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ORIGINAL RESEARCH

FTO rs17817449 Variant Increases the Risk of Severe Obesity in a Brazilian Cohort: A Case-Control Study

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Purpose: Obesity is a complex disease caused by a combination of genetic, environmental, and epigenetic factors, and is associated with an increased risk of chronic diseases. The leptin-melanocortin pathway integrates peripheral signals about the body's energy stores with a central neuronal circuit in the hypothalamus. This pathway has been extensively studied over the years, as genetic variations in genes related to it may play a crucial role in determining an individual's susceptibility to obesity. Therefore, we analyzed the association between obesity and specific polymorphisms in leptin-melanocortin-related genes such as *LEPR* rs1137101, *POMC* rs1042571, *LEP* rs7799039, *BDNF* rs6265, *FTO* rs17817449, *CART* rs121909065, and *NPY* rs16147/rs5574.

Patients and Methods: The study enrolled 501 participants from Rio de Janeiro, Brazil, with obesity class II or greater (BMI ≥ 35 kg/m2) and normal weight controls (18.5≤ BMI ≤24.9 kg/m2). We collected demographic, body composition, biochemical, and genotyping data by real-time PCR, and performed logistic and linear regression analyses to investigate the association of polymorphisms with severe obesity status and obesity-related quantitative parameters.

Results: Individuals with severe obesity had significantly higher anthropometric measures, blood pressure, and biochemical levels. The *FTO* rs17817449 TT genotype was associated with a significantly higher risk of developing severe obesity, and distinct cytokine expression was observed across the *FTO* rs17817449 genotypes. The *BDNF* rs6265 dominant-model and *NPY* rs16147 CC genotypes were associated with triglyceride levels and childhood obesity, respectively. Finally, individuals with obesity were more likely to carry a greater number of risk alleles than those without obesity.

Conclusion: Our study observed an important association between *FTO* rs17817449 polymorphism with obesity and obesity-related traits. Additionally, *BDNF* rs6265 dominant-model was associated with triglyceride serum levels, and *NPY* rs16147 may have a role in obesity onset.

Keywords: *FTO*, polymorphisms, severe, leptin-melanocortin pathway, cytokines expression

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Introduction

Obesity is a major global health epidemic. Currently, obesity affects 13% of adults and 124 million children worldwide.[1] According to The World Obesity Atlas 2023,[2] by 2035, this number is projected to increase to over 4 billion people, representing a prevalence of 24% worldwide. The most dramatic scenario is expected among children and adolescents, with a rise from 10% to 20% in boys and from 8% to 18% in girls. In Brazil, the prevalence of obesity is also on the rise, with projections indicating that 41% of adults will be obese by 2035.[2]

It's well known that obesity is a complex and multifactorial disease influenced by a combination of genetic, environmental, and epigenetic factors.[1] It is associated with an increased risk of cardiovascular disease, type 2 diabetes, cancer, hypertension[3] and increased oxidative stress.[4] Individuals with a BMI of 40 kg/m^2 or higher experience a significant reduction in life expectancy, with up to 13.9 years of life lost for those with a BMI of 55–59.9 kg/m^2, compared to individuals with a normal BMI range of 18.5–24.9 kg/m^2.[1,5] Additionally, severe obesity has been linked to an increased risk of severe outcomes and hospitalizations due to COVID-19.[6]

The high prevalence of obesity may be attributed partially to environmental factors, such as urban progress which promotes facilitation mechanisms to a sedentary lifestyle.[3,7] Besides the factors related to the decrease in energy expenditure, there is a concomitant increase in calorie consumption by the intake of foods with very high percentages of sugars and fat.[8] However, individuals exposed to the same obesogenic environmental factors may express different phenotypes, with or without obesity. Individual genetic background has been strongly shown to play a crucial role in susceptibility to external stimuli.[9] Over time, hypotheses have been raised to explain the different susceptibility to obesity among ethnicities, such as the "predation release", "drifty gene", and "thrifty epigenotype" hypotheses.[10] Interestingly, several loci have been described and associated with multifactorial and polygenic obesity, resulting from the interaction between the cumulative effect of genetic polymorphism with the environment.[11–16]

Most of the studied genes associated with obesity act directly or indirectly in a neuroendocrine system related to modulating the body's energy homeostasis by the control of appetite and energy expenditure.[17–19] This system called the leptin-melanocortin pathway integrates peripheral signals about the body's energy stores with a central neuronal circuit in the hypothalamus.[20,21] This circuit consists of two distinct groups of neurons in the arcuate nucleus: orexigenic neurons, which promote hunger and decrease energy expenditure, and anorexigenic neurons, which promote satiety and increase energy expenditure.[22] During fasting or calorie restriction, the stomach secretes the hormone ghrelin, which activates the orexigenic pathway. Ghrelin crosses the blood-brain barrier and binds to receptors on orexigenic neurons, thereby stimulating the production of neuropeptide Y (NPY) and Agouti-related protein (AgRP). NPY primarily stimulates food intake by activating Y1 and Y5 receptors on orexigenic neurons. Additionally, NPY binds to Y1 receptors on anorexigenic neurons in the hypothalamus, inhibiting these neurons and reducing their ability to suppress feeding.[23–25] Conversely, AgRP is a potent antagonist of the melanocortin-4 receptor (MC4R), which is a key regulator of food intake and energy expenditure.[26]

On the other hand, the anorexigenic pathway is activated in response to excess adiposity or recent feeding. Leptin, a hormone secreted by white adipose tissue, binds to receptors (LEPR) on both orexigenic and anorexigenic neurons after crossing the blood-brain barrier. While leptin inhibits the production of NPY and AgRP in orexigenic neurons, it stimulates the production of pro-opiomelanocortin (POMC) in anorexigenic neurons. POMC is cleaved into the neuropeptide α-melanocyte-stimulating hormone (α-MSH), which binds to MC4R. This binding triggers a cascade of events that leads to decreased hunger and increased basal energy expenditure.[27–29]

Moreover, there is a gene called *Fat mass and obesity-associated* (*FTO*) that has been previously associated with both childhood and adult.[19,30,31] The *FTO* gene is expressed in neurons of the arcuate nucleus, a region of the brain known to play a crucial role in energy homeostasis and responsive to leptin signaling.[32] Although the exact role of the *FTO* gene is not yet fully understood, it has been described as having multiple functions. For instance, it has been found to regulate gene expression through DNA demethylation,[33,34] which can influence the activity of other genes and may play a role in various biological processes, including energy balance. Additionally, FTO is involved in DNA repair and fatty acid metabolism.[35,36] Further research is needed to fully understand the role of the FTO gene in the regulation of energy

balance and contributing to obesity. However, the FTO gene may interact with the anorexigenic signaling pathway, along with other factors, to contribute to the development of obesity.[37,38]

This study aimed to examine the association of genetic polymorphisms, including *LEPR* rs1137101, *POMC* rs1042571, *LEP* rs7799039, *BDNF* rs6265, *FTO* rs17817449, *CART* rs121909065, *NPY* rs16147 and *NPY* rs5574 (Table 1) with obesity class II or greater and related obesity-traits in a Brazilian cohort, characterized by its unique genetic diversity from indigenous, European, and African ancestries.[39] We also have investigated the effect of combined risk allele variants in obesity susceptibility.

Materials and Methods

Study Population

This cross-sectional case-control study enrolled 501 participants (73.5% women and 26.5% men) aged 18 to 70 years from Rio de Janeiro, southeast of Brazil. The case group consisted of 305 participants with severe obesity (BMI ≥ 35 kg/m2) who were stratified into three groups based on the self-reported period of obesity onset. All participants were recruited from a non-governmental organization called Rescue Group to Self-Esteem and Citizenship of the Obese (in Portuguese, *Grupo de Resgate a Autoestima e Cidadania do Obeso*). All participants were candidates for bariatric surgery in our country. The control group consisted of 196 participants with normal weight (18.5≤ BMI ≤24.9 kg/m2) who were volunteers from public hospitals in the same city. The exclusion criteria were pregnancy, lactation, and the use of medication to lose or gain weight directly.

This study was performed according to the Declaration of Helsinki (1964) and approved by the Ethics Committee of the Oswaldo Cruz Foundation (CAAE: 09225113.0.0000/ Protocol N°: 346.634). All individuals accepted to participate and provided written informed consent before enrollment.

Demographic Variables

Race/skin color: Self-reported and categorized according to the criteria of the Demographic Census conducted by the Brazilian Institute of Geography and Statistics (IBGE). Marital status: Stratified as single, married/cohabiting, separated/divorced, and widowed. Physical activity: Classified as "yes" if the participant has been practicing activities during the last month, or "no" otherwise. All information was self-reported and collected using standardized questionnaires by trained interviewers.

Body Composition and Biochemical Analyses

All participants were examined after an overnight fast, as previously described.[19,40] Body weight, height, waist, and hip circumferences were obtained for each participant. Waist-to-hip ratio (WHR) was calculated to estimate the pattern of fat distribution. BMI was calculated as weight (kg) divided by the square of height (m). Body adiposity index (BAI) estimates the percentage of total fat and was calculated by the formula: hip circumference/(height$^{1.5}$)-18.[41] To record the participant's blood pressure, we used a wrist blood pressure monitor while they were in a seated position.[42]

Blood samples were collected to measure fasting plasma glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels using the oxidase-peroxidase method (BioSystems). Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula (LDL = TC - HDL - TG/5). C-reactive protein (CRP) levels were measured using the latex agglutination method. Serum glycated hemoglobin values were assessed turbidimetric inhibition immunoassay (TINIA). Individuals who were taking medication for any of these biochemical parameters or blood pressure were excluded from the statistical analyses.

