European Review for Medical and Pharmacological Sciences 2021; 25: 5463-5473

The *BDNF* rs7934165 polymorphism is a biomarker of central obesity and cardiometabolic risk in Mexican women

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Abstract. – OBJECTIVE: Brain-derived neurotrophic factor (BDNF) is a cornerstone in the hypothalamic regulation of food intake and energy homeostasis. Polymorphisms in the *BDNF* gene may thus contribute to obesity traits. The aim of this investigation was to analyze the association of rs6265 and rs7934165 *BDNF* polymorphisms in women from Northeast Mexico classified as obese or overweight using their BMI and waist-to-height ratio (WHtR).

PATIENTS AND METHODS: A total of 296 women were enrolled and further divided into normal weight and obese overweight groups according to their BMI status and WHtR classifications, which were low and high at < 0.50 and ≥ 0.50, respectively. Genotyping of *BDNF* rs6265 and rs7934165 polymorphisms was performed using a TaqMan assay. Distinct anthropometric, biochemical, clinical, and dietary parameters were obtained and used as covariates in the statistical analyses.

RESULTS: The rs6265-G allele and its homozygote state (GG) were the most prominent without statistically significant differences between groups ($p = 0.412$). The study of rs7934165 with BMI showed marginal associations. Moreover, the rs7934165-AA genotype was more frequent among individuals with a high WHtR than those with a low WHtR (43.4 *vs.* 25.2%, $p = 0.01$). This association was maintained after adjustments for age and caloric intake through logistic regression analysis (OR = 2.20, 95% CI = 1.15-4.18, $p = 0.016$).

CONCLUSIONS: The present study indicates that the *BDNF*-rs7934165-AA genotype is associated with a higher WHtR which is related to central obesity and its comorbidities. This suggests that this SNP could act as a potential biomarker for central obesity and cardiometabolic risk.

Key Words:
Brain-derived neurotrophic factor, Waist-to-height ratio, Polymorphism, Central obesity.

Introduction

Obesity and overweight are complex polygenic conditions, defined as excessive fat accumulation that poses a health risk[1]. Both have reached pandemic proportions and are causing increased mortality rates from severe metabolic diseases such as diabetes, cardiovascular diseases, and cancer[2,3]. These conditions create an economic burden on the public and health sectors of all affected countries, such as Mexico, where over 70% of the adult population suffers from obesity or is overweight[4,5].

The etiology of these conditions is explained as an energy imbalance (i.e., excessive caloric intake and reduced energy output). However, this has oversimplified a complex situation, evidenced by the fact that dietary and physical approaches alone tend to fail[6]. The multifactorial etiology of obesity and overweight include genetic predisposition, environmental factors, and lifestyle (e.g., unhealthy dietary patterns and low physical activity)[7,8]. Genetic contribution is a cornerstone in the development of obesity and overweight. In this regard, polymorphisms involved in neuroendocrine regulation of energy homeostasis may lead to hyperphagia, reduced resting metabolic rate, and thus obesity and overweight[9].

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The brain-derived neurotrophic factor (BDNF), a protein involved in satiety through leptin-mediated hippocampal signaling, partly regulates energy homeostasis[10]. Affections in *BDNF* gene could lead to hyperphagia[11]. Besides, BDNF has a key role in the browning of white adipose tissue (WAT), a complex process characterized by the induction of thermogenic adipocytes (i.e., beige) in human WAT in response to different stimuli (e.g., cold exposure, exercise, and environmental enrichment)[12-14]. The browning of WAT also contributes to energy homeostasis by an increased expression of uncoupling proteins (UCPs) in beige adipocytes, which promotes higher lipid and glucose oxidation[14]. Browning of adipose tissue by external cues has several regulators summarized elsewhere[13-15]. Of note, increased *BDNF* expression promotes browning of WAT[16]. Importantly, this upregulation is triggered by irisin activation, a hormone produced by muscle cells[17]. Thus, the crosstalk between muscle and WAT mediated by these myokines (i.e., irisin and BDNF), promotes UCP1 expression, browning of WAT and further lipolysis[18].

