# Relationship of short tandem repeats flanking leptin-melanocortin pathway genes with anthropometric profile and leptinemia in Brazilian individuals

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# Relationship of short tandem repeats flanking leptin-melanocortin pathway genes with anthropometric profile and leptinemia in Brazilian individuals

*Relação de* short tandem repeats *(STR) em genes envolvidos na via da leptina-melanocortina com o perfil antropométrico e a leptinemia em brasileiros*

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## ABSTRACT

**Objective:** To investigate the relationship of short tandem repeats (STR) near genes involved in the leptin-melanocortin pathway with body mass index (BMI) and leptinemia. **Subjects and methods:** Anthropometric variables and leptinemia were measured in 100 obese and 110 non-obese individuals. D1S200, D2S1788, DS11912, and D18S858 loci were analyzed by PCR and high-resolution electrophoresis. **Results:** Overall STR allele frequencies were similar between the obese and non-obese group ($p > 0.05$). Individual alleles D1S200 (17), D11S912 (43), D18S858 (11/12) were associated with obesity ($p < 0.05$). Individuals carrying these alleles showed higher BMI than non-carriers ($p < 0.05$). Moreover, a relationship between D18S858 11/12 alleles and increased waist circumference was found ($p = 0.040$). On the other hand, leptinemia was not influenced by the studied STRs ($p > 0.05$). **Conclusions:** D1S200, D11S912, and D18S858 loci are associated with increased BMI and risk for obesity in this sample. Arq Bras Endocrinol Metab. 2012;56(1):47-53

**Keywords**
STR; obesity; body mass index; letpin

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## RESUMO

**Objetivo:** Investigar a relação de *short tandem repeats* (STR) em genes envolvidos na via da leptina-melanocortina com índice de massa corporal (IMC) e leptinemia. **Sujeitos e métodos:** Variáveis antropométricas e leptinemia foram medidas em 100 indivíduos obesos e 110 não obesos. Os loci D1S200, D2S1788, DS11912 e D18S858 foram analisados por PCR e eletroforese de alta resolução. **Resultados:** As frequências globais dos alelos da STR foram similares entre os grupos obeso e não obeso ($p > 0,05$). Alelos individuais de D1S200 (17), D11S912 (43), D18S858 (11/12) foram associados com obesidade ($p < 0,05$). Indivíduos portadores desses alelos apresentaram valores de IMC maiores que os dos não portadores ($p < 0,05$). Além disso, a presença dos alelos D18S858 11/12 foi relacionada com circunferência abdominal elevada ($p = 0,040$). Por outro lado, a leptinemia não foi influenciada pelos STRs estudados ($p > 0,05$). **Conclusões:** Os loci D1S200, D11S912 e D18S858 são associados com IMC aumentado e risco de obesidade nesta amostra populacional. Arq Bras Endocrinol Metab. 2012;56(1):47-53

**Descritores**
STR; obesidade; índice de massa corporal; leptina

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## INTRODUCTION

Obesity is a common disease worldwide that is caused by interactions of genetic, environmental and behavioral factors resulting in excessive body fat accumulation (1). Gene-candidate and genome-scanning approaches have indicated numerous single nucleotide polymorphisms (SNPs) potentially linked with common forms of obesity.

Common SNPs located within or near genes encoding proteins involved in energy homeostasis, such as leptin (LEP), leptin receptor (LEPR), proopiomelanocortin (POMC), melanocortin 4 receptor (MC4R) and others, have been implicated in increased adiposity and susceptibility to obesity (2-4). More recently, SNPs in the fat mass and obesity-associated (FTO) gene have been shown to be risk factors for common obesity (5). These SNPs and other loci have modest effects on the susceptibility to common forms of obesity, but because of the high frequency, they may largely contribute to obesity in the general population (6,7).

Other forms of polymorphisms are short tandem repeats (STR), repeating sequences of 2-6 DNA base pairs, which constitute 3% of the human genome. STRs have multi-allelic nature and have been used in population genetic, forensic, and association studies. STRs located near the leptin-melaconortin pathway genes have been also found to be linked with obesity. We and other investigators have reported that a highly variable tetranucleotide repeat located at the 3'-flanking region of the *LEP* (3'HVR) is associated with obesity-related traits and leptinemia (8-11).