Obesity and Inflammatory Biomarkers

Leptin, resistin, adiponectin, monocyte chemoattractant protein-1/CCL2 (MCP1), and plasminogen activator inhibitor-1 (PAI-1) levels were quantified using the Human Adipocyte Magnetic Bead (Millipore-Merck [cat# HADCYMAG-61k]) on the Bio-Plex 200 Multiplexing Analyzer System, following the manufacturer's protocol. IL-6, IL-1β, TNF, and IFN-α levels were quantified by ELISA, following the R&D Systems' instructions.

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Table 1 Genetic variants included in this study

Gene	Chromosome Location	Biological Function	dbSNP#	Type	MAF	Results of Previous Studies
LEPR	1p31.3	*LEPR* encodes the leptin receptor. When activated by leptin, LEPR signals the brain to reduce food intake and increase energy expenditure.	rs1137101	Missense	0.42	Association with lower LDL in a Southern Chilean population (MANRIQUEZ et al, 2018)[67], protective factor for obesity in Brazilians (MENEZES et al, 2022)[89].
POMC	2p23.3	*POMC* encodes pro-opiomelanocortin, a precursor protein that is cleaved to produce several hormones, including alpha-melanocyte-stimulating hormone (α-MSH), that acts in the leptin-melanocortin anorexigenic pathway.	rs1042571	3'UTR	0.12	Association with BMI ≥30 kg/m2 in northern India cohort (SRIVASTAVA et al, 2016)[76]. No association was found in a Thailand family-study (KULANUWAT et al, 2015)[77].
LEP	7q32.1	*LEP* encodes leptin, a hormone produced by adipose tissue and binds to LEPR.	rs7799039	Upstream	0.40	Association with BMI and WC in European-Caucasian descents (MATTEVI; ZEMBRZUSKI; HUTZ, 2002)[70], (DE OLIVEIRA et al, 2013)[71]. No association in Mexican population (DIÉGUEZ-CAMPA et al, 2020)[72].
BDNF	11p14.1	*BDNF* encodes Brain-derived neurotrophic factor, that regulates energy homeostasis by modulating the production of orexigenic and anorexigenic neuropeptides in the hypothalamus.	rs6265	Missense	0.20	Association with eating disorders, metabolic imbalance, and increased obesity risk in different populations (AKBARIAN et al, 2018)[88].
FTO	16q12.2	*FTO* encodes fat mass and obesity-associated protein. The exact function of FTO is not fully understood, but it has been shown to play a role in regulating food intake and energy expenditure.	rs17817449	Intronic	0.31	Association with severe obesity in Brazilian (DA FONSECA et al, 2020)[52], non-Hispanic Caucasians (PRICE; LI; ZHAO, 2008)[53] and Spanish populations (GONZÁLEZ et al, 2012)[54].
NPY	7p15.2	*NPY* encodes neuropeptide Y, a neurotransmitter that is involved in regulating various physiological processes, such as appetite,	rs5574	Synonymous	0.37	Association with increased BMI in Caucasians (TIWARI et al, 2013)[80], and abdominal obesity (ZAIN et al, 2015) [81].
		stress response, and blood pressure. NPY is produced in the hypothalamus and signals the brain to increase food intake and reduce energy expenditure.	rs16147	Upstream	0.48	Association with increased higher BMI and WC in Spanish children (OLZA et al, 2013) [82], obesity risk in Asians (ZAIN et al, 2015) [81], central obesity and abdominal fat distribution in Caucasians (LIN et al, 2015) [79].

Abbreviations: BMI, Body mass index; dbSNP, Single nucleotide polymorphism database; LDL, Low-density lipoprotein; MAF, Minor allele frequency; SNP, Single nucleotide polymorphism; WC, Waist circumference.

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the QIAamp Blood Kit (Qiagen, Valencia, CA, USA), according to the manufacturer's protocol.

Genotypes for the *LEPR* rs1137101(A>G), *POMC* rs1042571 (G>A), *LEP* rs7799039 (G>A), *BDNF* rs6265 (C>T), *FTO* rs17817449 (T>G), *CART* rs121909065 (C>G), *NPY* rs16147 (T>C) and *NPY* rs5574 (T>C) polymorphisms were obtained by real-time PCR allelic discrimination using TaqMan® assays (ThermoFisher, Foster City, CA, USA). Amplification was carried out in a StepOne® Plus Real-Time PCR System (ThermoFisher Scientific, Waltham, MA, USA). Data analyses were done using StepOne software v2.3.

Statistical Analysis

To ascertain the necessary sample size, we employed an iterative technique focusing on the smallest participant number essential for effectively contrasting qualitative variables between case and control groups. In our analysis of diverse polymorphisms, we opted for a combination of conservative estimation and convenience sampling, aiming for 80% statistical power.[43]

The normality of continuous variables was analyzed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were not normally distributed and were presented as the median and interquartile range (IQR). Categorical variables were presented as numbers and percentages.

Differences between the case and control groups were evaluated using the Mann–Whitney test (quantitative parameters) or the chi-square test (qualitative parameters).

Genotypes and allele frequencies were estimated by gene counting. Hardy–Weinberg Equilibrium (HWE) was tested for all polymorphisms using the chi-square test. The association of each polymorphism with severe obesity status was performed by logistic regression analysis in additive, dominant, over-dominant, and recessive models. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. All analyses were adjusted for age, gender, race/skin color, marital status, and exercise habits.

The influence of each polymorphism on the obesity-related quantitative was tested using linear regression analysis after a logarithmic transformation of these parameters. Gender, age, race/skin color, marital status, and exercise habits were used as possible confounding variables for body weight and BMI. The confounders for all other continuous parameters studied included BMI and these variables.

The statistical analyses were conducted using SPSS software (IBM Corp., Armonk, NY, USA). To account for the increased likelihood of false positives when multiple statistical tests are performed simultaneously, Bonferroni correction for multiple comparisons was applied with a significance cutoff of $p \leq 0.007$. This correction is a method to adjust for the family-wise error rate and maintain the overall significance level of the study.

To visually represent cytokine expression across different *FTO* rs17817449 genotypes in the case group, we used the function heatmap.2 from the gplots package in R to create a heatmap cluster with a z-score. We analyzed the median serum levels of IL-1β, TNF-α, IL-6, MCP-1, adiponectin, leptin, resistin, and PAI-1 across each *FTO* rs17817449 genotype group. The analysis included 26 participants in the TT genotype group, 38 participants in the GT genotype group, and 21 participants in the GG genotype group.

Results

A cohort of 501 participants with a median age of 36 (27; 45) was included in this study. The participants were divided into two groups: 196 individuals with normal weight (median BMI 22.8 kg/m^2) and 305 people with severe obesity (median BMI 46.7 kg/m^2) stratified into groups based on the period of obesity onset: the childhood-onset group (0–11 years) comprised 106 patients, the adolescence/youth-onset group (12–21 years) included 72 patients, and the adult-onset group (>21 years) consisted of 127 patients. The participants with severe obesity had significantly higher anthropometric measures (weight, height, waist circumference, and BMI) than the normal-weight subjects. They also had higher blood pressure and biochemical levels (total cholesterol, LDL cholesterol, triglycerides, and fasting glucose), except for HDL cholesterol (Table 2).