Besides *BDNF* upregulation by external cues and other hormones, polymorphisms in *BDNF* gene have been related to an increased BMI using genetic association studies, yet with discrepancies between populations[12,19-21]. Among them, rs6265-A allele was associated with the abnormal packaging of pre-BDNF and decreased levels of mature BDNF in the cells[22]. Several studies[23-26] among European and Asian populations report that rs6265-AA genotype exhibited an obese phenotype and low plasma levels of BDNF. Moreover, some evidence from animal models revealed that the affected morphology of BDNF-rs6265-AA genotype could be alleviated after four weeks of physical exercise, restoring the adipocyte size distribution[27].

Several SNPs in the *BDNF* gene have been related to overweight and obesity through Genome-wide association studies (GWAS)[28,29]. However, discrepancies among different populations in replication studies are still a matter of debate[28,30-34]. This might be due to different sample sizes, ethnicity variability, and their effects on statistical power. Nonetheless, a meta-analysis[35] concluded that some polymorphisms of the *BDNF* gene, including rs6265, could be genetic determinants of obesity.

The lack of research into the *BDNF* polygenic variants in Mexican adults is detrimental to Mexico's ability to cope and manage their exorbitant rates of obesity and overweight. Another reason for discrepancies between studies is the assessment of obesity and overweight using BMI as the sole diagnostic tool for obesity, since other anthropometric parameters such as weight to height ratio (WHtR) show a higher discriminatory power than BMI in identifying adults with increased health risks related to obesity and overweight[36-38]. Therefore, given the complex genetic architecture of Mexican mestizo and the scarce analysis of other SNPs in the *BDNF* gene, our aim was to analyze the association of two polymorphisms of this gene (rs6265, rs7934165) with obesity, overweight, and the WHtR in a population of women from Northeast Mexico.

Patients and Methods

Study Population

A total of 296 women were included in this study, all of whom resided in the metropolitan area of Monterrey, Nuevo Leon, México, were aged 18-60 years, and had no previous diagnosis of a severe metabolic condition (i.e., insulin resistance, diabetes, cardiovascular disease, cancer, or a metabolic syndrome). The study was conducted at the Nutrition and Public Health Research Center (CINSP) of the Faculty of Public Health and Nutrition of the Autonomous University of Nuevo Leon (UANL) in collaboration with the National Institute of Genomic Medicine (INMEGEN). Each participant signed an informed consent letter validated by the Ethics Committee of the School of Public Health and Nutrition of the UANL.

The participants were divided into two groups: normal weight (NW) and overweight obesity (OW-OB) according to their BMI (kg/m^2), using the cut-off points of the World Health Organization. Overweight and obesity were determined by anthropometric measurements of height and weight using calibrated instruments (stadiometer SECA 217 and scale Tanita BC554). Individuals with a BMI of 18-24.9 kg/m^2 were classified as normal weight, from 25-29.99 kg/m^2 were overweight, and higher than 30 kg/m^2, were considered obese. Women with overweight and obesity were included in the same group (OW-OB). To determine genetic associations with the waist-to-height ratio (WHtR), we divided the population into low (<0.50) and high (≥0.50) health risks using previously reported cut-off points[39,40]. Waist circumference was measured according to the cri-

teria established by the World Health Organization (WHO) using the midpoint between the iliac crest and the lowest rib[41]. Other anthropometric variables were measured, such as skinfolds based on Lohman's criteria, fat percentage, and bone mineral density, using dual X-ray absorptiometry (DXA) with a Lunar densitometer (PRODIGY Advance, General Electric, Madison, WI, USA). Blood pressure was measured in a sitting position using a mercury column sphygmomanometer and carried out by a trained nurse, and all measurements were performed in duplicate[42]. Caloric intake was assessed using a 24-hour dietary recall performed by a trained nutritionist, and further analyzed using the ESHA Food Processor software (ESHA Research, Salem, OR, USA), to identify the macronutrients and total energy intake per patient[43].

