Annals of Obesity & Disorders

Open Access

Austin Publishing Group

Research Article

More Severe Obesity Phenotype Associated with Binge Eating in Youth, But No Influence of Snps in the Leptin and Leptin Receptor Genes

Fujiwara CTH[1,2]*, Melo ME[1,2,3], Fernandes AE[1,2], Pioltine MB[1,2], Santos AS[2], Matioli SR[4], Cercato C[3] and Mancini MC[1,2,3]

[1]Hospital das Clínicas of the Faculty of Medicine, University of São Paulo, Brazil

[2]Laboratory of Carbohydrates and Radioimunoassay/ LIM-18 of the Faculty of Medicine, University of São Paulo, Brazil

[3]Hospital das Clínicas of the Faculty of Medicine, University of São Paulo, Brazil

[4]Department of Genetics and Evolutionary Biology, University of São Paulo, Brazil

***Corresponding author:** Fujiwara CTH, Laboratory of Carbohydrates and Radioimunoassay/LIM-18, University of São Paulo, Faculty of Medicine, Av. DrArnaldo, 455, 3rd floor, room 3324, 01246-903 - São Paulo, Brazil

Received: March 19, 2016; **Accepted:** April 27, 2016; **Published:** April 29, 2016

Abstract

Introduction: Binge Eating (BE) is commonly associated with obesity and genetic factors participate in its multifactorial etiology. Single Nucleotide Polymorphisms (SNPs) in the Leptin (*LEP*) and Leptin Receptor (*LEPR*) genes may influence leptin expression and its signaling pathways of appetite regulation, thus contributing to the etiopathogenesis and maintenance of BE. The aim of this study was to investigate the association between BE and SPNs rs7799039 in the *LEP* gene and rs1137100, rs1137101 and rs8179183 in the *LEPR* gene and Cardio Metabolic Risk (CMR) factors in obese children and adolescents.

Materials and Methods: Cross-sectional study in which 465 obese youths aged seven to 19 years seeking treatment in the outpatient League of Childhood Obesity were enrolled and had anthropometric and metabolic data assessed. The CMR factors comprised the systemic hypertension, impaired fasting glucose, low HDL-cholesterol levels and hypertriglyceridemia. BE was evaluated through the Binge Eating Scale (BES). Genotyping was performed by real-time PCR and to assess the magnitude risk of the SNPs on BE, logistic regression was adjusted for confounding variables.

Results: 47.8% of obese children and adolescents (12.5 ± 2.9 years, 52.7% girls) fulfilled the criteria of BE. BE was more frequent in girls (OR= 2.146; 95% CI 1.461–3.152; p <0.001) and presented higher BES scores (18.7 ± 8.5 vs. 15.9 ± 8.2; p <0.001) than boys. Children and adolescents with BE showed higher BMI Z-score and waist-to-height ratio. Insulin levels were higher among girls with BE (27.2 ± 16.3 vs. 23.0 ± 14.8 ng/mL; p = 0.040), whereas boys with BE presented higher fat mass percentage (39.1 ± 6.3 vs. 37.2 ± 6.8; p = 0.026) in comparison to the group without BE. No association was found between BE and CMR factors and SNPs.

Conclusion: SNPs in the *LEP* and *LEPR* genes were not associated with BE. BE presented higher frequency among girls and was associated with a more severe adiposity and worse metabolic profile, but not with CMR factors in Brazilian obese children and adolescents.

Keywords: Childhood obesity; Binge eating; Polymorphism; Leptin; Leptin receptor, Cardiometabolic risk

Abbreviations

ARCn: Arcuate Nucleus; BE: Binge Eating; BED: Binge Eating Disorder; BES: Binge Eating Scale; CMR: Cardio Metabolic Risk; ED: Eating Disorders; HDL-C: High Density Lipoproteincholesterol; HOMA-IR: Homeostasic Model Assessment of Insulin Resistance; IFG: Impaired Fasting Glucose; LDL-C: Low Density Lipoproteincholesterol; *LEP*: Leptin Gene; *LEPR*: Leptin Receptor Gene; ObR: Leptin Receptor; SNP: Single Nucleotide Polymorphism; TG: Triglycerides; WtHR: Waist-to-Height Ratio; Z-BMI: BMI Z-Score

Introduction

Obesity is a worldwide epidemic and its prevalence is growing in adults, children and adolescents. In 2009-2010, the age-adjusted prevalence of obesity in children and adolescents in the USA was 16.9% [1]. Obese children and adolescents are more likely to be adversely impacted by comorbidities, such as dyslipidemia, hyperinsulinemia, Impaired Fasting Glucose (IFG), and hypertension, leading to higher cardiovascular risk [2]. Moreover, childhood obesity is associated with the persistence of excessive weight into adulthood [3]. Excessive weight is associated with Eating Disorders (EDs), especially Binge Eating Disorder (BED). BED prevalence is approximately 3-5% in the general population, but in obese individuals seeking treatment for excessive weight, it increases to 7.5-30% [4,5]. The main characteristics of BED are established by recurrent episodes of Binge Eating (BE), defined as the rapid ingestion of an exaggerated amount of food in a discrete period of time accompanied by loss of control over eating, followed by feelings of depression, distress, shame, guilt or upset in

Citation: Fujiwara CTH, Melo ME, Fernandes AE, Pioltine MB, Santos AS, et al. More Severe Obesity Phenotype Associated with Binge Eating in Youth, But No Influence of Snps in the Leptin and Leptin Receptor Genes. Ann Obes Disord. 2016; 1(1): 1003.

the absence of inappropriate compensatory behaviors [6].

