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Lack of association of the calpain-10 Indel-19 variant with chronic diseases in a Mexican population

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Abstract

Objective The *CAPN10* gene encodes a protein that regulates insulin secretion and glucose uptake. Its variant Indel-19 has been associated with an increased risk of type 2 diabetes mellitus, diabetes-related traits, and some chronic disorders, mainly obesity. This study aimed to investigate the association between the *CAPN10* Indel-19 variant and some clinical parameters in a Mexican population sample. We recruited 426 apparently healthy individuals over 30 years of age. We obtained anthropometric data, arterial pressure, fasting biochemical parameters, and genotyping for *CAPN10* Indel-19.

Results The frequency of overweight and obesity was 82.9%, hypertension 8%, hypercholesterolemia 14.8%, hypertriglyceridemia 31.9%, impaired plasma glucose 23.9%, and diabetes 4.7%. The genotype frequencies were 13.1%, 47.9%, and 39% for *del/del*, *del/ins*, and *ins/ins*, respectively; the allele frequencies were 37.1% for the *del* allele and 62.9% for the *ins* allele. The analysis of the continuous parameters according to the genotypes showed no significant differences. However, when these parameters were dichotomized (reference group *versus* high-level group), the *ins* allele was associated with a protective effect against high arterial pressure (prehypertension and hypertension). It is unclear whether the *CAPN10* Indel-19 variant increases the risk of chronic diseases, so further studies are needed to confirm or refute this issue.

Keywords *CAPN10* gene, Indel-19 variant, Chronic diseases

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Introduction

The calpain-10 (*CAPN10*) gene, located on chromosome 2q37.3 (GRCh38: 2:240,586,734 – 240,599,104), consists of 15 exons and encodes up to eight isoforms of protein by alternative splicing [1, 2]. Calpain-10 belongs to a family of calcium-dependent non-lysosomal cysteine proteases that may be involved in the regulation of insulin secretion [3–5] and glucose uptake by skeletal muscle cells [6, 7] and adipocytes [8]. Calpain-10 has also been implicated in signal transduction, cell proliferation, differentiation, apoptosis, cell cycle progression, membrane fusion, and platelet activation [9]. Moreover, it has been shown that acute exposure to a high glucose environment stimulates *CAPN10* gene expression in pancreatic INS-1 cells [4]. Initially, the *CAPN10* gene was associated with an increased risk of type 2 diabetes mellitus by the SNP-43 variant (rs3792267) and a haplotype composed of three variants, including the SNP-19 (Indel-19; rs3842570: 32 bp insertion/deletion in the intron 6) [2], of which the *del* allele is of minor frequency, ranging from 31.6% in Koreans to 45% in West Africans [10]. Because CAPN10 plays a role in cellular metabolism, some variants, such as Indel-19, have also been associated with several diabetes-related traits [11–17]. In addition, Indel-19 has been related to several chronic disorders in different populations worldwide, such as obesity [18–21], increased glycated hemoglobin (HbA_{1c}) [17], impaired plasma glucose and insulin resistance [19, 22], dyslipidemia [21, 22], and hypertension [22]. In this study, we investigated the association between the *CAPN10* Indel-19 variant and several clinical and metabolic parameters in a selected sample of a Mexican population.

Materials and methods

Analyzed subjects

Four hundred and twenty-six subjects over 30 years of age without a diagnosis of diabetes or arterial hypertension and who were unaware of their health status were consecutively selected to participate in this study. There were 319 women and 107 men between the ages of 30 and 64 years (mean 48.9 ± 8.6 years). All participants were recruited at the Genetics Laboratory of the Faculty of Medicine of the Universidad Autónoma de Sinaloa in Culiacán, Sinaloa México. Blood pressure, weight, height, and waist circumference were measured, and body mass index (BMI) was estimated. All these measurements were taken jointly by the same two investigators. BMI was classified as normal (≤ 24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30.0 kg/m^2). Blood pressure was classified as normal (119/79 mm Hg), prehypertension (120/80–139/89 mm Hg), and hypertension (≥ 140/90 mm Hg). Fasting biochemical parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and HbA_{1c} were determined using a KONTROLab AutoKem II™ analyzer. The reference values were as follows: for glucose, normal (< 100 mg/dl), impaired FPG (fasting plasma glucose) (100–125 mg/dl), and high (≥ 126 mg/dl); for cholesterol, normal (< 200.0 mg/dl) and high (≥ 200.0 mg/dl); for triglycerides, normal (< 150.0 mg/dl) and high (≥ 150.0 mg/dl). A blood sample was also taken for DNA isolation. This study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by our ethics committees. Informed consent was obtained from each participant before enrollment in the analysis.