Biochemical Analysis

Biochemical analyses were performed on the blood samples obtained from each participant after 12-14 h of fasting. Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and blood glucose, were determined using standardized spectrophotometric protocols with an analyzer a25 (Biosystems, Barcelona, Spain).

DNA Isolation and Genotyping

Genomic DNA was isolated from peripheral blood leukocytes using QIAamp DNA blood kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Genotyping of the *BDNF* polymorphisms was performed using a TaqMan assay with commercial probes for both SNPs: *BDNF*-rs6265 [VIC-TCCTCATCCAACAGCTCTTCTATCA [C/T] GTGTTCGAAAGTGTCAGCCAATGAT-FAM], and *BDNF*-rs7934165 [VIC-CTAGAGCTAGTATCCAGAGTTCTGA [A/G] TTGGTGCAAAGACACAAAGGACCCA-FAM] according to the manufacturer's instructions (Applied Biosystems, Carlsbad, CA, USA), at the National Institute of Genomic Medicine (INMEGEN). All reactions were set up in different batches of 96-well reaction plates with specific PCR conditions (pre-incubation for 10 min at 95°C followed by 45 cycles of 15 s at 95°C and 90 s at 60°C). Data acquisition was performed using the QuantStudio Real-Time PCR System (Applied Biosystems, Carlsbad, CA, USA), and experiments were performed blindly with respect to phenotype and quality control, and duplicate samples were genotyped randomly.

To compare the genetic frequencies obtained from the present study with other populations, we used 2315 individuals from the 1000 Genomes Project[44], including African, European, East, and South Asian populations, as well as those with Mexican ancestry from Los Angeles, CA, USA that were derived from the same project. Genetic differences between the populations were analyzed using multidimensional scaling plots with SPSS v.23 software (Chicago, IL, USA)[45].

Statistical Analysis

Genetic frequencies and linkage disequilibrium between loci were calculated using Arlequin suite software (version 3.5)[46]. Hardy-Weinberg's expectation was determined by Weir and Cocker ham's F statistics using 10,000 permutations with Genétix software (version 4.05)[47].

To determine the differences in continuous variables (caloric intake, biochemical parameters, and anthropometric measurements) between the NW and OW-OB groups, t-tests were performed after variable distribution analyses using the Kolmogorov-Smirnov test (K-S) with SPSS software (version 23)[45]. Differences in genetic frequencies were analyzed using the chi-square test and differences in continuous variables between genotypes were analyzed using one-way ANOVA with STATA 16.0 software[48]. Multiple logistic regression models for risk alleles were performed to identify the associations of the genotypes with either BMI or WHtR, adjusting for confounding variables such as age, caloric intake, or height.

Results

Anthropometric and Biochemical Measurements

The general characteristics of the OW-OB and NW groups are shown in Table I. As expected, anthropometric parameter values were higher in the OW-OB group than in the NW group (p = 0.0001). This was despite the caloric intake and macronutrient distributions being similar between the groups, suggesting that obesity and overweight are not just a matter of energy consumption and that measurements of caloric intake should be assessed using the differences in the individual's total metabolic rate. For the biochemical and clinical parameters, the OW-OB group was found to have higher levels of triglycerides and systolic and diastolic pressure but lower serum HDL cholesterol than the NW group (p = 0.0001).

Table I. Characteristics of normal weight and overweight-obese groups.

