



Association of polymorphism in leptin receptor gene with susceptibility of adolescent idiopathic scoliosis

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Received: 25 January 2023 / Revised: 3 August 2023 / Accepted: 14 September 2023 / Published online: 6 October 2023
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Abstract

Purpose Abnormal leptin bioavailability has play key roles in the etiology of adolescent idiopathic scoliosis (AIS). Both leptin and its receptor levels may be modulated by the presence of genetic polymorphisms. This study aimed to evaluate the role of polymorphisms in the leptin (*LEP*) and its main receptor (*LEPR*) genes in the AIS susceptibility in girls.

Methods A retrospective case–control study was conducted with 189 AIS and 240 controls. *LEP* rs2167270 and *LEPR* rs2767485 polymorphisms were genotyped using a TaqMan validated assay. Associations were evaluated by odds ratios (OR) and 95% confidence intervals (CI).

Results The AIS group showed a predominance of girls under 18 years old ($n = 140$, 74.1%), 148 (78.3%) had low or normal BMI, 111 (58.7%) had Cobb $\geq 45^\circ$ and 130 (68.7%) were skeletally mature. Minor allele frequencies of rs2167270 and rs2767485 were 35.7% and 18.3%, for AIS and 35.6% and 25.4% for controls, respectively. *LEPR* rs2767485 *T* and *TC + TT* were associated with higher risk of AIS (OR = 1.53; 95% CI = 1.09–2.13 and OR = 1.84; 95% CI = 1.69–2.01, respectively), since *CC* genotype was only present in the control group. In addition, the *LEP* rs2167270 *GA + AA* was more frequent in low weight group (BMI ≤ 24.9) of girls with AIS. There was no significant association between *LEP* rs2167270 and AIS susceptibility, and *LEPR* rs2767485 and BMI.

Conclusion The *LEPR* rs2767485 was associated with the genetic susceptibility of AIS and *LEP* rs2167270 with low BMI. These data can contribute to the identification of genetic biomarkers to improve the diagnosis and treatment.

Keywords Adolescent idiopathic scoliosis · Leptin · Leptin receptor · Genetic polymorphisms

Introduction

Adolescent idiopathic scoliosis (AIS) affects approximately 3% of adolescents and female patients have higher risk of curve progression [1, 2]. The exact etiology of AIS remains unknown, however, the interaction between genetic, hormonal, and environmental factors is widely discussed in the literature [2–5].

The leptin signaling pathway is crucial for bone formation and resorption and for the regulation of the body's energy intake and expenditure. Patients with AIS have lower peripheral blood leptin and higher soluble leptin receptor (sOB-R) levels compared to controls [6–8]. Leptin and its receptor are encoded by the *LEP* and *LEPR* genes and single nucleotide polymorphisms (SNPs) in both genes have been suggested to affect their expression and/or the susceptibility of AIS

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[9–12]. After evaluating 6 *LEPR* SNPs, only the rs2767485 was associated with AIS susceptibility, suggesting that the abnormal *LEPR* expression level plays an important pathogenic role in AIS [12]. The *LEP* rs2167270 SNP changes the leptin level and it has been studied as a risk factor for the development of several diseases, including obesity and intervertebral disk degeneration [13]. As far as we know, no studies have evaluated the combined effect of these SNPs with occurrence of AIS.

Therefore, in the present work, we aimed to describe the frequency of *LEP* rs2167270 and *LEPR* rs2767485 SNPs among Brazilian girls, and to evaluate their role in AIS susceptibility.

Materials and methods

Research question

Polymorphisms in *LEP* and *LEPR* genes may alter this signaling pathway, to induce the abnormal leptin bioavailability, and to support the precursor theories of AIS etiology [4, 7, 10, 12]. Thus, we suppose that *LEP* rs2167270 and *LEPR* rs2767485 polymorphisms can be associated with AIS susceptibility.

Study population and clinical evaluation

The analytical observational case–control study was approved by the Human Research Ethics Committees

(73527617.4.0000.5273). The study was conducted in accordance with the Helsinki Declaration.

Girls with AIS ($n = 189$) from a Brazilian reference center in Orthopedics, diagnosed with spinal curvatures exceeding 10° (Cobb measuring) by clinical and radiographic examination were included in the study. Men, patients with incomplete radiographic data, any underlying disease that could justify non-idiopathic scoliosis (neurological, neuromuscular and syndromic diseases) or absence of biological material for genetic analysis, were excluded. AIS cases were categorized according to the Cobb angle magnitude ($<45^\circ$ and $\geq 45^\circ$) and indication of surgical treatment for scoliosis (Fig. 1) [4, 5]. The skeletal maturity (Risser's sign) was assessed by ossification of the iliac apophysis, as the predictor of scoliosis progression [14]. All measurements were performed using the Surgimap Spine software (Nemaris Inc., New York, USA), version 2.2.15.5.