Genotyping

DNA was isolated from peripheral blood cells using the CTAB-DTAB method. Genotyping for the Indel-19 variant was performed by endpoint PCR using the following oligonucleotides 5'-GTTTGGTTCTCTTCAGCGTGGAG-3' and 5'-CATGAACCCTGGCAGGGTCTAAG-3', according to the conditions described previously [10]. Briefly, the reaction was performed in 20 µL containing 1X PCR buffer, 200 µM of each dNTP, 10 pM of each primer, 1.5 mM MgCl2, 5% dimethyl sulfoxide, 2.0 units of Taq Platinum DNA polymerase (Invitrogen, USA), and 50 ng of DNA. Amplification was performed as follows: initial denaturation at 96 °C/12 min, 35 cycles of 96 °C/30 s, 60 °C/30 s, and 72 °C/30 s, terminating at 72 °C/10 min. The allele with two repeats (*del*) yielded a fragment of 155 bp and the allele with three repeats (*ins*) rendered a band of 187 bp (not shown). Allele and genotype frequencies were determined from the genotypes obtained.

Statistical analysis

SPSS 24.0 software was used for statistical analysis. The Hardy-Weinberg equilibrium was estimated from genotype frequencies using the chi-squared test. Mean was calculated for each continuous variable, and a comparison of means among the three genotype groups was analyzed using the Kruskal-Wallis test. Qualitative variables, such as obesity, hypertension, hypercholesterolemia, and impaired FPG were dichotomized and evaluated by logistic regression, using the chi-squared test. The *del/del* genotype and the *del* allele were used as reference, and codominant (*del/del vs. del/ins*; *del/del vs. ins/ins)*, dominant (*del/del vs. del/ins + ins/ins)*, and recessive (*del/del + del/ins vs. ins/ins)* inheritance models were tested. The difference was considered statistically significant at $p \leq 0.05$.

Results

A total of 426 subjects were recruited, of whom 20 were detected with diabetes and 34 with hypertension. Table 1 shows the average clinical and metabolic traits of the analyzed sample; parameters are expressed

Table 1 Clinical and metabolic data in a selected sample of 426 Mexican subjects

Parameter	Value
BMI (kg/m^2)	29.1 ± 4.7
Waist circumference (cm)	96.1 ± 8.4
SP (mm Hg)	119.1 ± 23.4
DP (mm Hg)	78.7 ± 11.3
FPG (mg/dl)	95.2 ± 14.4
HbA_{1c} (%)	5.59 ± 0.54
Triglycerides (mg/dl)	139.2 ± 82.9
Total cholesterol (mg/dl)	188.2 ± 39.5
LDL cholesterol (mg/dl)	113.6 ± 31.7
HDL cholesterol (mg/dl)	49.7 ± 11.5

Notes: Data are expressed as mean ± standard deviation. BMI: Body mass index. SP: Systolic pressure. DP: Diastolic pressure. FPG: Fasting plasma glucose. HbA_{1c}: Glycated hemoglobin. LDL: Low-density lipoprotein HDL: High-density lipoprotein

as mean ± standard deviation. The genotype frequencies were 13.1%, 47.9%, and 39% for *del/del*, *del/ins*, and *ins/ins*, respectively; the allele frequencies were 37.1% for the *del* allele and 62.9% for the *ins* allele. The genotype frequencies were in Hardy-Weinberg equilibrium (χ^2=0.29; $p = 0.68$). Table 2 shows the analysis of clinical and metabolic parameters according to the genotypes. No significant differences were observed for any of them. Regarding qualitative characteristics, the frequency of overweight and obesity was 82.9%, prehypertension 15.7%, hypertension 8%, hypercholesterolemia 14.8%, hypertriglyceridemia 31.9%, impaired FPG 23.9%, and diabetes 4.7%. Table 3 shows the analysis of the dichotomized qualitative variables *versus* the genotype for each trait. No increased risk was found for any of the variables. On the contrary, the *ins* allele was associated with a protective effect against high arterial pressure (prehypertension and hypertension) (OR = 0.72, 0.52–0.99; $p < 0.05$).

Discussion

Despite the sampling of seemingly healthy individuals, 20 subjects with diabetes and 34 with hypertension were enrolled. This finding underscores the need to improve health campaigns for the early detection of these disorders in our population. Chronic diseases such as diabetes, obesity, hypertension, and dyslipidemia undoubtedly have a genetic background, but these conditions are also influenced by environmental factors that interact with genes to increase or decrease their risk [23–25]. In our study, none of the *CAPN10* Indel-19 genotypes was associated with an increase in any quantitative clinical or metabolic parameter. Rather, the *ins* allele was associated with a protective effect against arterial pressure ≥ 120/80 mm Hg.

