Seven Novel Deleterious LEPR Mutations Found in Early-Onset Obesity: a ΔExon6–8 Shared by Subjects From Reunion Island, France, Suggests a Founder Effect

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Context: Infrequent mutations have been reported in the leptin receptor (LEPR) gene in humans with morbid obesity and endocrine disorders. However LEPR mutations are rarely examined in large populations from different ethnicities in a given country.

Objective: We estimated the prevalence of LEPR mutations in French patients with severe obesity and evaluated mutated patients’ phenotype.

Design and Patients: We sequenced the LEPR gene in 535 morbidly obese French participants. We conducted clinical investigations to determine whether individuals with a novel shared mutation display particular characteristics relative to obesity history, body composition, hormonal functions, and the outcome of bariatric surgery.

Results: We identified 12 patients with a novel LEPR mutation (p.C604G, p.L786P, p.H800_N831del, p.Y422H, p.T711NfsX18, p.535–1G/H9004A, p.P166CfsX7). Six unrelated subjects were carriers of the p.P166CfsX7 mutation leading to deletion overlapping exons 6 to 8. All subjects originated from Reunion Island (France). Their clinical features (severe early-onset obesity, food impulsivity, and hypogonadotropic hypogonadism) did not differ from other new LEPR mutation carriers. Results concerning weight loss surgery were inconsistent in homozygous LEPR mutation carriers. Heterozygous LEPR mutation carriers exhibited variable severity of obesity and no endocrine abnormality.

Conclusion: Among seven newly discovered LEPR mutations in this French obese population, we identified a LEPR frameshift mutation shared by six subjects from Reunion Island. This observation suggests a founder effect in this Indian Ocean island with high prevalence of obesity and supports a recommendation for systematic screening for this mutation in morbidly obese subjects in this population. (J Clin Endocrinol Metab 100: E757–E766, 2015)

The genetic screening to identify causal mutations in obesity (1) appeared particularly successful in extreme obesities with the discovery of monogenic forms resulting from homozygous mutations that mostly affect genes of the leptin-melanocortin pathway (2). This pathway plays a pivotal role in the hypothalamic control of food intake (3). Complete leptin or leptin receptor (LEPR) deficiency is rare, and patients with LEPR mutations are characterized by severe early-onset obesity (before the age of 3 y) with hyperphagia and hypogonadotropic hypogonadism (4–11). Today, the phenotype of patients with heterozygous LEPR mutation in regard to body composition and endocrine anomalies still needs to be investigated (9, 11).

Whereas leptin-deficient patients can be treated by hormone replacement (12), medical treatment of LEPR deficiency is challenging. Drugs that could safely bypass normal leptin delivery systems are not available for humans (13), and outcomes after bariatric surgery in the first two reported patients showed limited and variable responses (14).

Few studies have investigated the prevalence of LEPR mutations occurring generally in subject groups with high levels of consanguinity. Prevalence was estimated to be 1.5%–2% among patients with obesity (15, 16). The high prevalence of obesity in Reunion Island justifies systematic screening for this mutation.
3% in 300 severely obese British subjects that included 90 probands from consanguineous families (9) and in a highly selected population of Pakistani children with severe obesity (11). The prevalence of LEPR mutations in patients with morbid obesity from other countries is not known. We addressed this question by systematically searching for LEPR mutations in 535 severely obese French patients, not parentally related. We discovered seven novel deleterious LEPR mutations, including one large deletion shared by six unrelated patients, all originating from Reunion Island (Indian Ocean, France). We subsequently examined clinical history and phenotypes in comparison to other mutation carriers.

Subjects and Methods

Study population

The study was conducted in 535 unrelated obese French subjects (children and adults) who were prospectively screened from 2007 for LEPR mutations because of severe obesity. The baseline characteristics of this population are described in Supplemental Table 1. For children, severe obesity was defined as an SD score for body mass index (BMI) of more than 3 SD values above the mean age and sex-specific BMI values in children in France (15). For adults, the criterion for inclusion was BMI of at least 35 kg/m². Informed consent was obtained for all subjects. Mutations in known obesity genes were ruled out using direct sequencing (LEP [leptin], PCSK1 [proprotein convertase subtilisin/kexin type 1], POMC [pro-opiomelanocortin], MC4R [melanocortin 4 receptor]). Four subjects were heterozygous for a MC4R frameshift mutation. In the case of LEPR mutations, the subject’s relatives were invited to participate in the study. The study protocol was approved by the Local Ethics Committee (Comités Consultatifs de Protection des Personnes dans la Recherche Biomédicale, Hôtel-Dieu, Paris).

