1]. The pathogenesis of T2DM includes both genetic and enviromental factors, and identifying candidate genes encoding proteins related to β-cell function, secretion and effect of insulin has increased in importance in recent years [2].

Calpain-10 is a member of the calpain superfamily [3]. The Calpain-10 protein which is synthesised from the Calpain-10 gene is an intracellular calcium-dependent cysteine protease and essential for the function of various cell types [3]. The Calpain-10 gene may play a role in the regulation of insulin secretion and effect [4]. Horikawa et al. [5] first reported a significant association between T2DM and the Calpain-10 gene, located on chromosome 2q37.3. Subsequent population studies

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found that polymorphisms in the Calpain-10 gene were related to the development of T2DM [6–11]. But some studies have not supported this relationship [12–15]. Thus, it is important to investigate the relationship between the variations in the Calpain-10 gene and T2DM in different populations. The aim of the present study was to investigate the linkage between SNP-19, -44 and -63 in the Calpain-10 gene and the development of T2DM in Turkish subjects. Moreover, the possible associations of these polymorphisms with body mass index (BMI), glycaemic control and lipid parameters were examined.

## Material and methods

The present study was performed in 118 patients diagnosed with T2DM and 93 unrelated healthy control subjects without diabetes. The patients and controls were recruited from subjects attending the outpatient diabetes, endocrine and internal medicine clinics of Gazi University. The diagnosis of T2DM was based on the American Diabetes Association (ADA) criteria [16]. To rule out diabetes or impared glucose tolerance, an oral glucose tolerance test was performed in control subjects. Detailed medical histories and the medications of the patients included in the study were recorded and physical examinations were performed. Height and weight were measured and BMIs were calculated. Fasting blood glucose (FBG), postprandial glucose (PPG), glycated haemoglobin ($HbA_{1c}$), total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides levels were measured from the collected blood samples. The study was approved by the Ethics Committee of Gazi University and informed consent was obtained from all subjects.

The Calpain-10 Single Nucleotide Polymorphism (SNP)-19, -44 and -63 genotyping were analysed using the polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) method (Biometra, Germany) in extracted DNA from 10 ml peripheral blood samples. SNP-19 and -44 genotyping were studied in the samples from 118 patients and 93 controls, and SNP-63 genotyping was studied in the samples from 111 patients and 93 controls.

### SNP-19
Forward primer 5′-GTTTGGTTCTCTTCAGCGT-GCAG-3′ and reverse primer 5′-CATGAACCCTG-GCAGGGTCTAAG-3′ were used for SNP-19 genotyping. PCR products were separated on 3% agarose gel and stained with ethidium bromide. The Calpain-10 SNP-19 was an insertion/deletion polymorphism and consisted of two or three repeats of a 32 bp sequence. The allele 2 (three repeats) was detected as a 178 bp band and allele 1 (two repeats) was detected as a 146 bp band.

### SNP-44
Forward primer 5′-GCAGGGCGCTCACGCTTGCCG-3′ and reverse primer 5′-GCA TGGCCCCCTCTCT-GATTC-3′ were used for SNP-44 genotyping. PCR products were digested with *Bst*FNI restriction enzyme. The digested products were separated on 3% agarose gel and stained with ethidium bromide. Allele (C) was detected as a 166 bp band.

### SNP-63
Forward primer 5′-AAGGGGGGCCAGGGCCT-GACGGGGGGTGGcG-3′ and reverse primer 5′-AG-CACTCCCAGCTCTCGATC-3′ were used for SNP-63 genotyping. PCR products were digested with *Hha*I restriction enzyme. The digested products were separated on 3% agarose gel and stained with ethidium bromide. Allele (C) was detected as a 192 bp band.