Table 2 Phenotypic characteristics of the study population

Parameters	n	All	n	Control	n	Case	*P**
Age (years)	501	36.0 (27.0; 45.0)	196	29.0 (24.0; 37.0)	305	40.0 (31.0; 48.0)	<0.001*
Gender (female/male)							
Female	501	368 (73.4)	196	121 (61.7)	305	247 (80.9)	<0.001*
Male		133 (26.6)		75 (38.3)		58 (19.1)	
Race/Skin color							
White	500	236 (47.2)	196	133 (67.8)	304	103 (33.9)	<0.001*
Brown		89 (17.8)		14 (7.2)		75 (24.7)	
Black		169 (33.8)		49 (25.0)		120 (39.5)	
Others		6 (1.2)		0 (0.0)		6 (1.9)	
Marital status							
Single	499	226 (45.3)	196	122 (62.3)	303	104 (34.3)	<0.001*
Married/cohabiting		218 (43.7)		63 (32.1)		155 (51.2)	
Separated/divorced		34 (6.8)		4 (2.0)		30 (9.9)	
Widower		21 (4.2)		7 (3.6)		14 (4.6)	
Smoking status							
Already smoked	493	56 (11.3)	195	18 (9.2)	298	38 (12.8)	0.228
Never smoked		437 (88.7)		177 (90.8)		260 (87.2)	
Physical activity practice							
Yes	497	160 (32.2)	196	94 (48.0)	301	243 (80.7)	<0.001*
No		337 (67.8)		102 (52.0)		58 (19.3)	
Weight (kg)	501	105.0 (67.0; 132.4)	196	62.9 (57.0; 70.0)	305	126.3 (109.2; 144.4)	<0.001*
Height (m)	501	1.65 (1.59; 1.71)	196	1.68 (1.62; 1.74)	305	1.63 (1.58; 1.69)	<0.001*
BMI (kg/m^2)	501	40.1 (23.3; 48.8)	196	22.8 (21.1; 23.9)	305	46.7 (41.8; 52.6)	<0.001*
Waist circunference (cm)	498	120.0 (84.0; 140.0)	196	81.0 (75.0; 85.5)	302	136.0 (125.0; 147.0)	<0.001*
Hip circunference (cm)	498	128.0 (99.5; 146.0)	196	98.0 (94.0; 101.5)	302	141.7 (131.5; 153.0)	<0.001*
WHR	498	0.91 (0.83; 0.98)	196	0.83 (0.78; 0.88)	302	0.96 (0.90; 1.00)	<0.001*
BAI	493	42.1 (28.1; 51.6)	191	27.0 (24.1; 29.6)	302	49.6 (44.3; 56.1)	<0.001*
Glucose (mg/dl)	388	93.0 (87.0; 103.0)	175	89.0 (84.0; 95.0)	213	98.0 (90.0; 110.0)	<0.001*
Total cholesterol (mg/dl)	427	187.0 (161.0; 216.0)	183	179.0 (156.0; 200.0)	244	193.0 (166.2; 224.0)	<0.001*
HDL-C (mg/dl)	427	51.0 (43.0; 61.0)	183	59.0 (48.0; 69.0)	244	47.0 (41.0; 53.0)	<0.001*
LDL-C (mg/dl)	420	110.0 (92.0; 135.0)	182	102.5 (86.7; 123.0)	238	118.0 (95.7; 168.0)	<0.001*
Triglycerides (mg/dl)	427	103.0 (74.0; 139.0)	183	77.0 (61.0; 101.0)	244	125.5 (96.0; 168.0)	<0.001*
Glycated hemoglobin	342	5.30 (4.30; 5.90)	164	5.10 (4.82; 5.40)	178	5.80 (5.10; 6.32)	<0.001*
CRP	338	0.44 (0.12; 1.11)	163	0.14 (0.08; 0.28)	175	1.00 (0.55; 1.55)	<0.001*
SBP	355	121.0 (111.0; 134.0)	182	118.0 (110.0; 126.0)	173	130.0 (117.0; 147.5)	<0.001*
DBP	355	80.0 (71.0; 90.0)	182	76.0 (68.0; 84.0)	173	85.0 (76.0; 92.0)	<0.001*
Leptin	120	2,323.0 (1,141.5; 3,057.7)	35	565.0 (210.7; 887.2)	85	2,656.2 (2,210.6; 3,432.1)	<0.001*
MCP1	120	256.7 (165.5; 363.4)	35	246.6 (140.7; 313.6)	85	258.0 (184.1; 390.2)	0.124
PAI1	120	26,233.2 (19,531.7; 31,683.1)	35	22,406.1 (16,573.4; 29,605.9)	85	27,461.2 (20,946.9; 33,222.9)	0.030
Resistin	120	8,370.4 (6,212.7; 10,663.9)	35	7,420.8 (4,673.5; 9,373.2)	85	8,618.1 (6,296.7; 11,190.0)	0.021

Notes: *for $p \leq 0.007$. Data are presented as median values with interquartile range (25th-75th percentile) for quantitative traits, and as n (%) for qualitative parameters. **Abbreviations**: BMI (Body Mass Index), BAI (Body Adiposity Index) WHR (Waist-hip ratio), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), HDL-C (High-density Lipoprotein Cholesterol), LDL-C (Low-density Lipoprotein Cholesterol), CRP (C-reactive Protein), PAI1 (Plasminogen Activator Inhibitor-1), MCP1 (Monocyte Chemoattractant Protein-1).

Association of Genetic Variants With Severe Obesity

We conducted a case-control analysis to investigate the association between genetic variants and severe obesity susceptibility. The results are presented in Table 3. Due to the low frequency of the *POMC* rs1042571 and *BDNF* rs6265 variant alleles, we only used the dominant and over-dominant models for these variants. Additionally, the *CART* rs121909065 variant allele was not observed in either the control or case groups, indicating that this variant is extremely rare in our cohort.

Our analysis revealed that individuals with the *FTO* rs17817449 TT genotype had a significantly higher risk of developing severe obesity (OR = 3.30, 95% CI = 1.66–6.55, $p = 0.001$). We also observed an association in the

Table 3 Genotypic and allelic frequencies

Polymorphisms	Control n (%)		Case n (%)		OR (95% CI)	*p*
	196		305			
LEPR rs1137101						
Genotype						
AA	67	(0,34)	78	(0,26)	1.00 (Ref.)	-
AG	84	(0,43)	161	(0,53)	1.57 (0.94 - 2.61)	0.081
GG	45	(0,23)	66	(0,22)	1.30 (0.71 - 2.37)	0.386
Dominant Model						
AA	67	(0,34)	78	(0,26)	1.00 (Ref.)	-
AG+GG	129	(0,66)	227	(0,74)	1.50 (0.92 - 2.36)	0.105
Recessive Model						
AA+AG	151	(0,77)	239	(0,78)	1.00 (Ref.)	-
GG	45	(0,23)	66	(0,22)	0.99 (0.59 - 1.67)	0.991
Over-dominant Model						
AA+GG	112	(0,57)	144	(0,47)	1.00 (Ref.)	
AG	84	(0,43)	161	(0,53)	1.40 (0.90 - 2.18)	0.130
Allele						
A	218	(0,56)	317	(0,52)	1.00 (Ref.)	-
G	174	(0,44)	293	(0,48)	1.17 (0.86 - 1.57)	0.307
POMC rs1042571						
Dominant Model						
GG	128	(0,65)	209	(0,69)	1.00 (Ref.)	-
AG+AA	68	(0,35)	96	(0,31)	0.72 (0.18 - 2.90)	0.647
Over-dominant Model						
GG+AA	133	(0,68)	215	(0,70)	1.00 (Ref.)	
AG	63	(0,32)	90	(0,30)	0.85 (0.53 - 1.34)	0.489
Allele						
G	319	(0,81)	508	(0,83)	1.00 (Ref.)	-
A	73	(0,19)	102	(0,17)	0.835 (0.55 - 1.25)	0.382
LEP rs7799039						
Genotype						
GG	87	(0,44)	154	(0,50)	1.00 (Ref.)	-
AG	78	(0,40)	129	(0,42)	1.24 (0.78 - 1.97)	0.366
AA	31	(0,16)	22	(0,07)	0.65 (0.31 - 1.34)	0.243

(*Continued*)

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Table 3 (Continued).

Polymorphisms	Control n (%)		Case n (%)		OR (95% CI)	*p*
	196		305			
Dominant Model						
GG	87	(0,44)	154	(0,50)	1.00 (Ref.)	-
AG+AA	109	(0,56)	151	(0,50)	1.08 (0.70 - 1.67)	0.718
Recessive Model						
GG+AG	165	(0,84)	283	(0,93)	1.00 (Ref.)	-
AA	31	(0,16)	22	(0,07)	0.58 (0.29 - 1.16)	0.127
Over-dominant Model						
GG+AA	118	(0,60)	176	(0,58)	1.00 (Ref.)	
AG	78	(0,40)	129	(0,42)	1.35 (0.90 - 2.09)	0.182
Allele						
G	252	(0,64)	437	(0,72)	1.00 (Ref.)	-
A	140	(0,36)	173	(0,28)	0.928 (0.67 - 1.28)	0.649
BDNF rs6265						
Dominant Model						
CC	149	(0,76)	242	(0,79)	1.00 (Ref.)	-
CT+TT	47	(0,24)	63	(0,21)	1.02 (0.60 - 1.73)	0.921
Over-dominant Model						
CC+TT	151	(0,77)	245	(0,80)	1.00 (Ref.)	
CT	45	(0,23)	60	(0,20)	0.98 (0.58 - 1.67)	0.953
Allele						
C	343	(0,88)	544	(0,89)	1.00 (Ref.)	-
T	49	(0,13)	66	(0,11)	1.06 (0.65 - 1.73)	0.810
FTO rs17817449						
Genotype						
GG	71	(0,36)	80	(0,26)	1.00 (Ref.)	-
GT	104	(0,53)	147	(0,48)	1.24 (0.77 - 2.02)	0.375
TT	21	(0,11)	78	(0,26)	3.30 (1.66 - 6.55)	0.001*
Dominant Model						
GG	71	(0,36)	80	(0,26)	1.00 (Ref.)	-
GT+TT	125	(0,64)	225	(0,74)	1.58 (0.99 - 2.50)	0.050
Recessive Model		(0,00)				
GG+GT	175	(0,89)	227	(0,74)	1.00 (Ref.)	-

(*Continued*)

Table 3 (Continued).

Polymorphisms	Control n (%)		Case n (%)		OR (95% CI)	*p*
	196		305			
TT	21	(0,11)	78	(0,26)	2.89 (1.55 - 5.38)	0.001*
Over-dominant Model						
GG+TT	92	(0,47)	158	(0,52)	1.00 (Ref.)	
GT	104	(0,53)	147	(0,48)	0.84 (0.54 - 1.29)	0.445
Allele						
G	246	(0,63)	307	(0,50)	1.00 (Ref.)	-
T	146	(0,37)	303	(0,50)	1.68 (1.22 - 2.31)	0.001*
NPY rs16147						
Genotype						
TT	72	(0,37)	89	(0,29)	1.00 (Ref.)	-
CT	80	(0,41)	137	(0,45)	1.60 (0.97 - 2.65)	0.065
CC	44	(0,22)	79	(0,26)	1.59 (0.88 - 2.88)	0.123
Dominant Model						
TT	72	(0,37)	89	(0,29)	1.00 (Ref.)	-
CT+CC	124	(0,63)	216	(0,71)	1.60 (1.00 - 2.55)	0.047
Recessive Model						
TT+CT	152	(0,78)	226	(0,74)	1.00 (Ref.)	-
CC	44	(0,22)	79	(0,26)	1.21 (0.72 - 2.02)	0.469
Over-dominant Model						
TT+CC	116	(0,59)	168	(0,55)	1.00 (Ref.)	
CT	80	(0,41)	137	(0,45)	0.75 (0.49 - 1.17)	0.213
Allele						
T	224	(0,57)	315	(0,52)	1.00 (Ref.)	-
C	168	(0,43)	295	(0,48)	1.28 (0.95 - 1.73)	0.095
NPY rs5574						
Genotype						
TT	31	(0,16)	64	(0,21)	1.00 (Ref.)	-
CT	87	(0,44)	135	(0,44)	0.90 (0.50 - 1.66)	0.754
CC	78	(0,40)	106	(0,35)	0.70 (0.38 - 1.30)	0.264
Dominant Model						
TT	31	(0,16)	64	(0,21)	1.00 (Ref.)	-
CT+CC	165	(0,84)	241	(0,79)	0.81 (0.46 - 1.42)	0.467

(*Continued*)

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Table 3 (Continued).