*LEPR* is located near the STR marker D1S200, which has been associated with increased body mass index (BMI) and fat mass (12). POMC, a pro-hormone regulated by leptin, is flanked by STR markers, including D21788, that were shown to be linked with leptinemia (13,14). MC4R is also involved in the modulation of energy intake and expenditure. D18S858 is a STR marker on the 14 cM chromosomal region flanking *MC4R,* which has been reported to be linked with obesity (15).

Uncoupling proteins (UCPs) are mitochondrial transporters that mediate thermogenesis and energy homeostasis. Polymorphisms in the *UCP2/UCP3* cluster have been considered candidate markers for fat metabolism, obesity, and diabetes in humans (16). D11S912 and other STR markers flanking *UCP2* and *UCP3* showed some evidence of linkage with obesity and BMI (15,17).

We have investigated the relationship of D1S200, D21788, D11S912, and D18S858 STRs with obesity-related traits and leptinemia in a sample of the Brazilian population.

## SUBJECTS AND METHODS

### Study population

Obese (n = 100) and non-obese (110) individuals randomly selected at the Instituto Dante Pazzanese de Cardiologia (IDPC) during cardiologic evaluation. Individuals were considered obese when BMI was higher than 30 kg/m$^2$ (18). Individuals of African or Asian ancestry (self-reported), as well as with thyroid, liver or kidney diseases, and pregnant women were not included in this sample. This study was approved by the Ethics Committees of IDPC and the Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, Brazil.

Information on age, hypertension, hyperglycemia, coronary artery disease (CAD) investigated by coronary angiography, smoking and sedentary lifestyle were recorded, and data were described elsewhere (19). Measurements of BMI, waist circumference (WC), waist-to-hip ratio (WHR) were taken. Plasma leptin was determined by an ELISA method (Alexis Biochemical/ Vendor BioAgency, Sao Paulo, Brazil).

### STR genotyping

Genomic DNA was extracted from 1 mL EDTA-anticoagulated whole blood by a salting-out method (20). The alleles of D1S200 $(CA)_n$, D2S1788 $(GATA)_n$, D11S912 $(CA)_n$, D18S858 $(ATA)_n$ STR were detected by polymerase chain reaction (PCR) and fragment analysis.

Genomic DNA (30 ng) was amplified in 50 µL tubes containing 200 nmol/L primers (Cy5-labelled, Syntegen, LLC, Houston, TX, USA; 56FAM-labelled, Integrated DNA Technologies, Inc, Coralville, IA, USA), 200 µmol/L dNTPs (Amersham Bioscience, USA), 1 U DNA polymerase (Biotools, Madrid, Spain). PCR assays were carried out in a PTC-200™ Thermal Cycler (M&J Research, Inc., Watertown, USA). Sequences of primers and PCR conditions are shown in table 1.

PCR products corresponding to the D1S200, D2S1788, and D11S912 alleles were analyzed by high resolution electrophoresis using an ALF express

**Table 1.** STR-related genes, chromosome location, and PCR conditions

| STR | Related genes | Locus* | Location** | PCR primers | Cycles/Annealing temperature |
|---|---|---|---|---|---|
| D1S200 | *LEPR* | Z16550 | UniSTS:56325 | (Cy5) 5'-gtactgtaacttgggtaactgaac-3' | 30/55°C |
| $(CA)_n$ | | | Chr1 c.77.73cM | 5'-tggcagacctgaacatcata-3' | |
| D2S1788 | *POMC* | G08189 | UniSTS:6210 | (Cy5) 5'-aatggatggacaaatgga tg-3' | 28/55°C |
| $(GATA)_n$ | | | Chr2 55.51cM | 5'-ccctccataattagatgagcc-3' | |
| D11S912 | *UCP2/UCP3* | Z16703 | Uni/sts:72663 | (Cy5) 5'-tcgtgagaatactgctttgg-3' | 30/56°C |
| $(CA)_n$ | | | Chr11 137.93cM | 5'-ttttgtctagccatgattgc-3' | |
| D18S858 | *MC4R* | G07975 | UniSTS:14041 | (Fam) 5'-agctggagagggatagcatt-3' | 28/55°C |
| $(ATA)_n$ | | | Chr18 80.41cM | 5'-tgcattgcatgaaagtagga-3' | |

n: number of repeat units; PCR: polymerase chain reaction; STR: short tandem repeats.
* GeneBank accession number; ** http://www.ncbi.nlm.nih.gov/unists.

sequencer (Amersham Biosciences, Uppsala, Sueden). D18S858-derived amplicons were detected by capillary electrophoresis using a MegaBACE 1000 sequencer (Amersham Biosciences, Uppsala, Sueden). Labeled DNA size markers were used to identify the STR alleles (Table 1). Two heterozygous DNA samples of each STR were used as allelic controls in each run. Fragment analysis readings were recorded by two independent investigators, and 30% of the DNA samples were randomly selected to be reanalyzed as controls for PCR and fragment analysis procedures.