### Statistical analysis
Statistical analysis was performed using SPSS for Windows (Statistical Package for Social Science, version 11.5; Chicago, IL, USA). All data was tested for normal distribution using the Kolmogorov-Smirnov test. Deviations from Hardy-Weinberg equilibrium was tested using $\chi^2$ goodness-of-fit test. Continuous variables were shown as arithmetic mean ± SD or median (minimum-maximum) and categorical variables were shown as number of subjects and ratio (%). Categorical variables were compared by using Pearson $\chi^2$ test. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Comparisons of the groups were examined by Student's *t* test for normally distributed data and Mann Whitney *U* test for non-normally distributed data. One-Way ANOVA test was used to compare normally distributed data of three groups. $p < 0.05$ was considered statistically significant for all analyses.

## Results

The clinical and laboratory features of the patients and controls are set out in Table I. The allelic frequencies of the SNP-19, -44 and -63 were in the Hardy-Weinberg equilibrium (p > 0.05). Since only one diabetic patient had SNP-44 CC genotype, TC/CC ratio was used to compare the frequencies of the patients and controls instead of CC alone. The genotype and allele frequencies of the SNPs studied did not differ between the patients with T2DM and controls (p > 0.05) (Table II). Regarding the frequencies of haplotype and haplotype combinations of SNP-19, -44 and -63; 121 haplotype was significantly more frequent in patients with T2DM compared to the control subjects (p < 0.05) and this haplotype was

**Table I.** *Clinical and laboratory features of the patients and controls*

**Tabela I.** *Cechy kliniczne i laboratoryjne pacjentów i osobników kontrolnych*

| | Controls (n = 93) | T2DM (n = 118) | p |
|---|---|---|---|
| Age (years) | 38.6 ± 13.6 | 55.5 ± 10.0 | < 0.001 |
| Gender (F/M) | 67/26 | 67/51 | 0.02 |
| BMI [kg/m²] | 26.3 ± 5.0 | 29.4 ± 5.1 | < 0.001 |
| Diabetes duration (years) | – | 5 (0.2–30.0) | – |
| HbA1c (%) | 5.3 (3.7–6.0) | 6.6 (5.7–11.3) | < 0.001 |
| FPG [mg/dL] | 87.0 (67.0–113.0) | 133.0 (87.0–391.0) | < 0.001 |
| PPG [mg/dL] | 99.0 (58.0–137.0) | 172.0 (83.0–469.0) | < 0.001 |
| Total cholesterol [mg/dL] | 182.5 (87.0–257.0) | 182.0 (99.0–330.0) | 0.65 |
| HDL cholesterol [mg/dL] | 42.0 (23.0–82.0) | 41.0 (19.0–82.0) | 0.19 |
| LDL cholesterol[mg/dL] | 112.8 (32.8–170.6) | 100.6 (40.6–198.0) | 0.53 |
| Triglycerides [mg/dL] | 123.0 (33–341.0) | 154.0 (51.0–522.0) | < 0.001 |

Data is expressed as mean ± standard deviation or median (minimum-maximum); T2DM — type 2 diabetes mellitus; BMI — body mass index; FPG — fasting plasma glucose; PPG — prandial plasma glucose

**Table II.** *Genotype and allele frequencies of the Calpain-10 polymorphisms*

**Tabela II.** *Częstości genotypowe i alleliczne polimorfizmów genu kodującego kalpainę-10*

| | Controls | T2DM | | Controls | T2DM |
|---|---|---|---|---|---|
| **Genotype frequencies** | | | **Allele frequencies** | | |
| SNP-19 | | | SNP-19 | | |
| del/del | 23 (24.7%) | 22 (18.6%) | deletion | 97 (52.2%) | 105 (44.5%) |
| del/ins | 51 (54.8%) | 61 (51.7%) | insertion | 89 (47.8%) | 131 (55.5%) |
| ins/ins | 19 (20.4%) | 35 (29.7%) | | | |
| SNP-44 | | | SNP-44 | | |
| TC/CC | 37 (39.8%) | 33 (28.0%) | C | 38 (20.4%) | 33 (14.0%) |
| TT | 56 (60.2%) | 85 (72.0%) | T | 148 (79.6%) | 203 (86.0%) |
| SNP-63 | | | SNP-63 | | |
| TT | 35 (40.2%) | 34 (30.6%) | T | 107 (61.5%) | 126 (56.8%) |
| CT | 37 (42.5%) | 58 (52.3%) | C | 67 (38.5%) | 96 (43.2%) |
| CC | 15 (17.2%) | 19 (17.1%) | | | |