Binge eating and leptin

Obese individuals with BED exhibit higher leptin levels than their peers without the disorder [7] and leptin levels are positively correlated with BE [8].Nevertheless, the relationship was not confirmed among women with BED [9] and animal models with induced BE behavior [10]. EDs are influenced by environmental, psychological, and biological factors, such as genetic components. Most studies address the investigation of ED with candidate genes related to appetite signaling pathways, as well as genes associated with obesity. It is noteworthy that energy homeostasis and body weight are coordinated by a complex network of central and peripheral components regulating body weight and leptin and its receptor (ObR) mRNA are abundantly expressed in hypothalamic areas [11]. In the hypothalamic Arcuate Nucleus (ARCn), leptin increases the excitability of anorexigenic neurons and inhibits orexigenic neurons, promoting the reduction of food intake, as well as increasing energy expenditure [12].

Polymorphisms in the leptin and leptin receptor gene

The leptin gene (*LEP*) is located in chromosome 7 (7q31.3) and presents three exons with rs7799039 (G-2548A, G>A), a Single Nucleotide Polymorphism (SNP) in the promoter region of the gene. The leptin receptor gene (*LEPR*) is situated in chromosome 1 (1p31). The extracellular domain of the ObR is encoded by exons 3 to 17, the transmembrane domain by exon 18 and the intracellular domain by exons 19 and 20 [13]. The rs1137100 (Lys109Arg, A>G) mutation is a conservative mutation characterized by the substitution of a lysine for an arginine in exon 4. Another amino acid substitution occurs in rs1137101 (Gln223Arg, A>G) in exon 6 and in rs8179183 (Lys656Asn, G>C) in exon 14, both consisting of two non-conservative mutations.

The influence of common polymorphisms in LEP and LEPR genes on obesity and metabolic disorders yields controversial results, suggesting a risk conferred by the variants [14,15], protective effects [16,17],or a lack of association [18]. Since major components of ingestion and satiety are centrally regulated in hypothalamic areas, our hypothesis relies on the fact that SNPs in the LEP and LEPR genes could influence their expression, and consequently influence central energy homeostasis signaling pathways, contributing to the etiopathogenesis of ED. Association studies regarding common polymorphisms with BE, especially in the pediatric population, are still scarce, and investigation may provide better comprehension about the contribution of genetic factors in the maintenance of this condition.

The aim of this study was to investigate the influence of polymorphisms rs7799039 in the *LEP* gene and rs1137100, rs1137101, and rs8179183 in the *LEPR* gene on BE and Cardiometabolic Risk (CMR) factors in obese children and adolescents.

Materials and Methods

Subjects and data assessment

Children and adolescents from seven up to 19 years of age seeking treatment for obesity in the outpatient League of Childhood Obesity were enrolled in the study prior to the beginning of treatment, between November 2009 and June 2014. The diagnosis of obesity was established by BMI Z Score (Z-BMI) ≥ 2.0, according to WHO growth charts [19]. Exclusion criteria comprised the diagnosis or clinical signs of established genetic syndromes and endocrine disorders associated to obesity or patients under treatment for obesity. The study was fully approved by the Ethics Committee of the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo and written informed consent was obtained from the patient's legal guardian prior to participation.

Weight and height were measured with patient wearing light clothes and no shoes. Waist circumference was measured at the midpoint between the bony markers of the ribs and superior iliac crest using a non-stretchable tape to establish the Waist-to-Height Ratio (WHtR). The estimation of fat mass percentage was determined bybioelectrical impedance analysis (RJL Systems Inc., Clinton Township, MI, USA) under standardized protocols [20]. The pubertal stage was evaluated according to the criteria proposed by Tanner [21] and patients were classified into groups of prepubertal (stage I or II of genitalia for boys and stage I of breasts for girls) or pubertal (from stage III of genitalia for boys and from stage II of breasts for girls).

Blood samples were obtained in the morning after a 12 hour fasting. Metabolic variables comprised fasting glucose, insulin and the Homeostasic Model Assessment of Insulin Resistance (HOMA-IR) [22]. IFG was established when glucose values were ≥ 100 mg/dL [23]. Blood pressure and heart frequency were determined using an oscillometric meter (Microlife Inc., Widnau, Switzerland) [24] in the right arm after the patient had rested for at least 5 minutes. The mean value obtained by three measures was considered to define the patient as hypertensive, established by Systolic Blood Pressure (SBP) and/or Diastolic Blood Pressure (DBP) percentiles ≥ 95 [25]. Total cholesterol, Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C) and Triglyceride (TG) levels were determined by automated enzymatic colorimetric method using commercial kits (Roche Diagnostics Corp., Indianapolis, IN, USA). Patients were considered with low HDL-C when levels were< 45 mg/dL, whereas hypertriglyceridemia was determined by TG ≥ 130 mg/dL for youngsters aged from 10 up to 19 years and ≥ 110 mg/dL for children under10 years old [26]. Serum leptin was determined by enzyme immunoassay using commercial kits (EMD Millipore Corp., St. Charles, MO, USA) and adjusted leptin was calculated by leptin levels divided by fat mass.

The BE was assessed through the Binge Eating Scale (BES), a self-assessment questionnaire which evaluates behavioral manifestations, feelings and cognitions involved in BE episodes developed by Gormally et al. [27], an instrument designed for screening BED symptoms in obese individuals [28]. Categories of BE were defined as: severe (score ≥ 27), moderate (score between 18 and 26) or absent (score ≤ 17) [28].Subjects were classified into groups of absent or present BE, comprising moderate and severe BE categories. Only youngsters with reading ability filled the questionnaire and, if required, assistance in reading specific questions was provided by the researcher.