Characteristics	Overweight-obese N = 148 media ± SD	Normal weight N = 148 media ± SD	*p*-value
Age, years	43.74 ± 12.27	30.30 ± 13.37	**0.0001**
Anthropometric parameters			
Weight, kg	75.80 ± 11.20	55.66 ± 6.42	**0.0001**
Height, cm	157.48 ± 5.48	159.53 ± 5.82	**0.002**
BMI, kg/m^2	30.53 ± 4.04	21.85 ± 2.07	**0.0001**
Waist, cm	97.52 ± 12.46	78.65 ± 7.09	**0.0001**
Hip, cm	109.67 ± 8.22	94.66 ± 5.36	**0.0001**
WHR	0.89 ± 0.09	0.83 ± 0.05	**0.0001**
WHtR	0.61 ± 0.08	0.49 ± 0.04	**0.0001**
Tricipital skinfold, mm	26.75 ± 5.87	20.24 ± 4.78	**0.0001**
Suprailiac skinfold, mm	27.63 ± 6.85	20.73 ± 6.46	**0.0001**
Abdominal skinfold, mm	28.68 ± 5.82	23.67 ± 5.43	**0.0001**
Fat mass, %	47.03 ± 5.06	35.15 ± 6.25	**0.0001**
Lean body mass, kg	37.85 ± 4.64	33.90 ± 3.67	**0.0001**
Bone Mineral Density, g/cm^2	1.15 ± 0.08	1.09 ± 0.08	**0.0001**
Caloric intake			
Food intake, kcal	2348.21 ± 685.70	2283.22 ± 885.81	0.6822
Fiber intake, g	38.89 ± 18.35	40.87 ± 23.72	0.6405
Biochemical and clinical parameters			
Blood Glucose, mg/dL	88.64 ± 23.83	82.47 ± 25.87	0.1180
Triglycerides, mg/dL	118.25 ± 54.63	78.97 ± 27.92	**0.0001**
Cholesterol, mg/dL	159.14 ± 39.08	154.48 ± 40.91	0.4593
HDL Cholesterol, mg/dL	42.82 ± 11.51	52.07 ± 10.64	**0.0001**
LDL Cholesterol, mg/dL	92.67 ± 38.80	86.61 ± 39.58	0.3245
Systolic pressure, mm Hg	114.86 ± 13.70	103.55 ± 12.62	**0.0001**
Diastolic pressure, mm Hg	72.31 ± 11.70	67.40 ± 9.85	**0.0001**

Values expressed as means ± standard deviations; *p* values were obtained from an t-student test; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein, WHR: Waist hip ratio WHtR: Waist to height ratio.

Genetic Statistical Descriptive Analysis

Genetic frequencies for all *loci* were calculated in the NW and OW-OB groups and are shown in Table II. No deviation from the Hardy-Weinberg equilibrium was found in any of the groups ($p > 0.05$). Linkage disequilibrium analyses demonstrated a strong LD between the rs6265 and rs7934165 polymorphisms (D' = 1, $p = 0.0001$). These results were expected due to proximity of the rs7934165 and rs6265 polymorphisms on chromosome 11.

The rs6265-G allele and its homozygote state (GG) were the most prominent among the groups (Table II). There was a slightly higher predominance in the OW-OB group (0.78) than in NW group (0.74), but it was not statistically significant ($p = 0.412$). Further analysis of the variables between the genotypes and dominant inheritance model (GG *vs.* GA+AA) suggested an association of the GG genotype with obesity and overweight (OR = 2.92, 95%CI = 1.10-4.18, $p = 0.030$), which was lost after adjustment for age, caloric intake, and BMI (OR = 1.31, 95%CI = 0.52-3.33, $p = 0.559$).

For rs7934165, the AA genotype was more frequent in the OW-OB group than in the NW group (0.43 *vs.* 0.31); however, this difference was not statistically significant ($p = 0.076$). Using the dominant genetic inheritance model AA vs. AG + GG, we found an association between the rs7934165-AA genotype and the OB-OW group (OR = 1.68, 95%CI = 1.04-2.72, $p = 0.031$). However, this was not supported after adjustments for age, BMI, and caloric intake (OR = 1.53, 95%CI = 0.89–2.61, $p = 0.119$). A significant difference in the waist circumference (WC) was found in AA individuals who exhibited higher WC than G allele carriers (90.05 ± 11.16 *vs.* 86.75 ± 15.10, $p = 0.04$).