### Statistical analysis

Statistical analysis was performed using the Sigma Stat software v. 3.5 (SPSS Inc., Chicago, USA). Relative frequencies of STR loci alleles were compared between the obese and non-obese groups by Kolmogorov-Smirnov test. Categorical variables were compared by the chi-square test or Fisher's Exact test. Continuous variables are presented as means ± SD and compared by *t*-test, and those without normal distribution (BMI and leptin) were transformed in log values. The level of significance was $p < 0.05$.

## RESULTS

Anthropometric and letpin data on the studied groups are shown in table 2. BMI, WC, and WHR mean values were significantly higher in obese than in non-obese individuals ($p < 0.001$), confirming that the selection of the subjects was adequate. Plasma leptin was also three times higher in the obese than in the non-obese group ($p < 0.05$), with a positive correlation with BMI values ($p < 0.05$; data not shown).

**Table 2.** Anthropometric data and leptin values in the obese and non-obese groups

| | Non-obese (110) | Obese (100) | p-value |
|---|---|---|---|
| Age, years | 45 ± 15 | 52 ± 13 | < 0.001 |
| Gender, women | 59% | 41% | 0.378 |
| Body mass index, kg/m²* | 24.2 ± 3.1 | 35.6 ± 4.7 | < 0.001 |
| Waist circumference, cm | 87.3 ± 10.8 | 109.6 ± 11.4 | < 0.001 |
| Waist-hip ratio | 0.87 ± 0.07 | 0.92 ± 0.06 | < 0.001 |
| Leptin, ng/mL* | 12.0 ± 12.0 | 35.1 ± 21.3 | < 0.001 |

Number of individuals is shown in parenthesis. Gender frequency was compared by chi-square test. Continuous variables are presented as mean ± SD and compared by *t-test*. * Values were log transformed.

The alleles of D1S200, D2S1788, D11S912, and D18S858 loci found in this sample population are shown in figure 1. Global frequencies of these alleles were similar between obese and non-obese individuals, when analyzed by Kolmogorov-Smirnov test ($p > 0.05$).

Analysis of the frequency of individual alleles showed that D1S200 17 allele, D11S912 43 allele, and D18S858 11 and 12 alleles were more frequent in the obese than in the non-obese group ($p < 0.05$). On the other hand, D2S1788 alleles had similar frequencies between these groups ($p > 0.05$). As shown in table 3, individuals carrying D1S200 17 allele, D11S912 43 allele, and D18S858 11 and 12 alleles had higher risk for obesity than non-carriers.

Individuals carrying D1S200 17 allele had higher BMI, WC, and WHR values than non-carriers ($p < 0.05$; Table 4). D18S858 11/12 allele was also associated with higher WC values ($p = 0.040$). Leptin levels were not influenced by 17, 43 or 11/12 alleles ($p > 0.05$).