The molecular study was performed in the Laboratory of Carbohydrates and Radioimmunoassay/LIM 18 of the Faculty of Medicine of the University of São Paulo. Genomic DNA was extracted from peripheral blood leukocytes, according to standard protocols described elsewhere [29]. The concentration and purity of

Table 1: Anthropometric, clinical and metabolic characteristics of obese children and adolescents.

	Total (N= 465)	Girls (N= 245)	Boys (N= 220)	*P*
Age (years)	12.5 ± 2.9	12.6 ± 3.0	12.4 ± 2.8	0.373
BES (score)	17.3 ± 8.5	18.7 ± 8.5	15.9 ± 8.2	<0.001
Z-BMI	3.27 ± 0.65	3.17 ± 0.65	3.40 ± 0.60	<0.001
Fat mass (%)	39.4 ± 6.8	40.7 ± 6.6	38.0 ± 6.7	<0.001
WHtR	0.66 ± 0.08	0.65 ± 0.08	0.66 ± 0.08	0.365
Leptin (ng/mL)	52.0 ± 28.5	57.7 ± 28.4	45.8 ± 27.3	<0.001
Adjusted leptin (ng/mL/kg)	1.64 ± 0.82	1.80 ± 0.76	1.46 ± 0.84	<0.001
SBP (percentile)	72.2 ± 24.0	72.7 ± 23.6	71.6 ± 24.5	0.667
DBP (percentile)	62.6 ± 22.5	61.2 ± 23.2	64.2 ± 21.8	0.248
Heart frequency (bpm)	83.0 ± 13.8	83.2 ± 14.2	82.8 ± 13.3	0.836
Fasting glucose (mg/dL)	80.0 ± 10.5	79.0 ± 10.8	81.3 ± 9.9	0.250
Fastinginsulin (U/ml)	25.0 ± 15.4	25.3 ± 15.7	24.5± 14.9	0.742
HOMA-IR	5.0 ± 3.4	5.1 ± 3.5	5.0 ± 3.2	0.856
Total cholesterol (mg/dL)	168.0 ± 34.4	167.3 ± 34.5	168.7 ± 34.4	0.443
LDL-cholesterol (mg/dL)	102.0 ± 30.0	101.7 ± 30.3	102.4 ± 29.8	0.616
HDL-cholesterol (mg/dL)	43.7 ± 9.6	43.9 ± 8.9	43.6 ± 10.4	0.395
Triglycerides (mg/dL)	110.9 ± 9.1	106.7 ± 44.9	115.7 ± 53.2	0.099

Data presented as mean ± SD; Student's t test for parametric and Mann–Whitney U test for nonparametric variables.
BES: Binge Eating Scale; Z-BMI: BMI Z Score; WtHR: Waist-to-Height Ratio; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HOMA-IR: Homeostasic Model Assessment of Insulin Resistance

genomic DNA samples were determined through an optical density spectrophotometer (Thermo Scientific Inc., Wilmington, DE, USA). The genotyping of LEP and LEPR polymorphisms were performed through real time PCR using TaqMan® assays (Applied Biosystems - Life Technologies Inc., Foster City, CA, USA).

Statistical analysis

Data are summarized as mean and Standard Deviation (SD), whereas for nominal variables, absolute and relative frequencies are presented. Continuous variables were submitted to Kolmogorov-Smirnov Test to verify distribution. Comparisons between BE groups were performed using Student's t test or Mann-Whitney U test. Frequencies of polymorphisms in the *LEP* and *LEPR* genes were tested for the Hardy-Weinberg Equilibrium through the Chi-Square Test (χ^2). The analyses of the polymorphisms were performed under the dominant inheritance model in which homozygotes for the ancestral allele are compared with carriers of the polymorphic allele. This inheritance model was established in order to reduce the number of classes, increasing the statistical power of tests. The estimation of linkage disequilibrium between SNPs was performed using the Cube X: Cubic Exact Solution software [30]. Frequencies of diplotypes (genotypes of haplotypes) were estimated using PHASE software 2.1 version [31,32].

The analysis was carried out considering all subjects and discriminately by gender to examine the association between polymorphisms, BE and CMR factors. In the comparison of SNPs frequencies between the groups of absent and present BE, logistic regression analysis was made adjusted for confounding variables (age, Z-BMI, gender and pubertal stage) and the magnitude risk of each SNP was presented as Odds Ratio (OR) and 95% Confidence Intervals (CI). Tests were performed with statistical significance level set at $p < 0.05$. All statistical analyses were conducted using SPSS® software 22.0 version (Statistical Package for the Social Sciences Inc., Chicago, IL, USA).

Results

Data of anthropometric, clinical, and metabolic parameters are shown in (Table 1). It was ascertained that 243 (52.2%) of obese children and adolescents fulfilled the criteria for absent BE, whereas 222 (47.8%) of patients were classified into the severe BE group (31.0% with moderate and 16.8% severe BE, respectively). Regarding the prevalence of CMR factors, it was found that HBP was present in 93 (21.2%) and IFG in 17 (3.7%) the sample, while low HDL-C and hypertriglyceridemia was observed in, respectively, 268 (58.4%) and 158 (34.8%) of children and adolescents.

When comparing children and adolescents by gender, girls presented higher BES scores, fat mass percentage, leptin, as well as adjusted leptin in comparison to boys. Meanwhile, mean Z-BMI was higher among boys ($p < 0.001$). Girls were more frequent in the BE group, after adjustment for age and Z-BMI (OR= 2.146; 95% CI 1.461 – 3.152; $p<0.001$), when compared to boys.