T2DM — type 2 diabetes mellitus; del — deletion; ins — insertion; p values > 0.05

found to be associated with a two times increased risk of T2DM [odds ratio (95% CI): 2.04 (1.04–4.01)] (Table III). Additionally, the frequency of 122/121 haplotype combination was significantly higher in the patients with T2DM than in control subjects (p < 0.05) and this haplotype combination was associated with a four times increased risk of T2DM [odds ratio (95% CI): 4.01 (1.30–12.34)] (Table IV).

BMI, FPG, PPG, HbA$_{1c}$, and lipid parameters were not different with respect to the variations in the Calpain-10 gene (p > 0.05). On the other hand, the male diabetic patients who had SNP-19 insertion/insertion showed significantly increased BMI compared to dele-tion/deletion and deletion/insertion (31.5 ± 5.6, 28.1 ± 4.4 and 27.3 ± 4.5, respectively; p < 0.05).

## Discussion

In the present study, genotype and allele frequencies of SNP-19, -44 and -63 in the Calpain-10 gene did not differ between the patients with T2DM and controls. However, regarding haplotype and haplotype combina-tions, we observed, as a new finding, that 121 haplotype and 122/121 haplotype combination of SNP-19, -44 and -63 are associated with two and four times increased risks of T2DM respectively.

**Table III.** *Haplotype frequencies of the Calpain-10 polymorphisms*
**Tabela III.** *Częstości haplotypowe polimorfizmów genu kodującego kalpainę-10*

| Haplotype | Controls (n = 87) | T2DM (n =111) | Odds ratio (95% CI) |
|---|---|---|---|
| 111 | 25 (28.7%) | 36 (32.4%) | 1.19 (0.64–2.19) |
| 121 | 16 (18.3%) | 35 (31.5%) | 2.04 (1.04–4.01)* |
| 221 | 1 (1.1%) | 4 (3.6%) | 3.21 (0.35–29.25) |
| 212 | 12 (13.7%) | 9 (8.1%) | 0.55 (0.22–1.37) |
| 112 | 30 (34.4%) | 31 (27.9%) | 0.66 (0.36–1.21) |
| 122 | 53 (60.9%) | 75 (67.5%) | 1.28 (0.71–2.30) |
| 211 | 19 (21.8%) | 18 (16.2%) | 0.69 (0.33–1.41) |

T2DM — type 2 diabetes mellitus; CI — confidence interval ' * p < 0.05; SNP-44: allele 1 T, allele 2 C, SNP-19: allele 1 del, allele 2 ins, SNP-63: allele 1 C, allele 2 T; Code 1: alleles of SNP-44, code 2: alleles of SNP-19 and code 3: alleles of SNP-63 in haplotypes

**Table IV.** *Haplotype combination frequencies of the Calpain-10 polymorphisms*
**Tabela IV.** *Częstości kombinacji haplotypów polimorfizmów genu kodującego kalpainę-10*