Phenotypic characterization

We examined patients harboring mutations for a series of clinical phenotypes using anthropometric measurements (weight, height, BMI) and body composition. During patient medical interviews, the physician recorded the ancestry of the patient and parents. We obtained weight history from the childhood health records when available. A pediatrician determined pubertal stage from secondary sexual characteristics. A registered dietician conducted a structured interview examining quantitative and qualitative food intake and eating behavior in each proband individually. We estimated body composition (percentage of fat and lean mass) by whole-body fan-beam dual-energy x-ray absorptiometry scanning (Hologic Discovery W, software version 12.6.2; Hologic Inc) as previously described (16). The percentage of body fat mass was calculated as the ratio of total body fat mass over total body mass. Basal resting metabolic rate was obtained using indirect calorimetry, after a 12-hour overnight fast, by an open-circuit ventilated-hood system (Deltatrac II MMB 200, Datex Instrumentarium Corp). We calculated basal metabolic rate by the equation supplied by the manufacturer and the predicted basal metabolic rate using the Harris and Benedict (HB) equation.

Blood samples were collected in the morning after an overnight fast. Plasma lipid levels were measured by standardized enzymatic assays (Roche Diagnostics for total cholesterol, ThermoElectron for triglycerides). High-density lipoprotein-cholesterol levels were determined by a direct method (ThermoElectron). We calculated plasma low-density lipoprotein-cholesterol using the Friedewald formula. Plasma leptin concentrations were measured by RIA (Linco Research, Inc). With the aim of determining whether plasma leptin concentrations were correlated with fat mass, we calculated the following ratio: leptin concentration (ng/mL)/fat mass (kg). A score around 1 indicated that plasma leptin concentrations were in correlation with fat mass. Plasma glucose and insulin concentrations were measured using the glucose oxidase method and a commercial immunoradiometric assay kit (Bi-INSULINE IRMA; CisBio International), respectively. The insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) index [glucose (mmol/L) × insulin (mU/L)/22.5]. In morbidly obese subjects, the mean value of HOMA-IR was 2 (17). We also defined insulin resistance as a value of the HOMA-IR > 2.

Direct nucleotide sequencing of the LEPR gene

We sequenced the LEPR gene as described in Ref. 14. We examined the in silico prediction of the deleterious effect of mutation with the Alamut Mutation Interpretation Software (Interactive Biosoftware), the PolyPhen (http://genetics.bwh.harvard.edu/pph2/), the Sift (http://sift.jcvi.org/), and the Mutation Taster (http://doro.charite.de/MutationTaster/index) web sites.

Characterization of the Δexon6–8 LEPR mutation

In families carrying the Δexon6–8 LEPR mutation, direct PCR amplification of the 18 coding LEPR exons from patient genomic DNA revealed the absence or presence of each LEPR gene exon sequence in the tested DNA. We used the multiplex ligation-dependent probe amplification (MLPA) technique to confirm and/or detect large homozygous or heterozygous genomic deletions from probands and DNA samples from relatives (Supplemental Data).

DNA samples from 189 controls and families of subjects were further analyzed for the presence of this large LEPR deletion
encompassing exons 6 to 8 by a quantitative PCR (qPCR) screening assay (Supplemental Data). The 189 controls (114 women, 75 men) were from the SU.VI.MAX cohort that is composed of 12,735 men and women in the general population aged from 35 to 60 years, as previously described (18). The mean age of the controls at inclusion was 50.1 ± 6.3 years, and their mean BMI was 23.8 ± 3.4 kg/m².

**Hormonal testing**

Using standard immunoassays, we tested the hypothalamic-pituitary axis of the LEPR mutation carriers, including measurements of serum cortisol and ACTH for the adrenal axis and of serum free T₄ and TSH for the thyroid axis. Serum FSH, LH, estradiol, and testosterone according to sex were measured for the gonadotropic axis. When necessary, we search for hypogonadotropic hypogonadism by an LHRH test. IGF-1 measurement was performed for the GH axis. In the case of low serum IGF-1, we search for GH insufficiency by a GH dynamic test.

**Statistical analyses**

Clinical data were expressed as medians and [ranges] or means ± SD. Statistical analysis was performed with the Kruskall-Wallis test on JMP statistics software (SAS Institute Inc.). A P < .05 was considered as significant.