Regarding quantitative variables, our results differ from those of other comparable studies. For example, the *ins/ins* genotype was associated with higher HbA_{1c} ($p = 0.024$) and higher BMI ($p = 0.003$) in Japanese [18], with higher oral glucose tolerance values ($p = 0.014$) and insulin resistance ($p = 0.022$) in Spanish [22], and with increasing FPG ($p = 0.02$) in Mexican children aged 4–18 years [19], the *del/ins* genotype was associated with higher LDL cholesterol levels and lower blood pressure (systolic, 0.007; diastolic, 0.005) in Spanish [22], higher mean in BMI ($p = 0.041$) and triglycerides ($p = 0.034$) in individuals from another Mexican population [21], while the *del/del* genotype was associated with higher HDL cholesterol ($p = 0.034$) in normoglycemic subjects from western Iran [26]. Furthermore, in a study conducted on women with gestational diabetes, the *ins/ins* genotype was associated with higher glucose levels ($p = 0.006$) in the Mexican population [27]. In contrast, the *del* allele was related to impaired glucose metabolism in pregnant women from a Chinese population ($p = 0.012$) [28]. However, studies performed for the *CAPN10* Indel-19 variant in healthy offspring of diabetic patients found no significant effect

Table 2 Analysis of clinical and metabolic parameters according to Indel-19 genotypes

Parameter	del/del *n* = 56	del/ins *n* = 204	ins/ins *n* = 166	*p* value*
Age (years)	47.3 ± 8.8	49.7 ± 8.3	48.5 ± 8.7	ND
BMI (kg/m^2)	29.8 ± 4.7	29.0 ± 5.1	29.1 ± 4.1	0.61
Waist circumference (cm)	97.8 ± 9.8	95.5 ± 8.3	95.4 ± 8.3	0.44
SP (mm Hg)	122.2 ± 18.0	119.3 ± 15.7	117.8 ± 10.9	0.52
DP (mm Hg)	81.9 ± 14.7	79.8 ± 11.0	75.9 ± 10.8	0.08
FPG (mg/dl)	97.6 ± 12.0	94.2 ± 16.8	95.0 ± 11.9	0.15
HbA_{1c} (%)	5.61 ± 0.53	5.58 ± 0.58	5.54 ± 0.44	0.95
Triglycerides (mg/dl)	133.6 ± 97.9	142.0 ± 82.1	137.8 ± 79.0	0.48
Total cholesterol (mg/dl)	191.4 ± 38.2	186.6 ± 37.9	189.5 ± 41.3	0.83
LDL cholesterol (mg/dl)	115.8 ± 39.8	110.3 ± 30.1	116.1 ± 36.2	0.43
HDL cholesterol (mg/dl)	50.1 ± 10.3	49.5 ± 10.7	50.4 ± 12.9	0.89

Notes: Data are expressed as mean ± standard deviation. BMI: Body mass index. SP: Systolic pressure. DP: Diastolic pressure. FPG: Fasting plasma glucose. HbA_{1c}: Glycated hemoglobin. LDL: Low-density lipoprotein HDL: High-density lipoprotein. ND: Not determined. *Kruskal-Wallis test*

Table 3 Analysis of the qualitative variables according to the genotypes and alleles of Indel-19

Genotype/Allele	Normal	High[a]	OR (95% CI)	*p*value[b]
BMI				
del/del	8	48	Reference	
del/ins	35	169	0.81 (0.35–1.85)	0.61
ins/ins	30	136	0.76 (0.32–1.76)	0.52
del	51	265	Reference	
ins	95	441	0.89 (0.62–1.30)	0.55
Arterial pressure				
del/del	39	17	Reference	
del/ins	151	53	0.81 (0.42–1.54)	0.51
ins/ins	135	31	0.53 (0.26–1.05)	0.07
del	229	87	Reference	
ins	421	115	**0.72 (0.52–0.99)**	**0.04**
Cholesterol				
del/del	45	11	Reference	
del/ins	175	29	0.68 (0.32–1.46)	0.32
ins/ins	143	23	0.66 (0.30–1.45)	0.30
del	265	51	Reference	
ins	461	75	0.85 (0.57–1.24)	0.40
Triglycerides				
del/del	41	15	Reference	
del/ins	132	72	1.49 (0.77–2.88)	0.23
ins/ins	117	49	1.15 (0.58–2.26)	0.70
del	214	102	Reference	
ins	366	170	0.97 (0.72–1.31)	0.87
Glucose				
del/del	35	21	Reference	
del/ins	146	58	0.66 (0.36–1.23)	0.19
ins/ins	123	43	0.58 (0.31–1.11)	0.10
del	216	100	Reference	
ins	392	144	0.79 (0.59–1.08)	0.14