Following these results and based on the higher capacity of the waist-to-height ratio (WHtR) to predict abdominal obesity and health cardiometabolic risk, the sample was divided into low (< 0.50) and high (≥ 0.50) risk according to the WHtR (Table III). Genetic frequencies of the rs6265 were similar between the high-and low-risk individuals, with GG being the most frequent genotype.

Table II. Genetic frequencies and descriptive parameters from *BDNF* polymorphisms among groups.

Population SNP	Allele frequencies		Genotype frequencies				Dominant					Recessive		
rs6265	**G**	**A**	**GG (N)**	**AG (N)**	**AA (N)**	***p* value**	**FIS**	**HWE (*p*-value)**	**GG (N)**	**AG+AA (N)**	***p* value**	**GG+AG (N)**	**AA (N)**	***p*-value**
NW	0.86	0.13	0.74 (110)	0.24 (36)	0.01 (2)	0.401	-0.037	0.775	0.74 (110)	0.25 (38)	0.412	0.98 (146)	0.01 (2)	0.409
OW-OB	0.87	0.12	0.78 (116)	0.18 (28)	0.02 (4)		0.117	0.143	0.78 (116)	0.21 (32)		0.97 (144)	0.02 (4)	
rs7934165	**G**	**A**	**GG**	**AG**	**AA**				**AA**	**AG+GG**		**AA+AG**	**GG**	
NW	0.41	0.58	0.13 (20)	0.55 (82)	0.31 (46)	0.076	-0.140	0.973	0.31 (46)	0.68 (102)	0.030	0.86 (128)	0.13 (20)	0.983
OW-OB	0.35	0.64	0.13 (20)	0.43 (64)	0.43 (64)		0.054	0.308	0.43 (64)	0.56 (84)		0.86 (128)	0.13 (20)	

p-values for chi^2 and exact test; OW-OB: overweight-obesity; NW: normal weight, FIS: Weir and Cocker ham F statistics; HWE: Hardy-Weinberg expectation

Table III. Genetic frequencies for rs7934165 among non-abdominal obesity and abdominal obesity, according to Waist-to-height ratio.

	WHtR ≥ 0.50% (N)	WHtR < 0.50% (N)	*p*-value
AA	43.4 (86)	25.2 (24)	0.011
AG	44.4 (88)	58.9 (56)	
GG	12.1 (24)	15.7 (15)	
Dominant			
AA	43.4 (86)	25.2 (24)	0.003
AG + GG	56.5 (112)	74.7 (71)	
Recessive			
AA + AG	87.8 (174)	84.2 (80)	0.387
GG	12.1 (24)	15.7 (15)	

p-values for chi^2 and exact test; WHtR: Waist-to-height ratio.

Interestingly, the rs7934165-AA genotype was more frequent among high-risk individuals than among low-risk individuals (0.43 *vs.* 0.25, *p*= 0.011). Moreover, this association was maintained after adjusting for age, BMI, and caloric intake through logistic regression analysis (OR= 2.20, 95% CI = 1.15-4.18, *p*= 0.016).

Comparisons with Other Populations

The Mexican population is young (9-15 generations) and admixed, resulting from the interbreeding of at least three populations (Native American, European, and African)[49]. Since genetic frequencies vary among populations, we compared those obtained from our study groups with different populations using the 1000 genomes data (Table IV)[44]. We observed that the *BDNF*-rs6265-G allele was the most frequent among all populations, with the highest frequency in African (0.99) and the lowest in East Asian populations (0.51). Our groups (~0.84) exhibited similar frequencies to those with Mexican an-

Table IV. Genetic frequencies and descriptive parameters from *BDNF* polymorphisms in the studied groups and populations from the 1000 genomes project.