| Haplotype | Controls (n=87) | T2DM (n=111) | Odds ratio (95% CI) |
|---|---|---|---|
| 212/112 | 3 (3.4%) | 1 (0.9%) | 0.25 (0.02–2.49) |
| 212/122 | 9 (10.3%) | 8 (7.2%) | 0.67 (0.24–1.82) |
| 211/211 | 1 (1.1%) | – | – |
| 211/112 | 5 (5.7%) | 8 (7.2%) | 1.27 (0.40–4.04) |
| 211/111 | 1 (1.1%) | 1 (0.9%) | 0.78 (0.04–12.68) |
| 211/122 | 10 (11.5%) | 6 (5.4%) | 0.44 (0.15–1.26) |
| 211/121 | 2 (2.3%) | 3 (2.7%) | 1.18 (0.19–7.22) |
| 112/112 | 3 (3.4%) | 1 (0.9%) | 0.25 (0.02–2.49) |
| 112/122 | 11 (12.6%) | 14 (12.6%) | 0.99 (0.42–2.32) |
| 111/111 | 1 (1.1%) | 1 (0.9%) | 0.78 (0.04–12.68) |
| 111/112 | 8 (9.2%) | 7 (6.3%) | 0.66 (0.23–1.91) |
| 111/122 | 9 (10.3%) | 16 (14.4%) | 1.46 (0.61–3.48) |
| 111/121 | 6 (6.9%) | 11 (9.9%) | 1.48 (0.52–4.18) |
| 222/122 | 3 (3.4%) | – | – |
| 221/122 | 1 (1.1%) | 3 (2.7%) | 2.38 (0.24–23.37) |
| 221/121 | – | 1 (0.9%) | – |
| 122/122 | 6 (6.9%) | 10 (9.0%) | 1.33 (0.46–3.83) |
| 122/121 | 4 (4.6%) | 18 (16.2%) | 4.01 (1.30–12.34)* |
| 121/121 | 4 (4.6%) | 2 (1.8%) | 0.38 (0.06–2.12) |

T2DM — type 2 diabetes mellitus; CI — confidence interval; * p < 0.05; SNP-44: allele 1 T, allele 2 C, SNP-19: allele 1 del, allele 2 ins, SNP-63: allele 1 C, allele 2 T; Code 1: alleles of SNP-44, code 2: alleles of SNP-19 and code 3: alleles of SNP-63 in haplotypes

The relationship between the Calpain-10 gene and the development of T2DM has been investigated in previous studies. But findings have varied according to different populations and ethnic groups. The study of Horikawa et al. [5] was the first to report that the Calpain-10 gene on chromosone 2 may contribute to the development of T2DM. In that study, SNP-19, -43 and -63 were found to be associated with T2DM in Mexican American and Northern European populations and 112/121 haplotype combination was associated with a 2.8 times increased risk of T2DM in Mexican-American, 4.9 times in German and 2.5 times in Finnish populations [5]. They also suggested that polymorphisms in the Calpain-10 gene, not individually but in combination, account for the increased risk of T2DM. Chen et al. [17] reported that subjects who had 221 haplotype of SNP-43, -56 and -63 showed increased risk of T2DM, whereas allele and genotype frequen-

cies of these SNPs did not differ between T2DM and controls in Nigerians. In a study evaluating SNP-43, -19 and -63 haplotype combinations, SNP-43 A allele was found to be associated with the risk of T2DM, and 121/221 haplotype combination was associated with T2DM, in a Tunisian population [18]. The study of Adak et al. [19] showed that the SNP-63 T allele and 112 haplotype combination of SNP-43, -19 and -63 were related to an increased risk of T2DM in an Indian population. In another study from the same population, those SNPs showed no significant differences between T2DM and controls individually but, when combined, 2111 haplotype combination was found to be associated with the development of T2DM [9]. Moreover, Orho-Malender et al. [20] reported SNP-43 G allele, SNP-63 T allele and 1121/1121 haplotype combination of SNP-44, 43, -19 and -63 to be related to the risk of T2DM in a Finnish population. Similarly, Cassell et al. [7] found that subjects with a 1112/1121 haplotype combination of the same polymorphisms had a 5-6 times increased risk of T2DM in an Indian population. Regarding SNP-44 alone, it has been reported that SNP-44, located in intron 3 and 11 bp from SNP-43, was independently associated with T2DM in an English population [21]. Also, a meta-analysis on the association between SNP-44 and T2DM showed that SNP-44 significantly contributes to the susceptibility to T2DM [22]. Also, a previous study from our country reported that SNP-44 TC genotype in the Calpain-10 gene was associated with T2DM in Turkish subjects [23]. The importance of our study is the haplotype analyses performed. These analyses showed that SNPs in the Calpain-10 gene in the development of T2DM are more prominent when combined.