Comparison of anthropometric, clinical and metabolic variables between binge eating groups

The comparison of anthropometric, clinical and metabolic variables between BE groups was performed stratified by gender due to differences in the frequency of classification in BE groups and in the BES mean scores observed among girls and boys (Table 2).

Girls in the BE group presented higher Z-BMI ($p = 0.005$), WHtR ($p < 0.001$), insulin ($p = 0.040$) and a trend towards higher HOMA-IR ($p = 0.065$) in comparison to the absent BE group.

The comparison of anthropometric parameters revealed that boys in the BE group exhibited higher Z-BMI ($p = 0.022$), fat mass percentage ($p = 0.026$), WHtR (0. $p = 0.006$) when compared to boys without BE (Table 2). A trend towards higher leptin levels among boys with BE group was observed, however, it did not reach statistical significance ($p = 0.072$).

The investigation of the influence of BE over CMR factors did not reveal differences among groups of BE neither in girls or boys after adjustment for age, Z-BMI and pubertal stage ($p > 0.05$, data not shown).

Assessment of polymorphisms in *LEP* and *LEPR* genes according to binge eating

The allelic and genotypic frequencies of polymorphisms in *LEP* and *LEPR* genes were in Hardy-Weinberg equilibrium ($p > 0.05$). The frequencies of SNPs were compared among BE groups, however, no statistically significant differences was observed in both genders, through the logistic regression adjusted for age, Z-BMI and pubertal stage as presented in (Table 3).

Linkage disequilibrium analysis

The linkage disequilibrium analysis was performed and the estimated values of D' and R^2 revealed the existence of disequilibrium

Table 2: Comparison of anthropometric, clinical and metabolic variables between binge eating groups.

	Girls			Boys		
	BE			BE		
	Absent (N= 110)	Present (N= 135)	*P*	Absent (N= 133)	Present (N= 87)	*P*
Age (years)	12.5 ± 3.1	12.7 ± 3.0	0.497	12.6± 2.8	12.1± 2.7	0.229
BES (score)	11.1 ± 4.0	24.9 ± 5.7	<0.001	10.6± 4.5	23.9 ± 5.5	<0.001
Z-BMI	3.04 ± 0.62	3.27 ± 0.65	0.005	3.30± 0.67	3.50± 0.58	0.022
Fat mass (%)	40.0 ±6.9	41.2 ± 6.2	0.111	37.2± 6.8	39.1 ± 6.3	0.026
WHtR	0.64 ± 0.07	0.67 ± 0.08	<0.001	0.65± 0.07	0.68± 0.08	0.006
Leptin (ng/mL)	54.7 ± 27.9	59.9 ± 28.7	0.087	42.5± 23.1	50.8± 32.1	0.072
Adjusted leptin (ng/mL/kg)	1.82 ± 0.70	1.78 ± 0.81	0.473	1.41± 0.82	1.54± 0.86	0.200
SBP (percentile)	72.0 ± 24.4	73.2 ± 23.0	0.811	71.5± 25.2	71.6 ± 23.5	0.824
DBP (percentile)	62.2 ± 24.3	60.4 ± 22.3	0.506	63.9± 21.7	64.5± 21.9	0.829
Heart frequency (bpm)	83.4 ± 13.8	83.0 ± 14.6	0.562	81.4± 12.1	84.8± 14.8	0.077
Fasting glucose (mg/dL)	79.3 ± 10.1	78.7 ± 11.4	0.925	80.9± 10.0	81.9± 9.8	0.575
Fastinginsulin (U/mL)	22.9 ± 14.8	27.2 ± 16.3	0.040	23.6 ± 14.2	26.2± 16.3	0.343
HOMA-IR	4.6 ± 3.3	5.4 ± 3.6	0.065	4.7 ± 2.9	5.4± 3.7	0.245
Total cholesterol (mg/dL)	165.4 ± 31.9	168.9 ± 36.5	0.504	169.2± 35.2	167.9± 33.4	0.800
LDL- cholesterol (mg/dL)	99.8 ± 27.1	103.4 ± 32.7	0.538	103.3± 31.1	100.9± 27.7	0.572
HDL- cholesterol (mg/dL)	44.5 ± 9.7	43.3 ± 8.2	0.426	44.1± 11.2	42.8± 9.1	0.484
Triglycerides (mg/dL)	106.4 ± 46.6	106.9 ± 43.5	0.828	113.7± 54.2	118.8± 51.7	0.302

Data presented as mean ± SD; Student's t test for parametric and Mann–Whitney U test for nonparametric variables. BES: Binge Eating Scale; Z-BMI: BMI Z Score; WtHR: Waist-to-Height Ratio; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HOMA-IR: Homeostasic Model Assessment of Insulin Resistance

Table 3: Frequency of polymorphisms among binge eating groups.

	Girls			Boys		
	BE			BE		
	Absent	Present	*P*	Absent	Present	*P*
	n(%)	n (%)		n (%)	n (%)	
rs7799039 (G>A)						
GG	48 (43.6)	63 (46.7)	0.747	52 (39.1)	35 (40.2)	0.707
GA/AA	62 (56.4)	72 (53.3)		81 (60.9)	52 (59.8)	
rs1137100 (A>G)						
AA	74 (67.3)	100 (74.1)	0.326	89 (66.9)	56 (64.4)	0.685
AG/GG	36 (32.7)	35 (25.9)		44 (33.1)	31 (35.6)	
rs1137101 (A>G)						
AA	35 (31.8)	47 (34.8)	0.691	39 (29.3)	23 (26.4)	0.688
AG/GG	75 (68.2)	88 (65.2)		94 (70.7)	64 (73.6)	
rs8179183 (G>C)						
GG	74 (67.3)	83 (61.5)	0.425	87 (65.4)	59 (67.8)	0.570
GC/CC	36 (32.7)	52 (38.5)		46 (34.6)	28 (32.2)	

Logistic regression adjusted for age, Z-BMI and pubertal stage.