	Allele frequencies		Genotype frequencies		
Population/SNP	G	A	GG	AG	AA
rs6265					
NW	0.86	0.14	0.74	0.24	0.01
OW-OB	0.88	0.12	0.78	0.19	0.03
AFR	0.99	0.01	0.98	0.02	-
MXL	0.80	0.20	0.67	0.27	0.06
CLM	0.83	0.17	0.69	0.30	0.01
EUR	0.80	0.20	0.64	0.32	0.04
EAS	0.51	0.49	0.27	0.48	0.25
SAS	0.80	0.20	0.64	0.31	0.04
rs7934165					
NW	0.41	0.59	0.14	0.55	0.31
OW-OB	0.35	0.65	0.14	0.43	0.43
AFR	0.56	0.43	0.33	0.48	0.19
MXL	0.41	0.59	0.15	0.51	0.33
CLM	0.49	0.51	0.22	0.53	0.25
EUR	0.53	0.47	0.28	0.49	0.23
EAS	0.58	0.42	0.36	0.45	0.19
SAS	0.68	0.32	0.46	0.44	0.10

NW= Normal weight (N=148) OW-OB= Overweight-obesity (N=148), AFR= Africans (N=661), MXL= Mexicans from Los Angeles (N=64), CLM= Colombians (N=94), EUR= Europeans (N=503), EAS= East Asians (N=504), SAS= South Asians (N=489).

cestry in Los Angeles, California (MXL), Colombian, South Asian, and European populations (~0.82).

For rs7934165, the A allele was the most common among the populations, except for the African and Asian populations. The rs7934165-AA genotype, which exhibited a higher frequency in the OW-OB group (0.43), was also the highest among all included populations. As expected, the NW (0.31) group showed similar frequencies to the MXL (0.33). Furthermore, European (0.23), African (0.20), and East Asian (0.20) populations had lower frequencies of the AA genotype.

Discussion

We evaluated the association of rs6265 and rs7934165 in the *BDNF* gene with obesity-overweight, and WHtR in a sample group of Mexican women. For rs6265, there was a slight difference in the GG genotype between groups, so we were not able to establish a statistical association between obesity and overweight in our population. The study of the rs7934165 showed that individuals carrying the rs7934165-AA genotype increased two-fold the risk of high WHtR.

Previous reports of rs7934165 have suggested that the AA genotype may be associated with anorexia and suicide[50,51]. While there have been no previous reports on rs7934165 in relation to either BMI or WHtR, our results are in line with evidence that identifies genes associated (*MC4R, PPARG, SLC6A4, FAAH, TAS1R2, CD36, FTO,* and *IL6R)* with a higher WHtR[52-55]. Moreover, a study of an Iranian adult population divided 610 subjects into those who were centrally obese (WHtR $\geq$ 0.50) and non-centrally obese (WHtR $<$ 0.50) and reported a three-fold increased risk for central obesity among individuals with AD-IPOQ-11391-GG genotype, which further supports the role of genetic factors in the WHtR[56]. No previous studies using WHtR have investigated *BDNF* gene polymorphisms, and further analyses should be performed to discuss and replicate our results.

Concerning *BDNF*-rs6265, our results are in line with a study in a Pakistani adult population with a similar stratification of groups in normal weight and overweight obesity, and with the lack of association of this SNP with obesity in a Croatian and German population[34,57,58]. More importantly, BDNF-rs6265 has been previously studied in the Mexican population, with conflicting results regarding its possible association with metabolic conditions. In this sense, the genetic frequencies found in the present study for rs6265 were similar to those previously reported for the Mexican population[59,60].

A recent genome-wide association study reported the effects of rs6265 alleles on obesity and BMI[35]. This was concordant with several studies that have highlighted the effect of the G allele in its homozygote state with BMI status[25,59]. Discrepancies around the risk allele have been noted in a pediatric cohort in Philadelphia where rs6265-AA carriers were related to a higher percentile BMI, on the contrary in a Croatian population the same genotype was more common in the normal-weight group than in their overweight-obesity group[24,61].