Participants from the control group ($n = 240$) were girls recruited at the hospital blood bank when they appeared to donate blood. All healthy volunteers were evaluated by an orthopedic spine surgeon to rule out any spine deformity [4, 5].

The body mass index (BMI) was calculated as the weight (kg) divided by the square of height (m^2) and it was classified as underweight (≤ 18.5), normal weight ($18.5 \leq \text{BMI} \leq 24.9$), overweight ($25 \leq \text{BMI} \leq 29.9$), obesity and morbid obesity (≥ 30) for adults (≤ 20 years old). For children and adolescents (≤ 19 years old), we determined age-corrected BMI z-scores using Anthroplus software v.1.0.4 (<http://www.who.int/growthref/tools/en/>, last accessed June 12, 2023) based on World Health Organization (WHO) growth charts:

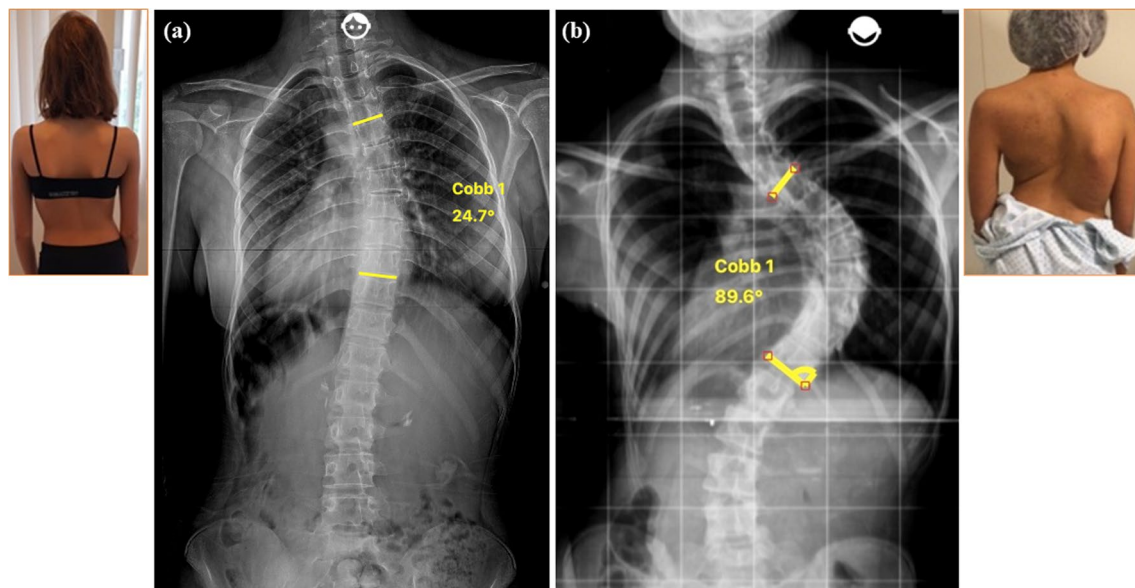


Fig. 1 Panoramic radiographs of the posteroanterior spine were taken to measure the Cobb angle. **a** Example of scoliosis patients with Cobb angle $<45^\circ$. **b** Example of scoliosis patients with Cobb angle $\geq 45^\circ$ and with indication of surgical treatment

accentuated thinness and thinness (underweight) with < -2 ; eutrophy (normal weight) between ≥ -2 and $\leq +1$; overweight between $\geq +1$ and $< +2$; obesity and severe obesity with $\geq +2$ z-score.

Polymorphisms genotyping analysis

The genomic DNA extraction was performed using an extraction kit (Qiagen, Hilden, Germany), following the procedures recommended by the manufacturer. The genotyping analysis of the *LEP* rs2167270 and *LEPR* rs2767485 polymorphisms were performed using TaqMan allelic discrimination assays (C_15966471_20 and C_16068395_10, respectively). The probes are marked with different fluorescence captured by the equipment software (7500 Real-Time System, Applied Biosystems, Foster City, CA, USA), discriminating the individual genotype (Fig. 2).

Data analysis

Categorical data were presented as number (n) and frequency (%) and analyzed using the Chi-squared (χ^2) statistic test or Fischer exact test, when applicable. Comparisons of continuous variables between cases and controls

were performed using the Student's t test, and data were presented as mean $\pm$ standard deviation (SD).

The polymorphisms alleles frequencies and genotypes distributions were derived by counting, and frequencies between the two groups were compared using the χ^2 test or, when appropriate, the Fisher's exact test. Deviations from Hardy–Weinberg equilibrium (HWE) in the polymorphism's frequencies were assessed by the goodness-of-fit χ^2 test.