Polymorphisms	Control n (%)		Case n (%)		OR (95% CI)	*p*
	196		305			
Recessive Model						
TT+CT	118	(0,60)	199	(0,65)	1.00 (Ref.)	-
CC	78	(0,40)	106	(0,35)	0.75 (0.47 - 1.18)	0.213
Over-dominant Model						
TT+CC	109	(0,56)	170	(0,56)	1.00 (Ref.)	
CT	87	(0,44)	135	(0,44)	1.15 (0.74 - 1.77)	0.532
Allele						
T	149	(0,38)	263	(0,43)	1.00 (Ref.)	-
C	243	(0,62)	347	(0,57)	0.82 (0.61 - 1.12)	0.219

Note: * for $p \leq 0.007$.

recessive model (OR = 2.89, 95% CI = 1.55–5.38, $p = 0.001$). Allelic tests showed that individuals carrying the risk allele (T) were 1.68 times more likely to develop severe obesity than the control group (OR = 1.68, 95% CI = 1.22–2.31, $p = 0.001$). Our analysis did not find a significant association between severe obesity and the *LEPR* rs1137101, *POMC* rs1042571, *LEP* rs7799039, *BDNF* rs6265, *CART* rs121909065, *NPY* rs16147, and *NPY* rs5574 polymorphisms. However, we observed a significant difference in the distribution of *NPY* rs16147 genotypes when we stratified the analysis by obesity onset periods. The CC genotype was found to occur at a higher frequency in the childhood-onset group ($p = 0.003$). The remaining five variants did not exhibit any significant differences ($p > 0.007$) among the different obesity onset periods.

Association of LEPR, LEP, FTO, and NPY Polymorphisms With Anthropometric, Blood Pressure, and Biochemical Parameters

We conducted an assessment of the potential influence of *LEPR, LEP, FTO*, and *NPY* polymorphisms on anthropometric, blood pressure, and biochemical parameters, as presented in Table 4. Our results revealed that the *FTO* rs17817449 polymorphism was significantly associated with body weight ($p = 0.003$), BMI ($p = 0.002$), and body adiposity index (BAI) ($p = 0.002$). Specifically, individuals with the TT genotype had higher values than those with the GT or GG genotypes. These results remained significant even after correcting for multiple tests. Furthermore, we found that the *LEPR* rs1137101 variant was significantly associated with PAI-1 serum levels ($p = 0.041$). The *LEP* rs7799039 polymorphism was significantly associated with waist circumference (WC) ($p = 0.029$), hip circumference (HC) (p = 0.015), glycated hemoglobin ($p = 0.047$), and circulating leptin levels ($p = 0.042$). The *NPY* rs5574 polymorphism was significantly associated with TG ($p = 0.048$). However, these associations did not remain significant after correcting for multiple tests. We did not observe any significant association with the *NPY* rs16147 variant.

Association of POMC and BDNF Dominant and Over-Dominant Models With Anthropometric, Blood Pressure, and Biochemical Parameters

In this study, we observed a low frequency of variant alleles for the *POMC* and *BDNF* genes. To address this issue, we used the dominant and over-dominant models in our analyses, as presented in Table 5. Our findings revealed that the *POMC* rs1042571 polymorphism was associated with PAI-1 ($p = 0.028$) and resistin ($p = 0.035$) using the dominant model. However, when using the over-dominant model, only the association with PAI-1 remained ($p = 0.016$). It is important to note that these associations did not remain significant after the Bonferroni test correction. In the analysis of

Table 4 Association of *LEPR, LEP, FTO* and *NPY* variants and anthropometric, biochemical and blood pressure variables

Parameters	*LEPR rs1137101*			*LEP rs7799039*			*FTO rs17817449*			*NPY rs16147*			*NPY rs5574*		
	Genotypes	*n*	Median (25; 75)	*Genotypes*	*n*	Median (25; 75)	*Genotypes*	*n*	Median (25; 75)	*Genotypes*	*n*	Median (25; 75)	*Genotypes*	*n*	Median (25; 75)
Weight (kg)	AA	145	99.1 (61.6; 129.5)	GG	241	106.6 (67.4; 131.5)	GG	151	99.1 (62.0; 127.7)	TT	161	100 (62.5; 128.8)	TT	95	106.6 (66.0; 138.0)
	AG	245	106.6 (71.1; 133.7)	AG	207	105.5 (68.0; 135.5)	GT	251	101.7 (66.2; 131.2)	CT	217	105.6 (68.0; 134.9)	CT	222	104.8 (67.0; 132.8)
	GG	111	106.5 (63.7; 135.8)	AA	53	74.4 (61.4; 129.9)	TT	99	120.2 (90.0; 140.6)	CC	123	106.5 (69.0; 134.0)	CC	184	102.4 (65.5; 130.6)
p			0.198			0.881			0.003*			0.150			0.330
BMI (kg/m2)	AA	145	37.5 (22.9; 47.1)	GG	241	41.0 (23.4; 48.9)	GG	151	36.0 (22.5; 46.9)	TT	161	38.2 (23.0; 47.1)	TT	95	42.2 (24.0; 50.6)
	AG	245	40.2 (23.9; 49.2)	AG	207	40.6 (23.6; 49.4)	GT	251	39.7 (23.5; 47.5)	CT	217	40.6 (23.5; 49.7)	CT	222	40.1 (23.4; 49.5)
	GG	111	40.5 (22.9; 49.5)	AA	53	24.7 (22.2; 45.3)	TT	99	45.0 (35.8; 52.3)	CC	123	41.2 (23.9; 49.5)	CC	184	38.9 (23.1; 47.2)
p			0.191			0.828			0.002*			0.131			0.202
BAI	AA	143	38,5 (27,6; 50,4)	GG	234	44,2 (28,9; 53,0)	GG	148	35.9 (26.8; 48.6)	TT	155	41,8 (27,2; 51,1)	TT	94	44,9 (30,8; 53,1)
	AG	239	43,1 (28,5; 51,8)	AG	204	41,6 (29,4; 51,4)	GT	245	41.8 (28.1; 52.0)	CT	212	42,5 (29,3; 51,7)	CT	214	41,7 (28,9; 51,6)
	GG	107	43,8 (30,4; 52,5)	AA	51	30,8 (26,7; 45,7)	TT	96	47.9 (37.7; 53.7)	CC	122	42,0 (29,5; 52,3)	CC	181	41,8 (27,5; 50,7)
p			0.141			0.442			0.002*			0.104			0.173
Waist circunference (cm)	AA	145	118.0 (81.0; 138.0)	GG	239	121.5 (83.5; 140.0)	GG	150	106.0 (80.0; 138.0)	TT	160	114.5 (82.5; 138.0)	TT	95	125.0 (86.0; 142.0)
	AG	242	121.8 (86.0; 142.0)	AG	206	123.5 (85.0; 140.3)	GT	250	118.0 (83.1; 138.6)	CT	215	121.0 (84.0; 141.5)	CT	220	121.0 (84.0; 141.9)
	GG	111	121.0 (82.0; 138.0)	AA	53	89.0 (78.0; 134.5)	TT	98	131.5 (114.7; 145.6)	CC	123	125.0 (85.0; 142.0)	CC	183	116.5 (82.0; 138.0)
p			0.603			0.029			0.072			0.442			0.832
Hip circunference (cm)	AA	145	122.5 (98.0; 143.5)	GG	239	130.0 (99.5; 145.0)	GG	150	121.7 (98.0; 142.0)	TT	160	125.7 (98.0; 144.7)	TT	95	132.0 (101.5; 147.5)
	AG	242	130.75 (101.0; 147.0)	AG	206	128.5 (101.0; 147.1)	GT	250	125.2 (99.0; 147.0)	CT	215	128.0 (100.0; 146.0)	CT	220	125.0 (99.1; 146.0)
	GG	111	128.0 (100.0; 144.0)	AA	53	103.0 (96.8; 142.5)	TT	99	136.0 (114.6; 148.2)	CC	123	130.0 (101.0; 146.0)	CC	183	128.0 (99.0; 144.0)
p			0.950			0.015			0.989			0.615			0.259
WHR	AA	145	0.91 (0.82; 0.96)	GG	239	0.9 (0.8; 1.0)	GG	150	0.9 (0.8; 1.0)	TT	160	0.9 (0.83; 0.97)	TT	95	0.9 (0.8; 1.0)
	AG	242	0.92 (0.85; 0.98)	AG	206	0.9 (0.8; 1.0)	GT	250	0.9 (0.8; 1.0)	CT	215	0.9 (0.84; 0.99)	CT	220	0.9 (0.8; 1.0)
	GG	111	0.90 (0.81; 0.97)	AA	53	0.9 (0.8; 1.0)	TT	98	0.9 (0.9; 1.0)	CC	123	0.9 (0.83; 0.99)	CC	183	0.9 (0.8; 1.0)
p			0.698			0.999			0.065			0.708			0.487
Total cholesterol (mg/dL)	AA	126	186.5 (164.0; 215.0)	GG	208	186.0 (161.3; 218.8)	GG	131	187.0 (161.0; 220.0)	TT	139	186.0 (162.0; 216.0)	TT	81	189.0 (164.0; 218.0)
	AG	210	185.5 (157.0; 216.0)	AG	174	187.0 (157.0; 216.0)	GT	221	186.0 (159.0; 214.5)	CT	185	187.0 (159.0; 216.0)	CT	186	184.0 (159.0; 215.0)
	GG	91	189.0 (161.0; 224.0)	AA	45	188.0 (169.0; 211.5)	TT	75	182.0 (161.0; 221.0)	CC	103	185.0 (161.0; 219.0)	CC	160	187.0 (161.0; 220.8)
p			0.929			0.179			0.768			0.677			0.430
HDL (mg/dL)	AA	126	49.5 (43.0; 63.2)	GG	208	51.0 (43.3; 61.0)	GG	131	53.0 (45.0; 61.0)	TT	139	52.0 (44.0; 64.0)	TT	81	51.0 (43.5; 59.5)
	AG	210	49.5 (43.0; 59.0)	AG	174	50.5 (43.0; 59.0)	GT	221	49.0 (43.0; 61.0)	CT	185	50.0 (43.0; 59.0)	CT	186	51.0 (43.0; 60.0)
	GG	91	53.0 (45.0; 62.0)	AA	45	51.0 (44.5; 64.0)	TT	75	49.0 (43.0; 58.0)	CC	103	51.0 (44.0; 60.0)	CC	160	50.5 (43.0; 62.8)
p			0.072			0.887			0.866			0.901			0.397
LDL (mg/dL)	AA	123	108.0 (92.0; 135.0)	GG	206	109.5 (89.8; 137.0)	GG	129	114.0 (93.0; 140.0)	TT	139	112.0 (92.0; 135.0)	TT	79	109.0 (95.0; 132.0)
	AG	206	109.5 (90.7; 133.0)	AG	169	110.0 (91.0; 135.0)	GT	218	109.5 (88.8; 133.0)	CT	185	110.0 (90.0; 137.7)	CT	181	106.0 (88.0; 132.0)
	GG	91	114.0 (93.0; 142.0)	AA	45	112.0 (99.5; 129.5)	TT	73	105.0 (95.0; 138.0)	CC	101	108.0 (95.0; 131.0)	CC	160	113.5 (93.0; 137.8)
p			0.853			0.418			0.666			0.648			0.119
Triglycerides (mg/dL)	AA	126	100.5 (77.0; 131.25)	GG	208	106.5 (74.0; 135.0)	GG	131	95.0 (69.0; 142.0)	TT	139	90.0 (70.0; 130.0)	TT	81	117.0 (80.0; 154.0)
	AG	210	104.5 (70.0; 141.25)	AG	174	103.5 (75.0; 152.0)	GT	221	102.0 (74.0; 134.5)	CT	185	106.0 (74.0; 147.0)	CT	186	104.0 (73.8; 139.8)
	GG	91	102.0 (74.0; 145.0)	AA	45	91.0 (68.0; 130.0)	TT	75	111.0 (79.0; 167.0)	CC	103	112.0 (77.0; 146.0)	CC	160	90.0 (70.0; 133.5)
p			0.112			0.207			0.597			0.095			0.048