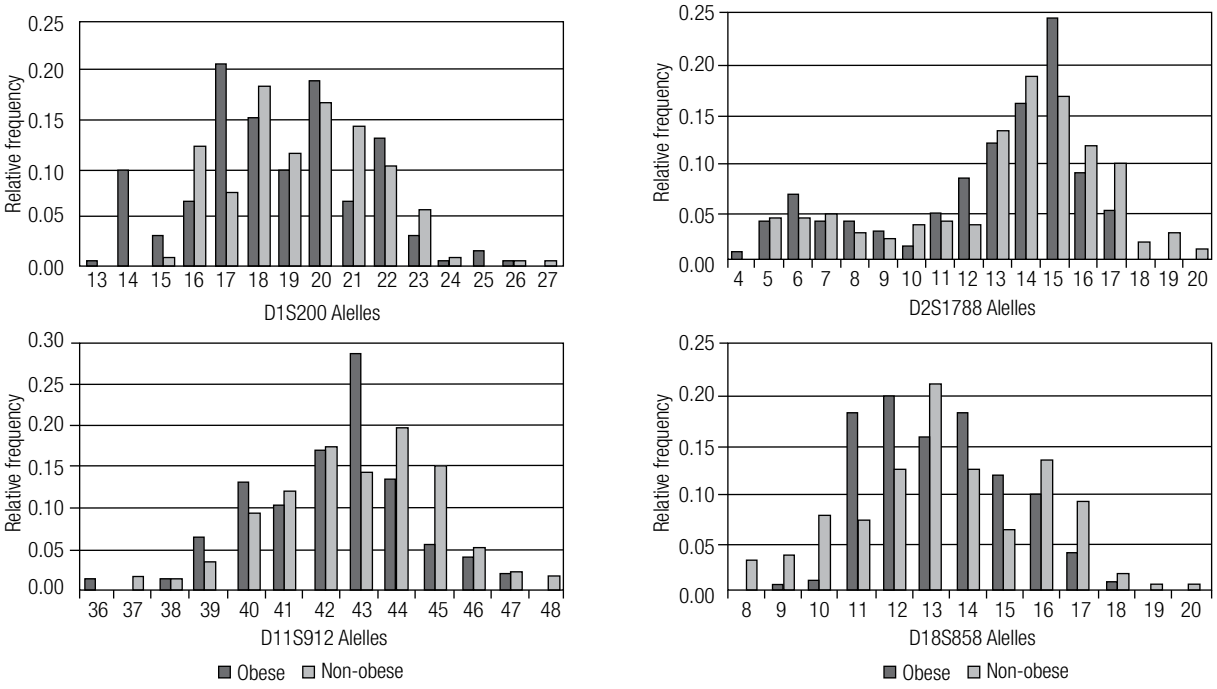


**Figure 1.** Allele frequencies of D1S200, D2S1788, D11S912, and D18S858 loci in obese and non-obese individuals. Data compared by Kolmogorov-Smirnov test ($p > 0.05$).

**Table 3.** Relationship between STR loci and obesity

| Variables | Categories | Odds Ratio | 95% CI | p-value |
|---|---|---|---|---|
| D1S200 | 17 allele | 3.288 | 1.780 – 6.074 | < 0.001 |
| | Others | 1.000 | – | – |
| D2S1788 | 15 allele | 1.659 | 1.025 – 2.683 | 0.051 |
| | Others | 1.000 | – | – |
| D11S912 | 43 allele | 2.430 | 1.491 – 3.960 | < 0.001 |
| | Others | 1.000 | – | – |
| D18S858 | 11 allele | 3.230 | 1.685 – 6.190 | < 0.001 |
| | 12 allele | 2.040 | 1.181 – 3.530 | 0.014 |
| | Others | 1.000 | – | – |

STR: short tandem repeats.

**Table 4.** Relationship between STR D1S200, D11S912, and D18S858 alleles and obesity-related variables in the overall sample

| Variables | D1S200 | | p-value | D11S912 | | p-value | D18S858 | | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | 17 allele (42) | Others (168) | | 43 allele (64) | Others (146) | | 11/12 allele (90) | Others (120) | |
| BMI, kg/m²* | 32.5 ± 5.9 | 29.3 ± 7.3 | 0.009 | 31.2 ± 6.9 | 28.9 ± 6.9 | 0.031 | 31.4 ± 6.7 | 28.4 ± 6.8 | 0.002 |
| WC, cm | 104 ± 15 | 96 ± 16 | 0.004 | 101 ± 17 | 97 ± 15 | 0.064 | 100 ± 15 | 96 ± 16 | 0.040 |
| WHR | 0.92 ± 0.07 | 0.89 ± 0.07 | 0.004 | 0.90 ± 0.07 | 0.89 ± 0.07 | 0.144 | 0.90 ± 0.06 | 0.89 ± 0.07 | 0.775 |
| Leptin, ng/mL* | 26.6 ± 22.2 | 23.9 ± 20.8 | 0.586 | 24.6 ± 20.8 | 22.2 ± 20.5 | 0.451 | 22.6 ± 21.0 | 22.5 ± 20.3 | 0.899 |

Number of individuals is shown in parenthesis. Variables are presented as mean ± SD and compared by *t*-test. * Values were transformed in log. BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; STR: short tandem repeats.