The associations between categorical variables and AIS were evaluated by determining the odds ratios (OR) and their respective 95% confidence intervals (95% CI). All analyses were performed using the IBM SPSS 20.0 Statistics for Windows (SPSS Inc., Chicago, IL, USA) and a significance level of 0.05 was adopted.

The sample size was calculated using Epi Info 7, version 7.1.3. (<http://www.cdc.gov/epiinfo/html/downloads.htm>) to detect a difference between case and control groups, assuming an OR of 2.0, based on previous evidence [4, 5], with a power of 0.8 and 5% type I error.

The mechanistic model to explain the hypothesis of *LEPR* polymorphism in AIS susceptibility was created with BioRender (<https://biorender.com/>).

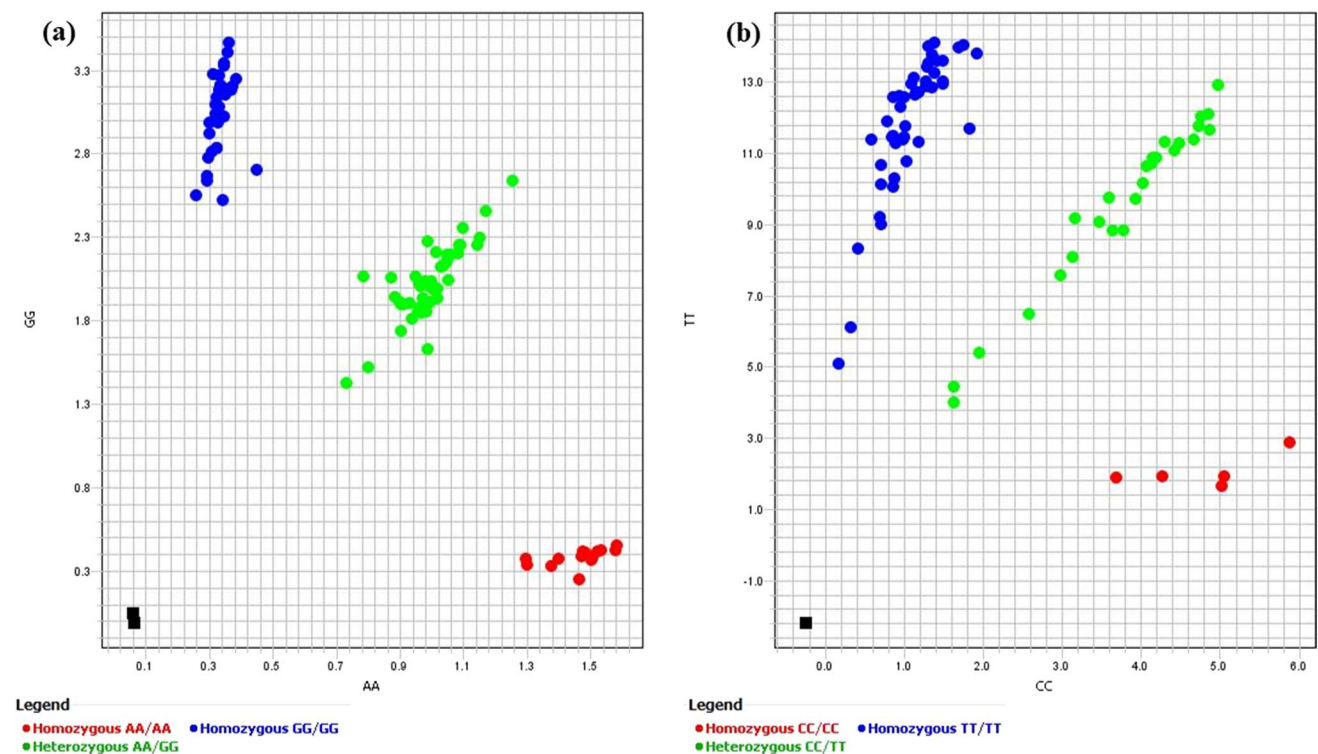


Fig. 2 Analysis of polymorphisms by real-time PCR using the TaqMan system. Black squares are negative controls, which should not present PCR amplification. The blue circles are patients with wild homozygous genotype. The red circles are the variant homozy-

gotes, and the green circles are heterozygotes, which presents fluorescence of both probes. **a** Example of *LEP* rs2167270 G>A analysis. **b** Example of *LEPR* rs2767485 T>C analysis

Results

Table 1 describes the continuous variables for AIS cases ($n = 189$) and controls ($n = 240$). Mean and median age, BMI, and BMI-for-age (z-score) in AIS group were significantly lower ($P < 0.05$) than in the controls. In addition, mean and median age in AIS group with Cobb $< 45^\circ$ was significantly lower ($P < 0.001$) than in the AIS Cobb $\geq 45^\circ$ group, while the BMI was similar among Cobb angle groups ($P > 0.05$). Table 2 shows the categorical demographic data of the 429 participants included in this study. Most AIS cases were aged less than or equal to 18 years, 79.5% had z-score between < -3 and $\leq +1$ (0.03 ± 1.2 vs. 1.17 ± 1.07) and 73.8% had low or normal BMI (22.7 ± 5.5 vs. 27.0 ± 4.2 kg/m²). Considering anthropometric categories (≤ 24.9 and ≥ 25 kg/m²), 36.7% of controls ($n = 88$) and 78.3% of cases ($n = 148$) had less than 25 kg/m². There were significant differences between cases and controls for age, BMI, anthropometric categories, and BMI-for-age ($P < 0.001$ and $P < 0.045$, respectively).