(*Continued*)

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Table 4 (Continued).

Parameters	*LEPR rs1137101*			*LEP rs7799039*			*FTO rs17817449*			*NPY rs16147*			*NPY rs5574*		
	Genotypes	*n*	Median (25; 75)	*Genotypes*	*n*	Median (25; 75)	*Genotypes*	*n*	Median (25; 75)	*Genotypes*	*n*	Median (25; 75)	*Genotypes*	*n*	Median (25; 75)
Glucose (mg/dL)	AA	109	92.0 (86.0; 101.0)	GG	184	92.0 (86.0; 102.0)	GG	127	93.0 (86.0; 105.0)	TT	130	93.0 (86.0; 109.0)	TT	72	92.0 (87.3; 100.5)
	AG	193	93.0 (88.0; 103.5)	AG	161	94.0 (87.5; 104.0)	GT	197	93.0 (87.0; 103.0)	CT	168	93.5 (87.0; 105.0)	CT	170	92.0 (86.8; 103.0)
	GG	86	94.0 (87.0; 103.25)	AA	43	92.0 (88.0; 99.0)	TT	68	102.0 (89.0; 114.7)	CC	94	96.0 (88.0; 105.2)	CC	146	94.0 (87.0; 103.0)
p			0.875			0.581			0.854			0.288			0.086
Glycated hemoglobin	AA	105	5.3 (5.0; 5.9)	GG	172	5.4 (5.0; 6.0)	GG	116	5.3 (4.9; 5.8)	TT	112	5.2 (4.9; 5.9)	TT	66	5.3 (4.8; 6.0)
	AG	167	5.4 (5.0; 6.0)	AG	131	5.3 (5.0; 5.8)	GT	171	5.3 (5.0; 5.9)	CT	141	5.4 (5.0; 5.9)	CT	145	5.3 (5.0; 5.9)
	GG	70	5.3 (4.8; 5.8)	AA	39	5.1 (4.7; 5.4)	TT	55	5.6 (5.0; 6.3)	CC	85	5.3 (4.9; 5.9)	CC	131	5.3 (4.9; 5.9)
p			0.776			0.047			0.665			0.695			0.451
CRP (mg/dL)	AA	104	0.45 (0.15; 0.97)	GG	170	0.5 (0.1; 1.3)	GG	116	0.3 (0.1; 1.0)	TT	115	0.5 (0.1; 1.11)	TT	64	0.5 (0.2; 1.0)
	AG	164	0.43 (0.11; 1.15)	AG	130	0.4 (0.1; 1.0)	GT	169	0.4 (0.1; 1.0)	CT	141	0.4 (0.1; 1.05)	CT	144	0.4 (0.1; 1.0)
	GG	70	0.32 (0.13; 1.12)	AA	38	0.2 (0.1; 0.7)	TT	53	1.0 (0.3; 1.4)	CC	82	0.4 (0.1; 1.13)	CC	130	0.6 (0.1; 1.2)
p			0.106			0.799			0.500			0.336			0.385
Leptin	AA	31	2644.0 (1153.4; 3879.9)	GG	61	2540.0 (1632.1; 3465.6)	GG	35	1745.0 (776.4; 3354.6)	TT	38	2293.0 (1470.5; 2966.3)	TT	34	2217.7 (1054.2; 3146.2)
	AG	48	1961.5 (946.5; 2619.0)	AG	50	1985.5 (757.5; 2794.4)	GT	53	2219.3 (1145.5; 2859.9)	CT	43	2540.0 (788.4; 3134.0)	CT	43	2540.0 (1000.5; 3099.5)
	GG	41	2601.7 (1195.1; 3185.2)	AA	9	2316.4 (643.6; 3347.8)	TT	32	2614.5 (1850.2; 3351.7)	CC	39	2216.1 (1153.5; 2823.5)	CC	43	2269.8 (1585.9; 2904.3)
p			0.689			0.042			0.740			0.133			0.197
PAI1	AA	31	28588.3 (23510.6; 31201.1)	GG	61	26234.8 (20197.4; 31688.3)	GG	35	24940.2 (19841.0; 32916.6)	TT	38	26745.3 (19517.4; 30839.1)	TT	34	23476.7 (14903.1; 34388.3)
	AG	48	24031.1 (16239.2; 31623.8)	AG	50	25164.5 (19262.9; 31559.2)	GT	54	23553.8 (19517.4; 28797.8)	CT	43	26257.8 (21135.9; 33860.2)	CT	43	28551.7 (22158.3; 34065.2)
	GG	41	25452.1 (18507.5; 33868.6)	AA	9	26884.9 (20486.0; 31667.5)	TT	31	29844.3 (23117.3; 34226.4)	CC	39	24968.0 (15732.7; 32219.9)	CC	43	25452.1 (20638.7; 29473.6)
p			0.041			0.474			0.526			0.361			0.222
Resistin	AA	31	10093.5 (6336.7; 11947.9)	GG	61	8741.2 (6509.1; 10757.8)	GG	35	7188.3 (6075.6; 9083.4)	TT	38	8663.2 (6302.7; 10727.7)	TT	34	8565.4 (6217.2; 10679.4)
	AG	48	8296.2 (5176.7; 10526.9)	AG	50	7877.7 (5795.4; 10727.7)	GT	54	8309.3 (6010.7; 10872.3)	CT	43	8214.7 (5822.2; 10433.1)	CT	43	7740.2 (5861.8; 10775.8)
	GG	41	8329.4 (6436.9; 9373.3)	AA	9	7420.8 (5874.7; 8933.6)	TT	31	9256.1 (6846.8; 11725.3)	CC	39	8385.4 (6328.1; 10377.3)	CC	43	8569.5 (6259.2; 10526.9)
p			0.220			0.782			0.125			0.163			0.253
MCP1	AA	31	248.6 (219.0; 321.8)	GG	61	248.6 (177.2; 361.5)	GG	35	246.9 (174.0; 332.5)	TT	38	243.3 (177.2; 314.5)	TT	34	263.8 (164.7; 411.6)
	AG	48	272.9 (177.8; 390.8)	AG	50	257.6 (144.1; 378.2)	GT	54	243.9 (154.4; 333.2)	CT	43	259.1 (188.1; 365.9)	CT	43	259.1 (181.4; 354.6)
	GG	41	240.8 (154.7; 314.5)	AA	9	314.5 (240.8; 369.1)	TT	31	285.6 (214.9; 376.6)	CC	39	261.6 (159.7; 390.3)	CC	43	246.6 (172.6; 341.3)
p			0.198			0.372			0.432			0.792			0.844
SBP (mm Hg)	AA	110	120.5 (110.0; 136.0)	GG	155	121.0 (111.0; 133.0)	GG	148	126.0 (112.2; 144.7)	TT	154	120.0 (110.0; 135.2)	TT	59	125.0 (115.0; 135.0)
	AG	171	121.0 (111.0; 134.0)	AG	155	122.0 (113.0; 135.0)	GT	239	123.0 (113.0; 136.0)	CT	209	126.0 (114.0; 140.0)	CT	162	124.0 (113.0; 137.0)
	GG	74	123.0 (114.23; 129.3)	AA	45	120.0 (110.0; 134.5)	TT	95	128.0 (128.0; 148.0)	CC	119	129.0 (115.0; 148.0)	CC	134	119.0 (110.0; 129.0)
p			0.350			0.751			0.013			0.217			0.121
DBP (mm Hg)	AA	110	80.0 (70.0; 90.0)	GG	155	80.0 (70.0; 90.0)	GG	148	80.0 (71.0; 91.0)	TT	154	80.0 (71.7; 90.0)	TT	59	83.0 (73.0; 90.0)
	AG	171	80.0 (70.0; 90.0)	AG	155	80.0 (73.0; 89.0)	GT	239	80.0 (70.0; 89.0)	CT	2089	80.0 (71.5; 90.0)	CT	162	80.0 (70.0; 90.0)
	GG	74	80.0 (73.0; 89.0)	AA	45	80.0 (69.0; 89.5)	TT	95	87.0 (79.0; 96.0)	CC	119	85.0 (73.0; 95.0)	CC	134	79.5 (70.0; 85.3)
p			0.119			0.131			0.186			0.945			0.679