Notes: Only the analysis under a codominant model is shown, but the analysis under other inheritance models also showed no significant differences. BMI. Body mass index.[a]*High (BMI ≥ 25 kg/m*^{2}*; arterial pressure ≥ 120/80 mmHg; cholesterol ≥ 200 mg/dl; triglycerides ≥ 150 mg/dl; glucose ≥ 100 mg/dl).*[b]*Chi square test*

on insulin sensitivity or intra-abdominal fat in Finnish subjects [29], nor on insulin resistance or impaired insulin secretion in healthy Scandinavian subjects [30]. As for qualitative traits, the *ins/ins* genotype was associated with overweight/obesity (OR = 1.60, 1.05–2.43; $p = 0.027$) under a recessive model in a young Colombian population. Unexplainably, this risk was higher in subjects with an active lifestyle (OR = 2.28, 1.13–4.62; $p < 0.021$) than in those with a sedentary lifestyle (OR = 1.34, 0.79–2.29; $p = 0.28$) [20]. This genotype also showed a trend for diabetes risk in Japanese (OR = 2.31, 0.64–8.36; $p = 0.2$) [18]. Genetics, sample heterogeneity, and diet specific to each population are probably the main reasons for the differences among the several studies.

On the other hand, the Indel-19 polymorphism has also been associated with the above-mentioned metabolic disorders in patients with diabetes. The *ins/ins* genotype was linked with elevated cholesterol in the Gaza population [13] and with increased mean BMI in Turkish men [15] as well as in the Bangladeshi population ($p < 0.001$) [17]. Furthermore, Ezzidi et al. found an association of this genotype with overweight (OR = 2.07, 1.28–3.33; $p = 0.003$) and obesity (OR = 1.83, 1.10–3.07; $p = 0.021$), but not with FPG ($p = 0.71$), HbA_{1c} ($p = 0.32$), and HDL cholesterol ($p = 0.56$) in Tunisian patients of Arab origin [12]. Sharma et al. also observed an increased risk of overweight/obesity in *ins* allele carriers (OR = 1.88, 1.19–2.98; $p = 0.007$) in a population from northwestern India [14]. The *del/ins* genotype was associated with increased waist circumference and triglycerides in a Mexican population [16], and with higher BMI ($p < 0.001$) and total cholesterol ($p < 0.001$) in the Bangladeshi population [17]. The *del/del* genotype was also associated with increased waist circumference and triglycerides [16] and with greater insulin sensitivity ($p = 0.017$) [11], but also with higher systolic blood pressure ($p < 0.001$) [17].

The association of the *CAPN10* Indel-19 variant with diabetes, obesity, hypertension, and dyslipidemia is not fully understood because it is an intronic polymorphism that may have a less functional impact than a change in

the coding or promoter region. However, it has been proposed that this variant may affect gene expression, as individuals carrying the *ins/ins* genotype have been found to have reduced calpain-10 mRNA expression [19], which may affect insulin secretion and glucose uptake and disrupt cell metabolism. Furthermore, we do not exclude the possibility of diet-induced epigenetic modifications [31]. Then, either a change in the expression of the gene or protein could affect its function and increase the risk of these conditions. Since metabolic dysregulation causes these chronic diseases, it is reasonable to assume that they overlap through metabolism and may share common risk factors, including genetics, lifestyle, and diet. However, further studies are needed to clarify this issue.

Limitations

The main limitation of this study is that the sample was over-represented by women at a ratio of 3:1, so we were unable to make comparisons between the sexes. In addition, we did not have the resources to sample more individuals to achieve greater statistical power. Still, we believe that our findings are robust and provide important information for further research.

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Author contributions
J.P.M.E. Conceptualization, design, investigation, analysis, and writing of the article. J.D.Z.R. and E.L.U. Molecular studies and data curation. V.J.P.C. and J.C.B. Samples collection and data curation. J.A.C.G. and M.L.V.G. Anthropometric data. J.M.M. and S.C.S. Laboratory studies. All the authors contributed to the critical review and approved the final version of the manuscript.

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Data availability
All data generated or analyzed during this study are included in this publication.

Declarations

Ethics approval and consent to participate
This study was approved by the Internal Bioethics and Biosafety Committee of the Matamoros School of Medicine of the Autonomous University of Tamaulipas and by the Research Ethics Committee of the School of Medicine of the Autonomous University of Sinaloa. In addition, the analysis was conducted following the tenets of the Declaration of Helsinki, and informed consent was obtained from each participant before enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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