According to the Risser scale, most AIS patients (68.7%) were classified as IV and V (mature grade). The mean Cobb angle of the greater curve (lumbar or thoracic) was $49.3 \pm 16.5^\circ$ and the majority (58.7%) presented Cobb angle $\geq 45^\circ$ (Fig. 1).

Table 1 Continuous variables of the studied population ($n = 429$)

Variables	Controls ($n = 240$)	AIS cases ($n = 189$)	Cobb $< 45^\circ$ ($n = 78$)	Cobb $\geq 45^\circ$ ($n = 111$)
Age				
Mean	36.7	16.7	14.8	18.1
Median	37	15.0	14.0	17.0
Std. Deviation	12.4	5.4	3.8	6.0
Minimum	16	10	10	10
Maximum	59	30	30	30
BMI (kg/m ²) ^a				
Mean	27.0	22.7	22.4	22.7
Median	26.7	21.3	22.5	21.3
Std. Deviation	4.3	5.5	4.6	5.7
Minimum	17.9	15.2	17.2	15.2
Maximum	48.3	39.9	28.5	39.9
BMI-for-age (z-score) ^b				
Mean	1.17	0.03	-0.06	0.12
Median	1.22	0.13	0.03	0.20
Std. Deviation	1.07	1.24	1.10	1.36
Minimum	-0.07	-3.25	-2.92	-3.25
Maximum	2.65	3.12	2.16	3.12

BMI—body mass index

^aBMI was calculated for 226 controls and 42 AIS cases

^bz-score was calculated for 14 controls and 147 AIS cases

Table 2 Demographic data of the studied population ($n = 429$)

Variables	Controls (<i>n</i> = 240)	AIS cases <i>n</i> = 189 <i>n</i> (%)	<i>P</i> value ^a
Age			
≤ 18	11 (4.6)	140 (74.1)	<0.001
19–25	49 (20.4)	30 (15.9)	
≥ 26	180 (75.0)	19 (10.0)	
BMI (kg/m ²) ^b			
≤ 18.50	3 (1.3)	9 (21.4)	<0.001
18.51–24.9	78 (34.5)	22 (52.4)	
25.0–29.9	96 (42.5)	6 (14.3)	
≥ 30	49 (21.7)	5 (11.9)	
BMI-for-age (z-score) ^c			
Underweight ^e	0 (0.0)	8 (5.4)	0.045
Normal weight ^f	7 (50.0)	109 (74.1)	
Overweight	4 (28.6)	22 (15.1)	
Obesity	3 (21.4)	8 (5.4)	
Anthropometric categories ^d			
Underweight	3 (1.2)	17 (9.0)	<0.001
Normal weight	85 (35.4)	131 (69.3)	
Overweight	100 (41.7)	28 (14.8)	
Obesity	52 (21.7)	13 (6.9)	