Notes: * for $p \leq 0.007$. The p-values for body weight and BMI were adjusted for gender, age, race/skin color, marital status, and exercise habits, while the p-values for other continuous parameters were adjusted for gender, age, race/skin color, marital status, exercise habits, and BMI.

Table 5 Association of POMC rs1042571 and BDNF rs6265 dominant and over; dominant models with anthropometric, biochemical and blood pressure variables

Parameters	*POMC* rs1042571					p	*BDNF* rs6265					p
	Models						*Models*					
	Dominant		p	*Over-Dominant*			*Dominant*		p	*Over-Dominant*		
	GG	AG+AA		GG+AA	AG		CC	CT+TT		CC+TT	CT	
Weight (kg)	105.3 (68.1; 133.8)	105.0 (63.9; 131.1)	0.259	105.4 (67.6; 133.9)	104.9 (64.3; 130.9)	0.273	105.3 (67.0; 132.5)	104.4 (64.6; 131.1)	0.834	105.4 (67.1; 132.5)	104.0 (64.6; 130.8)	0.930
BMI (kg/m2)	40.2 (23.6; 48.9)	38.6 (23.1; 48.8)	0.212	40.4 (23.6; 49.1)	38.5 (23.1; 48.3)	0.234	40.1 (23.5; 48.8)	38.8 (22.6; 49.5)	0.787	40.1 (23.5; 48.8)	38.7 (22.7; 49.5)	0.880
BAI	42.9 (28.1; 51.7)	39.9 (28.6; 51.6)	0.333	42.9 (28.1; 51.6)	40.0 (28.6; 51.7)	0.443	41.8 (28.4; 51.5)	43.2 (27.7; 53.0)	0.642	41.8 (28.5; 51.5)	43.2 (27.7; 52.6)	0.748
Waist circunference (cm)	120.0 (84.5; 140.0)	121.3 (82.0; 139.0)	0.799	120.0 (84.5; 140.0)	121.0 (82.0; 139.0)	0.774	120.0 (84.0; 139.0)	121.0 (81.8; 141.8)	0.700	120.0 (84.0; 139.1)	120.5 (82.0; 141.4)	0.888
Hip circunference (cm)	130.0 (100.0; 146.9)	125.0 (99.0; 144.3)	0.673	130.0 (100.0; 146.0)	125.0 (99.0; 145.0)	0.361	128.0 (100.0; 144.0)	127.5 (98.5; 148.5)	0.166	128.0 (100.0; 145.0)	126.3 (99.0; 147.8)	0.217
WHR	0.9 (0.8; 1.0)	0.9 (0.8; 1.0)	0.984	0.9 (0.8; 1.0)	0.9 (0.8; 1.0)	0.686	0.9 (0.8; 1.0)	0.9 (0.8; 1.0)	0.463	0.9 (0.8; 1.0)	0.9 (0.8; 1.0)	0.385
Total cholesterol (mg/dL)	184.0 (159.0; 216.0)	192.0 (164.5; 219.0)	0.170	184.5 (160.0; 217.5)	190.0 (163.0; 216.0)	0.897	187.0 (160.8; 218.0)	184.0 (160.5; 214.0)	0.715	186.0 (160.0; 217.0)	188.0 (161.0; 214.8)	0.870
HDL (mg/dL)	50.0 (44.0; 60.0)	52.0 (43.0; 65.5)	0.365	50.0 (44.0; 60.0)	52.0 (43.0; 65.0)	0.553	50.0 (43.0; 60.0)	53.0 (46.0; 65.0)	0.096	50.0 (43.0; 60.0)	53.0 (46.0; 65.8)	0.028
LDL (mg/dL)	109.0 (91.0; 135.0)	115.0 (95.0; 135.0)	0.564	110.0 (92.0; 137.0)	113.0 (93.0; 132.5)	0.985	109.0 (92.0; 135.0)	112.0 (90.0; 133.0)	0.679	109.0 (92.0; 135.0)	113.0 (90.0; 137.0)	0.461
Triglycerides (mg/dL)	104.0 (74.8; 138.3)	101.0 (71.5; 151.5)	0.310	106.0 (75.0; 139.0)	99.0 (70.0; 144.0)	0.869	108.0 (75.0; 147.5)	89.0 (68.5; 123.0)	0.008	108.0 (75.0; 147.0)	87.5 (69.0; 123.0)	0.007*
Glucose (mg/dL)	93.5 (87.0; 103.0)	92.0 (86.0; 102.0)	0.715	93.0 (87.0; 103.0)	92.0 (86.0; 102.0)	0.658	93.0 (87.0; 105.0)	92.0 (86.0; 98.0)	0.925	93.0 (87.0; 105.0)	92.0 (86.0; 98.0)	0.925
Glycated hemoglobin	5.3 (4.9; 5.8)	5.4 (4.9; 6.0)	0.555	5.3 (4.9; 5.8)	5.4 (4.9; 6.0)	0.482	5.3 (4.9; 5.9)	5.4 (4.9; 5.9)	0.341	5.3 (4.9; 5.9)	5.4 (4.9; 6.0)	0.261
CRP (mg/dL)	0.4 (0.1; 1.1)	0.5 (0.1; 1.1)	0.883	0.4 (0.1; 1.1)	0.5 (0.1; 1.2)	0.554	0.5 (0.1; 1.1)	0.3 (0.1; 1.0)	0.627	0.5 (0.1; 1.1)	0.3 (0.1; 1.0)	0.526
Leptin	2254.2 (1264.1; 3082.8)	2352.3 (972.2; 2918.7)	0.995	2228.9 (1168.3; 3057.7)	2391.6 (1031.5; 3039.2)	0.811	2238.5 (1145.5; 3100.2)	2365.3 (1124.5; 2858.5)	0.330	2238.5 (1137.5; 3100.9)	2365.3 (1391.6; 2742.9)	0.281
PAI1	27171.7 (20993.0; 31434.3)	23286.0 (14887.2; 32997.6)	0.028	27171.7 (21033.6; 31508.6)	23011.1 (14855.4; 33448.3)	0.016	25649.0 (19886.1; 31057.7)	27854.1 (18752.5; 39491.6)	0.262	25649.0 (19574.7; 31070.0)	27854.1 (18630.0; 39676.9)	0.387
Resistin	8801.5 (6491.1; 10796.9)	7091.9 (5291.7; 10087.8)	0.035	8679.4 (6327.2; 10768.2)	7297.7 (5908.7; 10269.7)	0.057	8329.4 (5861.8; 10433.1)	8933.6 (6438.9; 12326.0)	0.178	8329.4 (5874.7; 10504.2)	8933.6 (6527.3; 12120.2)	0.270
MCP1	245.4 (155.7; 357.0)	262.0 (214.3; 419.9)	0.783	245.4 (158.2; 360.0)	262.0 (205.2; 416.2)	0.918	257.2 (159.7; 362.9)	256.2 (206.1; 411.6)	0.631	256.2 (154.7; 361.9)	262.3 (208.5; 414.7)	0.556
SBP (mm Hg)	122.0 (112.0; 134.0)	120.0 (110.3; 133.8)	0.609	122.5 (112.8; 134.3)	120.0 (110.0; 131.0)	0.835	123.0 (112.0; 134.8)	120.0 (110.0; 131.0)	0.129	123.0 (111.5; 135.0)	120.0 (110.8; 130.3)	0.113
DBP (mm Hg)	80.0 (70.0; 90.0)	80.0 (71.0; 87.0)	0.867	80.0 (71.0; 90.0)	79.0 (70.0; 87.0)	0.998	80.0 (70.3; 90.0)	80.0 (71.0; 87.0)	0.543	80.0 (70.0; 90.0)	80.0 (71.0; 87.0)	0.561

Notes: * for $p \leq 0.007$. The p-values for body weight and BMI were adjusted for gender, age, race/skin color, marital status, and exercise habits, while the p-values for other continuous parameters were adjusted for gender, age, race/skin color, marital status, exercise habits, and BMI.

the *BDNF* rs6265 polymorphism using the dominant and over-dominant models, we found that the dominant model was associated with TG (p = 0.008). Additionally, the over-dominant model was associated with HDL (p = 0.028) and TG (p = 0.007). However, only the over-dominant model association with TG remained significant.