(p <0.001) between all SNPs in the LEPR gene (rs1137100, rs1137101 and rs8179183).

The gametic phase of diplotypes (genotypes of haplotypes) was estimated for SNPs in the *LEPR* gene and 14 different diplotypes were generated, respectively, from the allelic variants of SNPs rs1137100 (A>G), rs1137101 (A>G) and rs8179183 (G>C), as shown in (Table 4).Due to the small number of cases observed, diplotypes with frequency lower than 5% (identification 1, 3, 5, 8 10, 11 and 14) were assembled into a single group, designated as "rare", whereas all other diplotypes were maintained.

Assessment of diplotypes in *LEPR* gene according to binge eating

The assessment of observed frequencies of diplotypes in the *LEPR* gene among BE groups, shown that diplotype 12 (AAG/AGG) frequency among boys was higher in the BE group, however, the difference was marginally significant when adjusted for age, Z-BMI and pubertal stage (p = 0.052). No differences in both genders were found for the other diplotypes, as presented in (Table 5).

Discussion

In this cross-sectional study, we investigated the association between polymorphisms in genes related to energy homeostasis regulation, BE, and cardiometabolic risk factors in youths with severe obesity.

The observed frequency of BE revealed that 47.8% of the obese children and adolescents had moderate or severe BE. Accordingly, a study comprising 128 children and adolescents seeking treatment for overweight or obesity reported BE symptoms, assessed through the BES, in 39.1% of the population [33]. BE is commonly observed among youngsters, especially in the obese, although not necessarily fulfilling all the criteria for BED diagnosis [6]. Subclinical cases of

Table 4: Identification and frequency of *LEPR* gene diplotypes.

Identification	Diplotypes	n (%)
1	AAC/AAC	17 (3.7)
2	AAC/AAG	52 (11.2)
3	AAC/AGC	8 (1.7)
4	AAC/AGG	47 (10.1)
5	AAC/GGG	23 (4.9)
6	AAG/AAG	70 (15.0)
7	AAG/AGG	87 (18.7)
8	AAG/GAG	5 (1.1)
9	AAG/GGG	67 (14.4)
10	AGC/AGG	11 (2.4)
11	AGC/GGG	4 (0.9)
12	AAG/AGG	27 (5.8)
13	AGG/GGG	26 (5.6)
14	GGG/GGG	21 (4.5)

the ED frequently occur, in which the loss of control over eating is seen concomitantly with the absence of inappropriate compensatory behaviors [34]. Most studies address the genetic aspects related to anorexia and bulimia nervosa, while information related to BED and genetics is limited. Recently, and of particular relevance in obesity research, the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) elevated BED from a provisional to a formal diagnostic category [6].In a study that evaluated components associated with BED in obese youngsters, the authors observed BE episodes in 36.5% of the sample, suggesting this is a common condition among individuals treating excessive weight [35]. It is noteworthy that differences in the prevalence of BE among studies are mainly due to distinct aspects of BE, as well as the assessment tool adopted by the investigator. Dietary restriction, low self-esteem, and weight concern were important predictors for BE, and obese youths were more prone to these behaviors in a study enrolling 259 children and adolescents [36]. Overweight youngsters also exhibited more depressive symptoms and reported higher rates of loss of control over eating, which were directly associated with the severity of BE [37]. The attention concerning BE is particularly relevant, considering that

Table 5: Frequencies of diplotypes in the *LEPR* gene among binge eating groups.

		Girls			Boys		
		BE			BE		
		Absent	Present	*P*	Absent	Present	*P*
	Diplotype	n (%)	n (%)		n (%)	n (%)	
	Others	96 (87.3)	120 (88.9)	0.898	120 (90.2)	77 (88.5)	0.558
2	AAC/AAG	14 (12.7)	15 (11.1)		13 (9.8)	10 (11.5)	
	Others	99 (90.0)	119 (88.1)	0.891	119 (89.5)	81 (93.1)	0.295
4	AAC/AGG	11 (10.0)	35 (11.9)		14 (10.5)	6 (6.9)	
	Others	95 (86.4)	111 (82.2)	0.409	113 (85.0)	76 (87.4)	0.684
6	AAG/AAG	15 (13.6)	24 (17.8)		20 (15.0)	11 (12.6)	
	Others	83 (75.5)	113 (83.7)	0.146	108 (81.2)	74 (85.1)	0.481
7	AAG/AGG	27 (24.5)	22 (16.3)		25 (18.8)	13 (14.9)	
	Others	91 (82.7)	120 (88.9)	0.117	112 (84.2)	75 (86.2)	0.666
9	AAG/GGG	19 (17.3)	15 (11.1)		21 (15.8)	12 (13.8)	
	Others	104 (94.5)	127 (94.1)	0.764	129 (97.0)	78 (89.7)	0.052
12	AAG/AGG	6 (5.5)	8 (5.9)		4 (3.0)	9 (10.3)	
	Others	105 (95.5)	126 (93.3)	0.403	124 (93.2)	84 (96.6)	0.324
13	AGG/GGG	5 (4.5)	9 (6.7)		9 (6.8)	3 (3.4)	
	Others	97 (88.2)	109 (80.7)	0.126	106 (79.7)	64 (73.6)	0.311
	Rare	13 (11,8)	26 (19,3)		27 (20,3)	23 (26,4)	

Logistic regression adjusted for age, Z-BMI and pubertal stage.

childhood and adolescence are periods of greater vulnerability for the onset of EDs [38].