BMI—body mass index

^aPearson's Chi-square test (χ^2) or Fisher's exact test, when necessary

^bBMI was calculated for 226 controls and 42 AIS cases

^cz-score was calculated for 14 controls and 147 AIS cases

^dBMI for adult and z-score for children and adolescents were grouped together

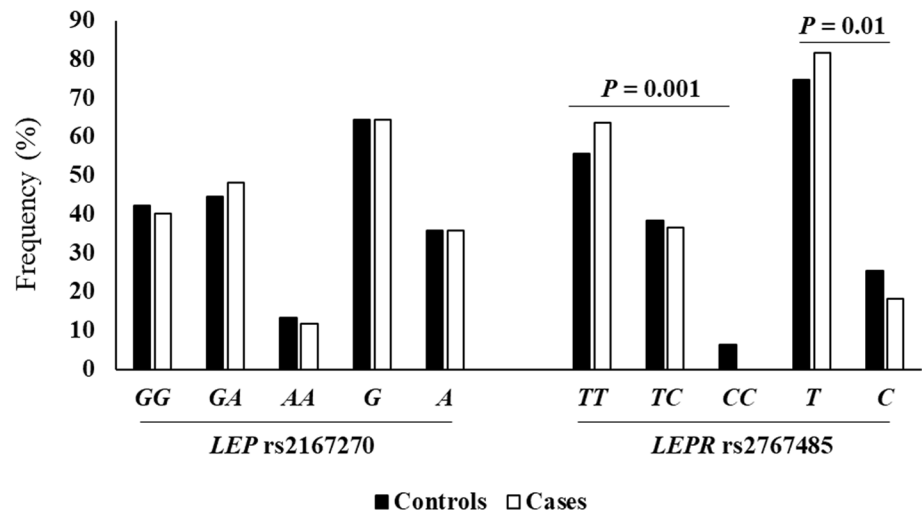
^eAccentuated thinness and thinness

^fEutrophy

The *LEP* rs2167270 polymorphism was in HWE in both subgroups: controls ($P = 0.87$) and AIS cases ($P = 0.54$). However, the *LEPR* rs2767485 polymorphism was in HWE only among the controls ($P = 0.10$ for controls and $P = 0.001$ for AIS group). The alleles and genotypes distribution of both polymorphisms in cases and controls is illustrated in Fig. 3. The variant allele and genotype frequencies of *LEP* rs2167270 were 35.7% (A) and 11.7% (AA), respectively, for AIS cases, and 35.6% (A) and 13.3% (AA), respectively, for controls; while for *LEPR* rs2767485 they were 18.3% (C) and 0% (CC), for AIS cases, and 25.4% (C) and 6.2% (CC) for controls, respectively. The significant differences between cases and controls were observed only in allelic and genotypic frequencies of the *LEPR* rs2767485 SNP, showing a higher frequency of both *LEPR* T allele and TT genotype in the AIS group compared to the control group.

An association analysis was performed to assess the risk of both polymorphisms of developing AIS and different

Fig. 3 Genotypic and allelic distribution of *LEP* rs2167270 and *LEPR* rs2767485 polymorphisms in adolescent idiopathic scoliosis cases and controls. ^aPearson's Chi-square test (χ^2) or Fisher's exact test, if necessary



Cobb angles, as shown in Table 3. The *LEPR* rs2767485 *T* allele and *TT* and *TC* genotypes or the dominant model (*TC+TT*) were risk factors for the prevalence of AIS, either considering Cobb angle groups $< 45^\circ$ or $\geq 45^\circ$. There was no significant association between *LEP* rs2167270 polymorphism and AIS. A combined analysis of the two polymorphisms was performed to investigate their interaction on the risk of AIS. However, there was no significant association between *LEP-LEPR* combined polymorphisms and AIS prevalence (data not shown).

In addition, the association of the polymorphisms and low BMI was made considering only the girls of AIS group. Anthropometric categories were categorized into two groups (≥ 25 and ≤ 24.9 kg/m²) based on BMI-for-age. Table 4 shows the association analysis of the *LEP* rs2167270 and *LEPR* rs2767485 polymorphisms between BMI groups in AIS cases. There was a significant difference for *LEP* rs2167270 polymorphism between the two groups, with a predominance of *LEP* GA + AA girls in low weight group, being a risk factor for BMI ≤ 24.9 in AIS cases.

Based on these findings and the biological importance of the *LEPR* rs2767485 polymorphism, we hypothesized the possible relationship of LEP-LEPR signaling and bone remodeling in the development of AIS (Fig. 4).

Discussion

The present study described the association of a polymorphism from a gene involved in the LEP-LEPR signaling with the risk of AIS and low BMI in 189 girls treated in a public orthopedic referral hospital in Brazil. Most patients were referred from other facilities for surgical treatment, contributing to the delay in definitive diagnosis and initiation of appropriate treatment. Thus, the AIS group with indication for surgical treatment of scoliosis (Cobb $\geq 45^\circ$) were

significantly older than AIS group with Cobb $< 45^\circ$. Our group has been dedicated to the search for genetic polymorphisms, which may be associated with risk of development and progression of scoliosis, to allow the monitoring of at-risk individuals, avoiding frequent follow-up, poor health quality of life and high costs with the disease treatment [4, 5].

The LEP-LEPR signaling pathway has been attributed to the etiology of AIS [7, 10, 15]. Both leptin and its receptor levels may be modulated by the presence of polymorphisms in regulatory regions of their respective genes [10, 16]. A genome-wide association study (GWAS) identified the *LEPR* rs2767485 polymorphism associated with sOB-R levels [16]. In this sense, our findings retake the discussion initiated by Liu et al., 2015, who observed the same association between the *LEPR* rs2767485 polymorphism and AIS susceptibility, since *T* allele showed a risk of AIS occurrence (~ 1.5 -fold). As observed in the Chinese Han population [12], here, no AIS case had the *LEPR* rs2767485 *CC* genotype; and *TC* or *TT* genotypes and *T* allele were associated with risk (~ 2 -fold) of AIS prevalence in Brazilian population. To our knowledge, no other study has evaluated the influence of the *LEPR* rs2767485 polymorphism on the susceptibility of AIS.