## DISCUSSION

In this study, the overall allele frequencies of D1S200, D2S1788, D11S912, and D18S858 loci in obese individuals did not differ from non-obese subjects. Interestingly, the analysis of individual alleles evidenced a relationship with obesity.

D1S200 17 allele was shown to be related with susceptibility to obesity. It was also associated with obesity-related phenotype, such as increased BMI, waist circumference, and waist-hip ratio. This result is in accordance with a previous study that demonstrated a linkage between the near-*LEPR* D1S200 marker and increased BMI (12).

Other microsatellite markers flanking *LEPR* by approximately 9 and 3 cM, such asD1S3728 and D1S1665, were suggested to contribute to plasma leptin concentrations, adiposity and body weight in individuals with dislipidemia (21). Two STRs located at introns 3 $(CA)_n$ and16 $(CTTT)_n$ of *LEPR* were shown to be related, respectively, to BMI and fat free mass in the Quebec Family Study (22). A 3' UTR *indel* polymorphism in *LEPR* was also associated with increased body weight in patients enrolled in the Finish Diabetes Prevention Study (23). The results from our and other studies suggest that microsatellite markers near-*LEPR* influence adiposity, waist circumference, and BMI.

D18S858 11/12 allele was associated with increased BMI and waist circumference in this sample. Accordingly, a linkage between *MC4R*- near D18S858 STR and obesity was previously reported (15). This locus was also found to be related with systolic blood pressure (24) and cancer (25), which were shown to be risk factors for obesity (1). A recent genome-wide association study (GWAS) has identified 14 known obesity susceptibility variants, and 18 new loci that were associated with BMI (26). Some loci at *MC4R*, *POMC,* and others, map near key hypothalamic regulators of energy balance. In a recent review on GWAS, it was shown that common variants near *MC4R* are associated with fat mass, BMI, and risk of obesity (27).

We also found a relationship between the 43 allele of D11S912STR and increased BMI. This result is in agreement with that of the genome-wide linkage scan study on the Framingham Heart Study families (28). Other studies have suggested that loci flanking *UCP2* and *UCP3* genes are unlikely to have a substantial effect on the expression of obesity-related phenotypes in Caucasian and Mexican American populations (29,30). A recent study in Finnish diabetic patients reported an association of variants within *UCP2-UCP3* cluster, abdominal obesity and serum lipid levels, suggesting a contribution of these loci to metabolic alterations observed in obese and diabetic patients (31).

D2S1788 STR located ~15 cM from *POMC* has been associated with BMI in the Framingham Heart Study families, and with plasma leptin levels in African-Americans and Hispanic sample populations (28,32,33). A trend towards linkage between microsatellite markers around *POMC* and variations of leptin concentrations was reported in Caucasian families (34). Conversely, a relationship between D2S1788 locus and obesity or leptinemia was not found in this study. It is plausible to consider that this genomic marker has a minor influence on adiposity, but more investigations should be conducted with larger samples of our population to confirm this hypothesis.

Results from candidate gene and genome-wide association studies have shown that 40%-70% of variation in obesity-related phenotypes is attributable to underlying genetic variation (35). This study confirms the results from previous candidate loci approaches in other sample populations, suggesting that hypervariable regions, such as STRs, may influence the variability of body weight. STRs are genomic elements with high variability, which are produced by two possible mechanisms: recombination and strand-slippage replication. STRs often occur within coding and regulatory regions of eukaryotic genes. It has been proposed that STRs have important roles in the regulation of gene expression and mRNA metabolic process, and other regulatory and biological functions at molecular level (36). However, the effects of STRs on expression of obesity-related genes remain to be investigated. It is noteworthy that association studies are affected by small size and heterogeneity of the sample population (6), which represents an important limitation on our study.

The lack of relationship between microsatellite markers and leptin plasma levels may be influenced by sample characteristics such as age, gender, sample size, ethnicity, and environmental factors. Therefore, their influence on leptinemia needs further studies to be confirmed in our population.

In conclusion, STR D1S200, D11S912, and D18S858 alleles are suggested to be linked to obesity-

related traits, but they did not influence leptin levels in this sample population.

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