In our study, BE was associated with a more severe degree of adiposity as the BE group presented higher Z-BMI and WHtR. The use of WHtR is possibly an advantage over the use of the isolated measure of the waist circumference, which especially reflects the abdominal fat accumulation and represents an indirect measure of central obesity. The adjustment by height allows the establishment of a single cutoff point, regardless of differences in ethnicity, age, and gender [39]. WHtR is strongly associated with increased cardiovascular risk and provides a more accurate assessment of adiposity, even compared to BMI [40,41].

Moreover, girls classified with BE exhibited higher insulin levels and a trend towards higher HOMA-IR when compared to those without BE. These findings suggest that BE not only negatively impacts Z-BMI and body fat distribution, but also may be associated with a worse metabolic profile among girls. Insulin-resistant individuals typically present a phenotype characterized by excessive weight, along with greater abdominal fat accumulation, which is strongly correlated with metabolic syndrome components [42]. Furthermore, it is known that diets with high contents of saturated fatty acids and refined carbohydrates may contribute to the increase in insulin resistance [43]. In a study that evaluated the diet composition of children and adolescents through laboratorial meals, there was an association between loss of control over eating with higher intake of sugars (mainly desserts and snacks) and lower of protein (meat and dairy products, especially) [44]. Accordingly, minor energy intake from protein and higher from fatty acids has been described in obese women with BED [45]. The analysis of food diaries of individuals reporting BE episodes showed a low intake of dairy products [46], a high frequency of unbalanced meals, and greater preference for sweets [47].Thereupon, we cannot exclude the possible presence of distinct dietary patterns among the BE groups influencing glucose levels and HOMA-IR, though we did not assess the dietary intake of our cohort.

We observed a high prevalence of hypertension, low HDL-C, and hypertriglyceridemia, even though we did not find any association between BE and CMR factors after adjustments for age, Z-BMI and pubertal stage. It is difficult to separate the effects of BE on blood pressure and lipid levels; in addition, our youngsters are still growing and body mass gain could also play an influence on metabolic parameters [48].

The BES score was higher among girls, and were significantly more likely to present BE than boys. Our findings support the assumption that ED is more common among females. The estimated female: male ratio for anorexia nervosa is approximately 9:1, whereas for BED this ratio is close to 3:2 [49]. Considering the potential influence of gender, it is appropriate to perform the statistical analysis separately by gender. One possible explanation for the increase the risk of ED among females arises from sociocultural aspects, such as the greater weight concern and distorted body image influenced by current beauty standards [50]. Biological factors, such as leptin, might also represent a physiological component contributing to a greater prevalence of BED among girls, considering that leptin is positively correlated with the symptoms of BE [8,51,52]. Women present higher serum leptin levels and it is possible that leptin resistance might impact appetite regulation, contributing to the recurrent occurrence of BE episodes in these individuals [7].

The lack of association between SNPs in the *LEP* and *LEPR* genes with BE was observed in our study. The frequency of the diplotype 12 (AAG/AGG) in the *LEPR* gene was higher among boys in the BE group; nevertheless, it was not considered due to the marginal statistical significance and the small number of cases. The investigation of genetic factors in the etiopathogenesis of ED represents a field of great importance; however, as complex diseases, the lack of association between candidate genes and the susceptibility to ED is described in the literature. Data on twins suggest that the heritability - which expresses the relationship between the genotypic and phenotypic variance - of BED is greater than 40% [53]. Studies with this type of design might be potentially useful because they provide a measure of the genetic influence over a particular phenotypic attribute, once differences between a pair of monozygotic twins result solely from environmental factors. Meanwhile, association studies are also of interest considering that endogenous components, through biochemical and physiological mechanisms, and candidate genes, representing the hereditary component, may influence the development of the disease of interest [54].

The investigation of mutations in the *LEP* gene and nearby regions showed the lack of association with these EDs [55]. Similarly, no relationship between the polymorphisms rs1137100, rs1173101, and rs8179183 in the *LEPR* gene and anorexia nervosa was found in a case-control study with 304 women [56].

Our study relied on the assumption that the SNP rs7799039 in the promoter region of the *LEP* gene could modulate leptin expression and its serum levels, whereas the rs1137100, rs1137101, and rs8179183 SNPs could affect ObR expression or its binding sites, modifying leptin signaling pathways. As leptin is known to be an important appetite regulator, these SNPs might influence BE; however, we could not confirm this hypothesis as no association between leptin levels and BE was observed.

Among the limitations of the present study, should be considered the size and ethnical complexity of the studied population, as well as the limited number of polymorphisms examined. In addition, BE was assessed through a questionnaire developed for screening behaviors related to BED, which shows a high sensitivity but presents a low specificity, thus not being proper for BED diagnosis, which is established through a clinical interview. Nevertheless, to the best of our knowledge, this is the first study that assessed polymorphisms in both the LEP and LEPR genes and BE in a Latin American population. It is worth emphasizing that association studies regarding the influence of polymorphisms over EDs among children and adolescents are still limited, and further research is necessary to better comprehend these mechanisms.

Conclusion

SNPs rs7799039 in the LEP gene and rs1137100, rs1137101 and rs8179183 in LEPR gene were not associated with binge eating in obese youngsters. Binge eating was associated with more severe adiposity mass and distribution and worse metabolic profile, but not with cardiometabolic risk factors in Brazilian obese children and adolescents.