The Brazilian population was formed by extensive admixture from different ancestral roots, and therefore, extrapolating data from other ethnic groups is not appropriate [17]. In the current study, the frequency distribution of the *LEPR* rs2767485 in the control group was in agreement with another study involving Brazilians subjects without scoliosis [18]. Furthermore, the absence of the *LEPR* rs2767485 *CC* genotype in the AIS group must have contributed to the lack of HWE only in this group, which supported the relevant and older finding on the significantly increased sOB-R level in AIS patients compared to normal healthy girls [8].

Table 3 Analysis of association of the *LEP* rs2167270 and *LEPR* rs2767485 polymorphisms with adolescent idiopathic scoliosis susceptibility and according to Cobb angle

Polymorphisms	Controls (<i>n</i> = 240) <i>n</i> (%)	Scoliosis cases (<i>n</i> = 189) <i>P</i> value ^a	OR ^b (95% CI)	Cobb < 45° (<i>n</i> = 78)	OR ^c (95% CI)	Cobb ≥ 45° (<i>n</i> = 111)	OR ^d (95% CI)
<i>LEP</i> rs2167270							
<i>GG</i>	101 (42.1)	76 (40.2)	0.73	32 (41.0)	1 ^e	44 (39.6)	1 ^e
<i>GA</i>	107 (44.6)	91 (48.1)		35 (44.9)	1.13 (0.75–1.70)	56 (50.5)	1.20 (0.74–1.94)
<i>AA</i>	32 (13.3)	22 (11.7)		11 (14.1)	0.91 (0.49–1.70)	11 (9.9)	0.79 (0.37–1.71)
<i>GG</i>	101 (42.1)	76 (40.2)		32 (41.0)	1 ^e	44 (39.6)	1 ^e
<i>GA+AA</i>	139 (57.9)	113 (59.8)	0.70	46 (59.0)	1.08 (0.73–1.59)	67 (60.4)	1.11 (0.70–1.75)
<i>G</i>	309 (64.4)	243 (64.3)		99 (63.5)	1 ^e	144 (64.9)	1 ^e
<i>A</i>	171 (35.6)	135 (35.7)	0.98	57 (36.5)	1.00 (0.76–1.33)	78 (35.1)	0.98 (0.70–1.36)
<i>LEPR</i> rs2767485							
<i>CC</i>	15 (6.2)	0 (0.0)	0.001	0 (0.0)	1 ^e	0 (0.0)	1 ^e
<i>TC</i>	92 (38.3)	69 (36.5)		21 (26.9)	1.75 (1.53–2.00)	48 (43.2)	1.52 (1.35–1.71)
<i>TT</i>	133 (55.5)	120 (63.5)		57 (73.1)	1.90 (1.69–2.14)	63 (56.8)	1.47 (1.34–1.62)
<i>CC</i>	15 (6.2)	0 (0.0)	0.002	0 (0.0)	1 ^e	0 (0.0)	1 ^e
<i>TC+TT</i>	225 (93.8)	189 (100)		78 (100)	1.84 (1.69–2.01)	111 (100)	1.49 (1.39–1.61)
<i>C</i>	122 (25.4)	69 (18.3)	0.01	21 (13.5)	1 ^e	48 (21.6)	1 ^e
<i>T</i>	358 (74.6)	309 (81.7)		135 (86.5)	1.53 (1.09–2.13)	174 (78.4)	1.23 (0.85–1.81)

Significant results are shown in bold

OR—odds ratio, CI—confidence interval, (–) it was not possible to determine the value of OR and 95% CI