Inflammatory and Adipokine Expression Across FTO rs17817449 Genotypes

Our heatmap analysis reveals distinct cytokine expression across the *FTO* rs17817449 polymorphism genotypes. The TT genotype group shows a significant cytokine expression increase, including PAI1, Resistin, Adiponectin, MCP1, TNF-α, and IL1-β. Interestingly, the GG mutant genotype exhibits an elevated leptin expression. Despite an expression increase in the heterozygous GT group, IL-6 expression remains consistent between the TT and GG groups (Figure 1).

Combined Effects of Risk Alleles on Obesity

Regarding the distribution of risk alleles between groups, the study found that the prevalence of individuals with 8 or more risk alleles was significantly higher in the cases group (24%) compared to the control group (11.8%), with a p-value of 0.001. Additionally, the mean number of risk alleles was significantly higher in the cases group (7.10 ± 1.92) compared to the control group (6.40 ± 1.84), with a p-value of 0.013. The frequency of individuals with eight or more risk alleles was higher in the cases group, highlighting the potential role of these risk alleles in the development of obesity. The graph (Figure 2) emphasizes the importance of considering the combined effect of multiple risk alleles on the development of obesity. It is important to note that the significance level was adjusted for multiple tests, and the corrected p-value was 0.007. These findings suggest that individuals with obesity are more likely to carry a greater number of risk alleles than those without obesity.

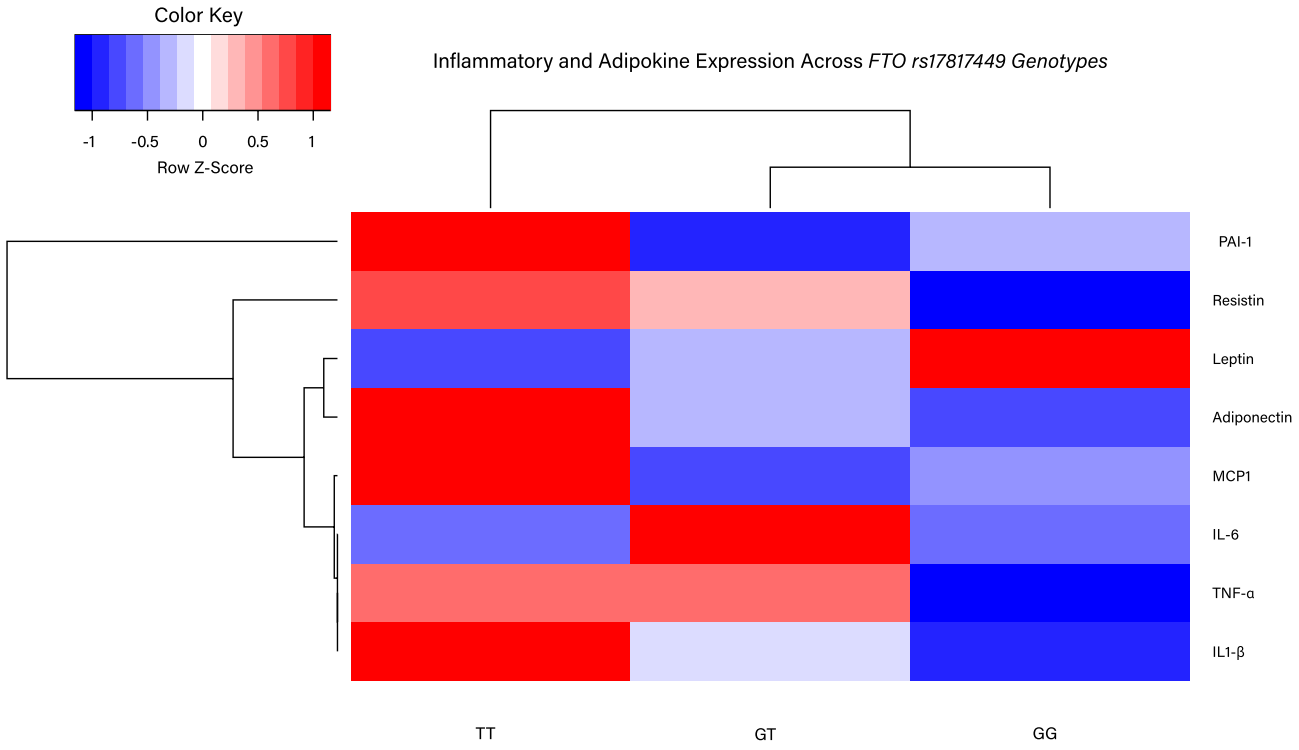

Figure 1 Inflammatory and adipokine expression varies across *FTO* rs17817449 genotypes. The TT genotype group exhibits a significant increase in cytokine expression, while the GG mutant genotype shows elevated leptin expression. IL-6 expression remains consistent between the TT and GG genotypes.

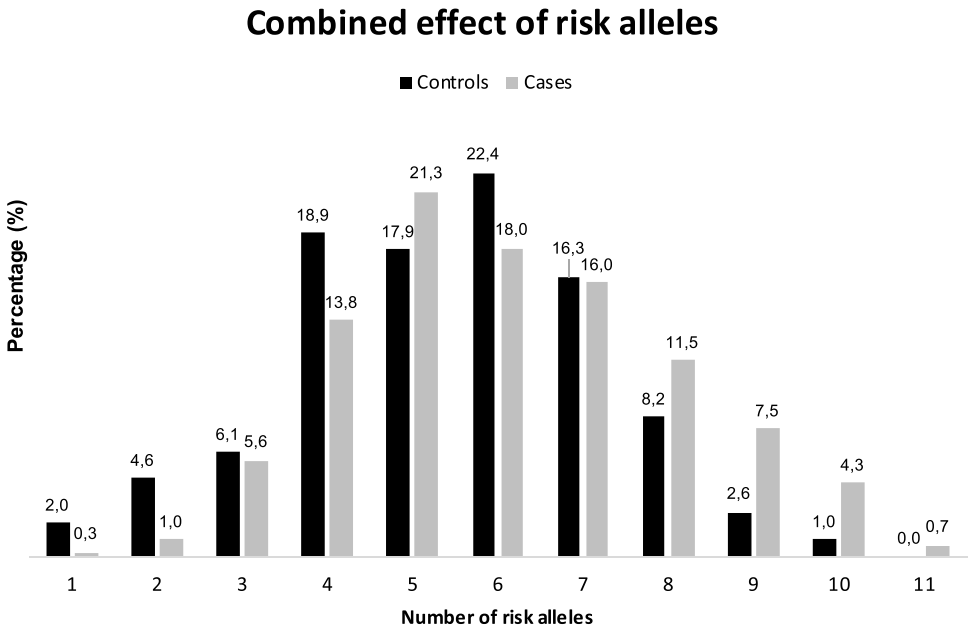

Figure 2 Combined Effect of the Risk Alleles of the Studied Polymorphisms. The graph illustrates the prevalence of individuals with eight or more risk alleles in the cases and control groups, with a significant difference (p= 0.001) observed between the two groups.

Discussion

Obesity is a complex disease. The prevalence of obesity has increased globally, and it is expected to continue increasing in the next years. The high prevalence of obesity is attributed to several factors, including environmental changes and genetic background. Genetic factors play an important role in obesity, in which some genes, such as those in the leptin-melanocortin pathway, have been identified as being associated with the development of this disease.

FTO is highly expressed in the hypothalamus, visceral fat, and liver, and plays a decisive role in regulating neuronal circuits related to feeding behavior, appetite, and energy homeostasis.[44] Previous animal studies showed that FTO deficiency decreases body weight and fat mass, mainly in white adipose tissue (WAT), and enhances the browning of adipose tissue.[45,46] Furthermore, individuals who carry the obesity risk allele of *FTO* show fat cell lipolysis, which may elucidate the primary role of the *FTO* gene in lipidic metabolism.[47] Several *FTO* variants have been linked to obesity and/or related traits, such as BMI, WC, fat mass, and insulin resistance, such as the rs17817449. This variant has been associated with higher BMI and fast insulin among obese children from Egypt.[48] However, the FTO-obesity association may differ across populations and ethnicities, and depend on other factors, such as age, gender, lifestyle, and diet.[49–51]

In our study, we observed a statistically significant association between the *FTO* rs17817449 T allele with weight, BMI, and BAI. Furthermore, a recent preliminary study by our group evaluated the contribution of two *FTO* polymorphisms (rs9939609 and rs17817449) for extreme obesity in a Brazilian cohort. Interestingly, individuals with extreme obesity had higher rs17817449 TT allele frequency. Homozygous carriers had a 3.3-fold risk of extreme obesity and heterozygous showed a 1.24 greater risk. Moreover, this previous study also observed an association with body weight, BMI, and triglyceride levels.[52] In addition to these findings, a strong association with extreme obesity was observed in a non-Hispanic Caucasian sample consisting of 583 cases, 544 controls, and a subset of discordant sister pairs, with 99 obese sisters and 99 thin sisters,[53] which further supports our results. Furthermore, the *FTO* variant studied by GONZÁLEZ et al (2012)[54] was associated with obesity in a homogeneous Spanish population with a family history.