Acknowledgements

The study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo - FAPESP (#11/23340-6; #11/05322-0).

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014; 311: 806-814.
2. Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. Diabetes. 2002; 51: 204-209.
3. Lombard CB, Deeks AA, Teede HJ. A systematic review of interventions aimed at the prevention of weight gain in adults. Public Health Nutr. 2009; 12: 2236-2246.
4. Ricca V, Mannucci E, Moretti S, Di Bernardo M, Zucchi T, Cabras PL, et al. screening for binge eating disorder in obese outpatients. Compr Psychiatry. 2000; 41: 111-115.
5. Spitzer RL, Yanovski S, Wadden T, Wing R, Marcus MD, Stunkard A, et al. Binge eating disorder: its further validation in a multisite study. Int J Eat Disord. 1993; 13: 137-153.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders DSM-IV. 5th ed. Washington DC: APA. 2013.
7. Monteleone P, Di Lieto A, Tortorella A, Longobardi N, Maj M. Circulating leptin in patients with anorexia nervosa, bulimia nervosa or binge-eating disorder: relationship to body weight, eating patterns, psychopathology and endocrine changes. Psychiatry Res. 2000; 94: 121-129.
8. Lofrano-Prado MC, Prado WLd, de Piano A, Tock L, Caranti DA, Nascimento CMOd, et al. Eating disorders in adolescents: Correlations between symptoms and central control of eating behavior. Eating Behaviors. 2011;12: 78-82.
9. Adami G, Campostano A, Cella F, Ferrandes G. Serum leptin level and restrained eating: study with the Eating Disorder Examination. Physiol Behav. 2002; 75: 189-192.
10. Artiga AI, Viana JB, Maldonado CR, Chandler-Laney PC, Oswald KD, Boggiano MM. Body composition and endocrine status of long-term stress-induced binge-eating rats. Physiol Behav. 2007; 91: 424-431.
11. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest. 1996; 98: 1101-1106.
12. Van den Top M, Lee K, Whyment AD, Blanks AM, Spanswick D. Orexigen-sensitive NPY/AgRP pacemaker neurons in the hypothalamic arcuate nucleus. Nat Neurosci. 2004; 7: 493-494.
13. Thompson DB, Ravussin E, Bennett PH, Bogardus C. Structure and sequence variation at the human leptin receptor gene in lean and obese Pima Indians. Hum Mol Genet. 1997; 6: 675-679.
14. Boumaiza I, Omezzine A, Rejeb J, Rebhi L, Ouedrani A, Ben Rejeb N, et al. Relationship between leptin G2548A and leptin receptor Q223R gene polymorphisms and obesity and metabolic syndrome risk in Tunisian volunteers. Genet Test Mol Biomarkers. 2012; 16: 726-33.
15. De Luis DA, Gonzalez Sagrado M, Aller R, Izaola O, Conde R. Influence of Lys656Asn polymorphism of leptin receptor gene on insulin resistance in patients with diabetes mellitus type 2. Diabetes Res Clin Pract. 2008; 81: e9-e11.
16. Ben Ali S, Kallel A, Sediri Y, Ftouhi B, Feki M, Slimene H, et al. LEPR p.Q223R Polymorphism influences plasma leptin levels and body mass index in Tunisian obese patients. Arch M ed Res. 2009; 40: 186-190.
17. Salopuro T, Pulkkinen L, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, et al. Genetic variation in leptin receptor gene is associated with type 2 diabetes and body weight: The Finnish Diabetes Prevention Study. Int J Obes (Lond). 2005; 29: 1245-1251.
18. Heo M, Leibel RL, Fontaine KR, Boyer BB, Chung WK, Koulu M, et al. A meta-analytic investigation of linkage and association of common leptin receptor (LEPR) polymorphisms with body mass index and waist circumference. Int J Obes Relat Metab Disord. 2002; 26: 640-646.
19. De Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007; 85: 660-667.
20. NIH Consensus statement. Bioelectrical impedance analysis in body composition measurement. National Institutes of Health Technology Assessment Conference Statement. December 12-14, 1994. Nutrition. 1996; 12: 749-762.
21. Tanner JM. Normal growth and techniques of growth assessment. Clin Endocrinol Metab. 1986; 15: 411-451.
22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28: 412-419.
23. American Diabetes Association. Standards of Medical Care in Diabetes - 2014. Diabetes Care. 2014; 37: S14-S80.
24. Topouchian JA, El Assaad MA, Orobinskaia LV, El Feghali RN, Asmar RG. Validation of two devices for self-measurement of brachial blood pressure according to the International Protocol of the European Society of Hypertension: the SEINEX SE-9400 and the Microlife BP 3AC1-1. Blood Press Monit. 2005; 10: 325-331.
25. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004; 114: 555-576.
26. Simão AF, Precoma DB, Andrade JP, Correa FH, Saraiva JF, Oliveira GM, et al. I Brazilian Guidelines for cardiovascular prevention. Arq Bras Cardiol. 2013; 101: 1-63.
27. Gormally J, Black S, Daston S, Rardin D. The assessment of binge eating severity among obese persons. Addict Behav. 1982; 7: 47-55.
28. Freitas S, Lopes CS, Coutinho W, Appolinario JC. Tradução e adaptação para o português da Escala de Compulsão Alimentar Periódica. Revista Brasileira de Psiquiatria. 200; 23: 215-220.
29. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988; 16: 1215.
30. Gaunt TR, Rodríguez S, Day IN. Cubic exact solutions for the estimation of pairwise haplotype frequencies: implications for linkage disequilibrium analyses and a web tool 'CubeX'. BMC Bioinformatics. 2007; 8: 428.
31. Stephens M, Donnelly P. A comparison of bayesian methods for haplotype reconstruction from population genotype data. Am J Hum Genet. 2003; 73: 1162-1169.
32. Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data. Am J Hum Genet. 2001; 68: 978-989.
33. Lourenço BH, Arthur T, Rodrigues MD, Guazzelli I, Frazzatto E, Deram S, et al. Binge eating symptoms, diet composition and metabolic characteristics of obese children and adolescents. Appetite. 2008; 50: 223-230.
34. Goldschmidt AB, Jones M, Manwaring JL, Luce KH, Osborne MI, Cunning D, et al. The clinical significance of loss of control over eating in overweight adolescents. Int J Eat Disord. 2008; 41: 153-158.
35. Decaluwé V, Braet C, Fairburn CG. Binge eating in obese children and adolescents. Int J Eat Disord. 2003; 33: 78-84.
36. Allen KL, Byrne SM, La Puma M, McLean N, Davis EA. The onset and course of binge eating in 8- to 13-year-old healthy weight, overweight and obese children. Eat Behav. 2008; 9: 438-446.
37. Goossens L, Braet C, Bosmans G. Relations of dietary restraint and depressive symptomatology to loss of control over eating in overweight youngsters. Eur Child Adolesc Psychiatry. 2010; 19: 587-596.
38. Nicholls DE, Lynn R, Viner RM. Childhood eating disorders: British national surveillance study. Br J Psychiatry. 2011; 198: 295-301.