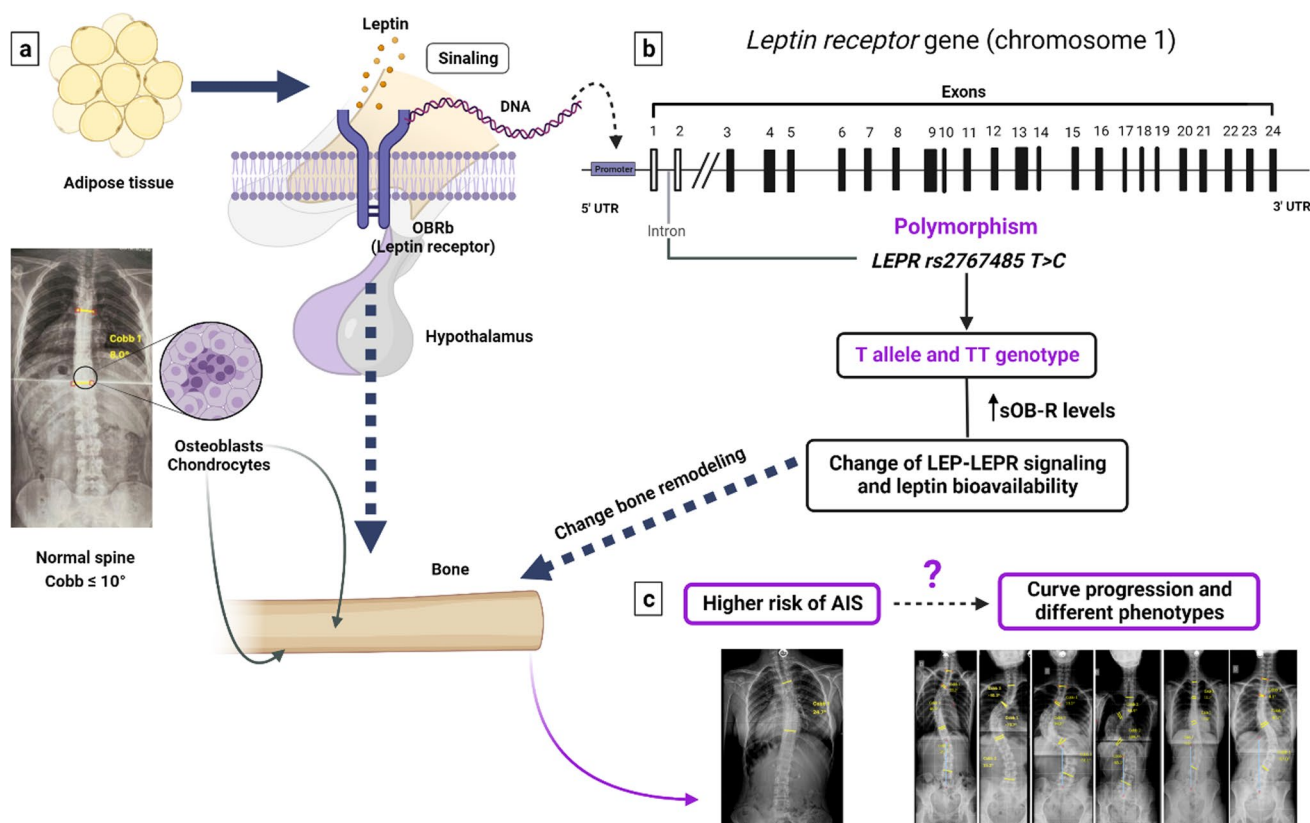
^aPearson's Chi-square test (χ^2) or Fisher's exact test, when necessary^bOdds ratio to Controls *versus* Scoliosis cases^cOdds ratio to Controls *versus* Cobb angle below 45°^dOdds ratio to Controls *versus* Cobb angle above or equal 45°^eReference group

Table 4 Association analysis of the *LEP* rs2167270 and *LEPR* rs2767485 polymorphisms and the anthropometric categories in adolescent girls with idiopathic scoliosis

Polymorphisms	Anthropometric categories		P value ^c	OR (95% CI)
	≥ 25 kg/m ^{2a} (n = 41)	≤ 24.9 kg/m ^{2b} (n = 148)		
<i>LEP</i> rs2167270	n (%)			
GG	23 (56.1)	53 (35.8)	0.02	1 ^d
GA + AA	18 (43.9)	95 (64.2)		2.29 (1.13–4.62)
G	59 (72.0)	184 (62.2)	0.10	1 ^d
A	23 (28.0)	112 (37.8)		1.56 (0.91–2.67)
<i>LEPR</i> rs2767485				
CC	0 (0.0)	0 (0.0)	–	1 ^d
TC + TT	41 (100)	148 (100)		–
T	20 (24.4)	49 (16.6)	0.10	1 ^d
C	62 (75.6)	247 (83.4)		1.63 (0.90–2.93)

Significant results are shown in bold

OR—odds ratio, CI—confidence interval

^aPatients with overweight (25–29.9 kg/m²) and obesity and morbid obesity (≥ 30 kg/m²)^bPatients with low weight (≤ 18.5 kg/m²) and normal weight (18.6–24.9 kg/m²)^cPearson's Chi-square test (χ^2) or Fisher's exact test, when necessary^dReference group, (–) it was not possible to evaluate the OR due to not having found the CC genotype of the *LEPR* rs2767485 polymorphisms in the cases group**Fig. 4** Mechanistic model to explain the relationship of LEP-LEPR signaling (a), in which the *LEPR* rs2767485 polymorphism changes bone remodeling (b), contributing to the scoliosis occurrence (c)

On the other hand, there was no association between *LEP* rs2167270 and AIS susceptibility in Brazilian population. However, an increased risk of a lower BMI in the presence of this SNP was observed among girls with AIS. The *LEP* *G*>*A* polymorphism is within the regulatory region and, therefore, can alter the levels of the LEP protein [10]. To our knowledge, this is the first study to evaluate this polymorphism with the occurrence of AIS. Liang et al., 2012 selected six tag SNPs of the leptin gene and found no significant association with susceptibility or curve severity in AIS. However, the authors observed a low serum leptin in those patients, suggesting that this event is possibly secondary, and it may be related to the low capacity of adipogenesis in AIS [10].