Additionally, there have been other reports showing the possible protective effect of Calpain-10 gene on T2DM. Wu et al. [24] reported that the presence of 112/221 haplotype combination of SNP-43, -19 and -63 may have a protective role in the development of T2DM. A study from a Northern Han Chinese population [25] also suggested that 1112/1221 haplotype combination of SNP-44, -43, -19 and -63 is a protective factor for T2DM. In our study, we did not observe any protective effects of SNPs studied on the development of T2DM.

On the other hand, some previous studies have reported a lack of association between SNPs in the Calpain-10 gene and T2DM. The study of Evans et al. [21] found that SNP-19, -43 and -63 in the Calpain-10 gene did not contribute to the risk for T2DM in an English population. In line with this data, Malecki et al. [6] observed similar genotype, allele and haplotype frequencies of SNP-19 -43 and -63 in either T2DM or controls in a Polish population. However, they suggested that 121/121 haplotype combination may increase the development of T2DM only in patients with a positive family history of diabetes. Additionally, the study of Rasmussen et al. [26] in Scandinavians and the study of Fingerlin et al. [14] in a Finnish population did not find any relationship between the SNP-19, -43, -56, -63 in the Calpain-10 gene and the development of T2DM. These controversial results may arise from ethnic heterogeneity or possible interactions between genetic, behavioural and enviromental factors.

Regarding the mechanisms by which Calpain-10 gene influences the development of T2DM, Baier et al. [27] suggested that polymorphisms in the Calpain-10 gene lead to decreases in glucose oxidation and turnover in skeletal muscle in Pima Indians with normal glucose tolerance. Another study showed that Calpain-10 polymorphisms are associated with insulin resistance and increased free fatty acids [20]. A recent study also showed that a polymorphism in the Calpain-10 gene may have an effect on insulin sensitivity in metabolic syndrome [28]. However, the underlying mechanisms of the relationship between the Calpain-10 gene and T2DM are not fully known.

A recent animal study suggested that Calpain-10 may have a role in the regulation of obesity in mice [29]. In the present study, we observed that the SNP-19 (insertion/insertion) is associated with increased BMI in male diabetic patients. In accord with our result, Shima et al. [30] found that SNP-19 insertion/insertion is associated with increased BMI in both genders. Demirci et al. [23] also reported increased BMI in patients with T2DM who had SNP-44 TC genotype. Similarly, the frequency of SNP-44 CC genotype was found to be increased in obese patients with T2DM compared to non-obese patients [25].

Taken together, Calpain-10 gene may be a risk factor for obesity in patients with T2DM. In our study, the reason why the relationship between SNP-19 and increased BMI has been detected only in men is unclear. Most previous studies on Calpain-10 did not find a gender-specific effect of this gene on metabolic parameters. On the other hand, a previous study including offspring of patients with T2DM showed that SNP-43, but not SNP-19 or -44, was associated with the intra-abdominal fat area in men and the authors suggested that Calpain-10 may increase the risk of T2DM via affecting abdominal obesity in men with high risk for T2DM [31]. Therefore, the relationship between Calpain-10 and increased BMI in men presented in our study needs to be investigated extensively.

In conclusion; although we found similar genotype and allele frequencies between the patients with T2DM and controls, we showed that 121 haplotype and 122/121 haplotype combination of SNP-19, -44 and -63 in the Calpain-10 gene were associated with the development of T2DM in this Turkish population.

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