A study conducted on the western Saudi population indicated that the *FTO* rs17817449 variant is significantly associated with susceptibility to Polycystic Ovary Syndrome (PCOS), which is characterized by infertility, obesity, and insulin resistance in women. However, the researchers observed a significant association of BMI only with the *FTO* rs8050136 variant.[55] Additionally, the FTO rs17817449 variant was considered a risk allele for obesity in an American

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PCOS family-based and case-control study.[56] Therefore, it may suggest that the results are nationality-related, and other specificities of these populations must be analyzed and counterpointed.

Additionally, we investigated the relationship between *FTO* rs17817449 genotypes and cytokine expression in the case group. The results of our analysis revealed distinct cytokine expression across the *FTO* rs17817449 polymorphism genotypes. The TT genotype group showed a significant cytokine expression increase, including PAI1, Resistin, Adiponectin, MCP1, TNF-α, and IL1-β. In contrast, a study conducted on a Romanian children's cohort found that individuals with the TT genotype had lower adiponectin levels.[57] We also observed an increase in leptin expression in the GG mutant genotype, which is consistent with the results of the Quebec Family study, prior to BMI adjustment.[58] However, the leptin levels were the same in Saudi individuals with obesity, regardless of the *FTO* rs17817449 genotypes and gender.[59] Furthermore, the G allele was linked to reduced leptin levels in a Swedish cohort, even after adjusting for WC and BMI.[60] Altogether, these findings suggest that the relationship between FTO rs17817449 genotypes and cytokine expression is complex and highlight the need for further research to fully understand the relationship between FTO rs17817449 genotypes and cytokine expression, as well as the potential impact on obesity and related health outcomes. It is worth noting that our analysis has some limitations. The sample size was relatively small, which may limit the generalizability of our findings. Furthermore, the ethnic plurality of the Brazilian population, resulting from the miscegenation of native Amerindians, Europeans, Africans, and more recent migratory groups, could also be a potential limitation. Additionally, the results were not independent of body adiposity.

Leptin is a 16 kD hormone encoded by the *LEP* gene.[61] This hormone is secreted predominantly by white adipose tissue and its expression is proportional to the body's fat mass storage.[62,63] By diffusion transport, leptin crosses the blood-brain barrier and binds to the LEPR located in the hypothalamus. It activates a signaling cascade that promotes a decrease in food intake and an increase in energy expenditure. In addition, leptin acts on immune and endocrine modulation.[17,64] Some studies have shown that variations in the *LEP* gene can affect leptin expression and circulation, for example, the *LEP* rs7799039 variant.[61,63,65,66]

Our study found no significant variation in allele and genotype frequencies between cases and controls. Similarly, although there was a statistical association with WC, HC, glycated hemoglobin, and circulating leptin levels, the significance was lost due to the correction for multiple tests. Interestingly, a case-control study in a Southern Chilean reported that the *LEP* rs7799039 allele A was associated with lower total and LDL cholesterol levels, but the difference was not statistically significant after adjusting for multiple comparisons.[67]

The leptin receptor is a transmembrane protein that belongs to the cytokine receptor family.[68] Variations in the *LEPR* gene can lead to improper protein function.[69] Several variants were studied in this gene, including a missense *LEPR* rs1137101 polymorphism. This variant has been linked to leptin resistance and obesity. Previous studies have found that the *LEPR* rs1137101 polymorphism is associated with obesity in European-Caucasian descent Brazilians. Mattevi et al[70] observed a significant effect of this variant on BMI, and De Oliveira et al[71] found that the presence of the G allele was associated with increased levels of leptin and WC. The GG genotype was associated with an increased risk of obesity. However, our study did not find any positive correlation between the *LEPR* rs1137101 polymorphism and obesity. This may be explained by the genetic admixture that is characteristic of the state of Rio de Janeiro, where the sample was recruited. Our findings are in line with a study with Mexican young adults, which also did not find any correlation between the *LEPR* rs1137101 polymorphism and obesity. This suggests that the association between the *LEPR* rs1137101 and obesity could be specific to European-Caucasian descent populations.[72]

POMC is a precursor protein that is encoded by the *POMC* gene. It is processed by the prohormone convertase enzyme to form melanocyte-stimulating hormones (MSHs), which interact with MC4R and MC3R modulating energy expenditure and food intake.[9] Some studies have reported that variations in the sequence of the *POMC* gene can lead to improper processing of proopiomelanocortin.[73–75] One such mutation is the SNP rs1042571.

A study in northern India found that individuals who carried the mutant allele (T) of *POMC* rs1042571 had a BMI of ≥30 kg/m^2 or normal.[76] However, a family-based study in Thailand found that the rs1042571 mutant allele (T) did not show any correlation with obesity, anthropometric, or biochemical parameters.[77] Our study also found no significant correlation between the *POMC* rs1042571 polymorphism and obesity in our Brazilian sample. These findings are

consistent with the findings of the Thai study, and they suggest that the role of *POMC* rs1042571 may be population-specific.

NPY gene encodes a protein, which is a key regulator of appetite, energy balance, and body weight. Few studies have investigated the association between the polymorphism *NPY* rs5574 and obesity traits.[78,79] TIWARI et al (2013)[80] observed a significant association between this SNP and body mass increase in European ancestry patients treated with clozapine or olanzapine. Likewise, a longitudinal birth cohort study linked *NPY* rs5574 TT carriers with increased abdominal obesity.[78] Conversely, a case-control study with Malaysian children reported that allele T was associated with a reduced risk of obesity.[81]

The *NPY* rs16147 is another variant related to obesity. In Spanish children, this variant was associated with higher BMI and WC.[82] A case-control study and meta-analysis observed that the *NPY* rs16147 variant was significantly associated with obesity risk in Asians, but not in Caucasians.[81] Lin et al (2015) investigated the association between central obesity and abdominal fat distribution. They found a significant association between central obesity and abdominal fat distribution in Caucasians, but not in African Americans or Hispanics.[79] In our study, we identified an association between obesity and the *NPY* rs16147 dominant model (OR = 1.60, 95% CI = 1.00–2.55, p = 0.047). However, this association did not remain significant after the Bonferroni test. In the stratified analysis by the period of obesity onset, we observed a significant association between childhood-onset obesity and the rs16147 CC genotype (p = 0.003) of the *NPY* gene. Nevertheless, we did not detect any significant associations between the NPY rs5574 variant and obesity-related traits. These findings suggest that the *NPY* gene may have a role in the development of obesity across different populations, particularly in childhood-onset obesity. However, further studies are necessary to fully comprehend the mechanisms underlying this association.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of proteins that play important roles in neuronal survival, proliferation, differentiation, apoptosis, excitability, and synaptic plasticity.[83,84] **BDNF** has been proposed to be involved in the regulation of appetite and metabolism.[85,86] The *BDNF* rs6265 is the most commonly studied variant. This SNP has been linked to impaired functioning of several processes involved in the regulation of extracellular BDNF levels.[87] In addition to being broadly associated with neuronal processes, the aforementioned SNP has been recently linked to eating disorders, metabolic imbalance, and obesity risk increase in several populations.[88] However, due to the Bonferroni correction for multiple comparisons, only the association between *BDNF* rs6265 over-dominant model and TG (p = 0.007) remained statistically significant. Therefore, the significance of the association between *BDNF* rs6265 and TG is strengthened by the application of this correction.

Our study has some limitations. 1- This study's cross-sectional design limits our ability to establish causality, as the anthropometric and biochemical status may change over time and influence the observed associations. 2- While we controlled for various confounding factors, unmeasured variables may impact the results. 3- Additionally, the lack of functional validation limits our understanding of the biological mechanisms underlying the polymorphisms' effects on severe obesity.

Conclusion

In our study, we investigated the association of genetic polymorphisms with severe obesity in a Brazilian cohort. Our findings indicate that individuals with the *FTO* rs17817449 TT genotype are at higher risk of severe obesity as they tend to have greater body weight and BMI. We also observed a significant association between the over-dominant model of *BDNF* rs6265 and TG. Moreover, we stratified the analysis by obesity onset periods, we found a significant difference in the distribution of *NPY* rs16147 genotypes. Specifically, the CC genotype was associated with childhood-onset obesity. Our study also revealed that the prevalence of individuals with eight or more risk alleles was significantly higher in the cases group than in the control group. The cases group also had a significantly higher mean number of risk alleles than the control group. Finally, in our heatmap analysis of cytokine expression across *FTO* rs17817449 genotypes, we found that subjects with the TT genotype had increased cytokine expression, while those with the GG genotype exhibited elevated leptin expression. Although our study has a few limitations, it still provides valuable insights.

Ethics Approval and Informed Consent

The Ethics Committee of the Oswaldo Cruz Foundation approved the studies involving human participants (CAAE: 09225113.0.0000/ Protocol N°: 346.634). The patients/participants gave written informed consent before enrollment.

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Disclosure

The authors report no conflicts of interest in this work.

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