39. Ashwell M, Hsieh SD. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. Int J Food Sci Nutr. 2005; 56: 303-307.

40. Bosy-Westphal A, Geisler C, Onur S, Korth O, Selberg O, Schrezenmeir J, et al. Value of body fat mass vs anthropometric obesity indices in the assessment of metabolic risk factors. Int J Obes (Lond). 2006; 30: 475-483.

41. Khoury M, Manlhiot C, McCrindle BW. Role of the waist/height ratio in the cardiometabolic risk assessment of children classified by body mass index. J Am Coll Cardiol. 2013; 62: 742-751.

42. Ritchie SA, Connell JM. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. Nutr Metab Cardiovasc Dis. 2007; 17: 319-326.

43. Newsholme P, Cruzat V, Arfuso F, Keane K. Nutrient regulation of insulin secretion and action. J Endocrinol. 2014; 221: R105-120.

44. Tanofsky-Kraff M, McDuffie JR, Yanovski SZ, Kozlosky M, Schvey NA, Shomaker LB, et al. Laboratory assessment of the food intake of children and adolescents with loss of control eating. Am J Clin Nutr. 2009; 89: 738-745.

45. Yanovski SZ, Leet M, Yanovski JA, Flood M, Gold PW, Kissileff HR, et al. Food selection and intake of obese women with binge-eating disorder. Am J Clin Nutr. 1992; 56: 975-980.

46. Theim KR, Tanofsky-Kraff M, Salaita CG, Haynos AF, Mirch MC, Ranzenhofer LM, et al. Children's descriptions of the foods consumed during loss of control eating episodes. Eat Behav. 2007; 8: 258-265.

47. White MA, Grilo CM. Psychometric properties of the Food Craving Inventory among obese patients with binge eating disorder. Eat Behav. 2005; 6: 239-245.

48. Tanofsky-Kraff M, Shomaker LB, Stern EA, Miller R, Sebring N, Dellavalle D, et al. Children's binge eating and development of metabolic syndrome. Int J Obes (Lond). 2012; 36: 956-962.

49. Russell PG. Neurobiology in the Treatment of Eating Disorders: Edited by Hans W. Hoek, Janet L. Treasure and Melanie A. Katzman. The British Journal of Psychiatry. 2000; 176: 200.

50. Smink FR, Van Hoeken D, Hoek HW. Epidemiology of eating disorders: incidence, prevalence and mortality rates. Curr Psychiatry Rep. 2012; 14: 406-414.

51. Adami GF, Campostano A, Cella F, Scopinaro N. Serum leptin concentration in obese patients with binge eating disorder. Int J Obes Relat Metab Disord. 2002; 26: 1125-1128.

52. D'Amore A, Massignan C, Montera P, Moles A, De Lorenzo A, Scucchi S. Relationship between dietary restraint, binge eating, and leptin in obese women. Int J Obes Relat Metab Disord. 2001; 25: 373-377.

53. Bulik CM, Sullivan PF, Wade TD, Kendler KS. Twin studies of eating disorders: a review. Int J Eat Disord. 2000; 27: 1-20.

54. Helder SG, Collier DA. The genetics of eating disorders. Curr Top Behav Neurosci. 2011; 6: 157-175.

55. Hinney A, Bornscheuer A, Depenbusch M, Mierke B, Tölle A, Middeke K, et al. No evidence for involvement of the leptin gene in anorexia nervosa, bulimia nervosa, underweight or early onset extreme obesity: identification of two novel mutations in the coding sequence and a novel polymorphism in the leptin gene linked upstream region. Mol Psychiatry. 1998; 3: 539-543.

56. Quinton ND, Meechan DW, Brown K, Eastwood H, Blakemore AI. Single nucleotide polymorphisms in the leptin receptor gene: studies in anorexia nervosa. Psychiatr Genet. 2004; 14: 191-194.

Citation: Fujiwara CTH, Melo ME, Fernandes AE, Pioltine MB, Santos AS, et al. More Severe Obesity Phenotype Associated with Binge Eating in Youth, But No Influence of Snps in the Leptin and Leptin Receptor Genes. Ann Obes Disord. 2016; 1(1): 1003.