Previous studies of *BDNF*-rs6265 with overweight and obesity in the Mexican mestizo population are scarce, and our results differ from them. However, three studies have reported the association of rs6265 alleles with either BMI, obesity, or overweight. One of the studies was performed among patients with bipolar disorder and it was concluded that the *BDNF*-rs6265-G allele was associated with BMI only in these patients[59]. This is consistent with the reports of León-Mimila et al[60], who associated the same allele with obesity, especially when comparing the normal weight group with the class III obese group. It is worth mentioning that these two previous reports had similar genetic frequencies to our study; hence, the rs6265-G allele was the most prominent among the groups. In contrast, a third study on the Mexican population reported an association of the *BDNF*-rs6265-AA genotype with obesity and overweight in a pediatric population[26]. A possible explanation for these discrepancies is the heterogeneity of the sample sizes and methods used to establish the association of the rs6265 alleles with the anthropometric traits of obesity. In addition, most of the studies ignored the environmental cues that affect BDNF expression, such as its roles in adipose tissue browning, increased metabolic rates through non-shivering thermogenesis, and satiety through hypothalamic pathways. Proper adjustments for other factors, such as cold exposure, exercise, and nutritional agents, may thus address these discrepancies.

Furthermore, these experiments were performed in a complex admixed population (Mexican mestizo), where false associations are more likely due to the ethnic dissimilarities which may account for genetic associations instead of

the genes for the condition or disease. It is noteworthy that only León-Mimila et al[60] study was adjusted by admixture and the association of the *BDNF*-rs6265-G allele with obesity remained significant; furthermore, they also used a larger sample size[60].

In this regard, our study has limitations due to the small sample size, insufficient data to adjust for environmental cues which could potentially affect BDNF expression (e.g., exercise or physical activity), and the absence of a genome control group or further adjustments by ethnicity. Moreover, our results should be taken with caution, as replication studies are required. Nonetheless, some novelties from the present study are the use of a different measure related to abdominal obesity (WHtR), instead of BMI, which, by itself, increased the information about our population. The present study also constitutes the first report of *BDNF*-rs7934165 in the Mexican mestizo population, revealing a new potential genetic marker for the study of metabolic conditions. Finally, the comparison with other populations (European, Asian, and African populations using the 1000 genomes as well as with the Mexican mestizo population) has strengthened our results.

Conclusions

The present study supports the association of the *BDNF*-rs7934165-AA genotype with a higher WHtR. This suggests that this SNP could act as a biomarker of central obesity and cardiometabolic risk. Further replication analyses should be performed to elucidate the gene-gene or gene-environment effects on obesity, overweight, and WHtR.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

The authors thank the Centro de Investigación en Nutrición y Salud Pública (CINSP) at the Universidad Autónoma de Nuevo León (UANL), and to Instituto Nacional de Medicina Genómica (INMEGEN) for the facilities, equipment, and reagents used in this work. We would also like to extend our gratitude to the volunteers who participated in this study.

Funding

This work was supported in part by using a fellowship from the Consejo Nacional de Ciencia y Tecnología (Grant No. 610443) given to IGC. The UANL-PAICYT program provides the necessary financial resources for this project (Project No.SA682-18).

Authors' Contribution

Israel Guerrero-Contreras was responsible for data acquisition, performed the experiments and drafting of manuscript. Esther Alhelí Hernández-Tobías collaborated in study design, performed analysis and interpretation of data, and drafting of manuscript. Erik Ramírez-López carried out anthropometric parameters determination and contributed to interpretation of data and critical revision of manuscript. Rafael Velázquez-Cruz and Eduardo Campos-Góngora participated in study design and critically revised the manuscript. Zacarías Jiménez-Salas was responsible for the study conception and design, drafting and revision of the manuscript for important intellectual content of the article. All authors read and approved the submitted article.

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