The exact relationship between AIS etiology, leptin levels and genetic factors remains an area of substantial controversy and our findings will likely shed light on these complex processes. Based on the risk effect of the *LEPR* rs2767485 polymorphism with the genetic susceptibility of AIS [12], we proposed a mechanism of this polymorphism on the LEP-LEPR signaling pathway with the AIS development. Leptin receptors are widely expressed in the hypothalamus and, besides the direct anabolic effect that leptin has on osteoblasts and chondrocytes, it also acts indirectly through binding to LEPR in the hypothalamus, modulating bone formation (Fig. 4a). The *LEPR* rs2767485 *T* or *TT* have already been associated with higher levels of sOB-R [16] (Fig. 4b). Thus, the *LEPR* rs2767485 polymorphism may alter the LEP-LEPR signaling pathway, inducing abnormal leptin bioavailability and, therefore, changing bone remodeling and contributing to the risk of AIS development (Fig. 4c).

In addition to the genetic factors, some known parameters have already been related to scoliosis curve progression (Fig. 4c), such as: younger age (< 12 years), premenarcheal status, high peak velocity, Tanner and Risser stage, status of triradiate cartilage, main curve Cobb angle at diagnosis and localization of the main curve [19]. Here, the *LEPR* rs2767485 polymorphism was associated with risk of AIS, either in cases with no indication for surgical treatment and in the severe cases group of the disease (Cobb $\geq 45^\circ$). Recently, our group also showed the association of polymorphisms in the *FBN1* and *PAX-1* genes with AIS susceptibility in the Brazilian population. However, the *FBN1* rs12916536 polymorphism was associated only with AIS susceptibility and not with disease severity [4]. In contrast, the *PAX-1* rs6137473 polymorphism was associated with the lumbar modifier (B and C) in 59 cases of Lenke type I and II, with surgical indication of scoliosis correction [5].

A few limitations of the current study must be mentioned. First, the small number in each sub-groups of disease severity. Second, the leptin levels and sOB-R expression, besides of their levels corresponding to different SNPs genotypes could not be directly identified. Third, the information about

patients amenable for brace treatment, the nutritional status and BMI information should have been collected throughout the medical follow-up. However, our results are in agreement with a recent study that observed significant lower BMI in patients with curves exceeding 45° compared with Cobb under 45° [20]. Thus, a longitudinal study is necessary to investigate the LEP and LEPR expression in different SNP genotypes and to account other non-modifiable factors for developing AIS, such as polymorphisms in strong linkage disequilibrium with *LEPR* rs2767485, which have also been associated with changes in receptor levels [16].

Our study has also distinct strengths: it is the first report of the distribution of two polymorphisms involved in LEP-LEPR signaling pathway in an admixed population, bringing together two precursor theories, which play pivotal roles in the etiology of AIS [4, 7, 10, 19, 20]. Second, we validated the same association observed in Han Chinese AIS individuals. Third, all participants were evaluated by experienced spine surgeons, confirming the diagnosis according to the severity of the disease and excluding spine deformities in the control group. Finally, the current study showed the real-life of diagnosing and treating AIS in a public hospital from a developing country. As it is an idiopathic and multifactorial disease, combining research and medical care in the identification of genetic biomarkers and in the design of appropriate clinical studies, makes possible to provide additional subsidies for treatment planning, in order to identify individuals at risk of development and progression of the disease.

Conclusion

In summary, the *LEPR* rs2767485 *T* allele, *TC* and *TT* genotypes play a risk non-modifiable factor for disease development, and *LEP* rs2167270 *GA* and *AA* genotypes were associated with low BMI in AIS girls, which represents an advance in understanding the etiology of this disease.

Authors' contributions AEPAJ, HLAD and JAP participated in conception and design of study. AEPAJ, GBLA, LAMM, RHT and JAP collated the data and developed the database. JVC, GRS and JAP performed the experiments and statistical analysis. AEPAJ, JVC and JAP carried out the analysis and interpretation of the data and wrote the manuscript. JAMG and HLAD participated in the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Funding This work was supported by the Brazilian agency Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro—FAPERJ, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—CAPES and Conselho Nacional de Desenvolvimento Científico e Tecnológico—CNPq. Funding body contributed to acquisition of research inputs.

Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval and consent to participate This study was approved by the Human Research Ethics Committee of the Instituto Nacional de Traumatologia e Ortopedia, Rio de Janeiro, Brazil (protocol number 73527617.4.0000.5273). All participating provided written informed consent. The study was conducted in accordance with the Helsinki Declaration.

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