**Results**

**Seven novel LEPR gene mutations in French morbidly obese subjects**

Sequence analysis of the whole coding region of the LEPR gene revealed eight mutations (c.1871Adup, c.1810T>G, c.2357T>C, c.2491G>A, c.Δexon6–8, c.1604–1G>A, c.1264T>C, c.2131dup) in 12 unrelated subjects (2.24% of the cohort) (Supplemental Figure 1). These mutations were predicted to alter the LEPR protein sequence (p.N624KfsX21, p.C604G, p.L786P, p.H800_N831del, p.P166CfsX7, p.535–1G>A, p.Y422H, p.T711NfsX18) and were new except for p.N624KfsX21, previously found in a French patient (14). Subjects were homozygous (n = 9) or compound heterozygous (n = 3) for each mutation (Table 1). So, 1.68% of the 535 participants were homozygous carriers of a LEPR mutation, and 0.56% were compound heterozygous. According to prediction software or RT-PCR analysis (Supplemental Data), five of eight mutations led to a nonfunctional truncated protein. The three others were highly predicted to be deleterious for the receptor function (Table 1).

Parents of the probands were heterozygous for the LEPR mutation, except for the p.N624KfsX21 mutation as described (14) (Table 1, Figure 1, and Figure 2, A–C). Familial consanguinity was noted in three families.

**Identification of the same frameshift mutation in patients from Reunion Island**

Surprisingly, we observed that six unrelated subjects displayed the same large deletion overlapping exons 6, 7, and 8 (Δexon6–8) (families 5 to 10). By exploring the patient and family origin, we found that all of them originated from Reunion Island. The Δexon6–8 was predicted to lead to a frameshift in exon 9 starting at proline 165+1 and to generate a stop codon seven positions further (p.P166CfsX7). This mutation was predicted, if synthesized, to result in a truncated LEPR of 172 amino acids, lacking a large part of its extracellular domain.

**Table 1. LEPR Mutations in Subjects With Severe Obesity and in Their Relatives**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Amino Acid Changes</th>
<th>Predicted Protein</th>
<th>Family ID</th>
<th>No. of Carriers</th>
<th>Ancestry</th>
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<td><strong>Homozygous</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>c.1871A dup</td>
<td>p.N624KfsX21</td>
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<td>c.1810T&gt;G</td>
<td>p.C604G</td>
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<td>p.L786P</td>
<td>Probably damaging</td>
<td>3</td>
<td>1</td>
<td>Portuguese</td>
</tr>
<tr>
<td>c.2491G&gt;A</td>
<td>Splicing defect, p.H800_N831del</td>
<td>Probably truncated protein</td>
<td>4</td>
<td>1</td>
<td>Turkish</td>
</tr>
<tr>
<td>c.Δexon6–8</td>
<td>p.P166CfsX7</td>
<td>Truncated protein</td>
<td>5 to 9</td>
<td>5</td>
<td>French (Reunion Island)</td>
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<tr>
<td><strong>Compound heterozygous</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>c.1604–1G&gt;A and</td>
<td>p.535–1G&gt;A (probably exon 12 skipping) and p.P166CfsX7</td>
<td>Probably truncated protein and truncated protein</td>
<td>10</td>
<td>1</td>
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<td>11</td>
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<tr>
<td>c.1264T&gt;C and</td>
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<td></td>
</tr>
<tr>
<td>c.2131dup</td>
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<td>2</td>
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<td>Probably damaging</td>
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<tr>
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<td>Splicing defect, p.H800_N831del</td>
<td>Probably truncated protein</td>
<td>4</td>
<td>2</td>
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<tr>
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<td>5 to 9</td>
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<td>c.2131dup</td>
<td>p.T711NfsX18</td>
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as well as transmembrane and intracellular domains. This deletion was homozygous in five of the six subjects (Table 1) and led to the absence of any PCR amplification product for exons 6, 7, and 8 (Figure 2D). All the other coding regions were amplified easily, excluding the presence of a PCR inhibitor in the DNA sample (Figure 2D, and data not shown). The sixth proband was heterozygous for this mutation and for another novel variant (c.1604–1G>A) that was predicted to alter mRNA splicing with exon 12 skipping. Parent DNA was not available, and it was therefore not possible to confirm his real compound heterozygosity.

**Genetic exploration of families from Reunion Island**

To further understand the segregation of LEPR alleles in patients from Reunion Island, the LEPR coding region was sequenced in relatives of three families who agreed to participate in the study (Figure 2, A–C). None of the relatives were homozygous carriers of the mutation. The degree of inbreeding in our six homozygous subjects originated from Reunion Island is one of six (16.7%). We examined six known polymorphisms of the LEPR gene coding region (c.326A>G, c.668A>G, c.1029T>C, c.1968G>C, c.3057G>A, and insertion in 3′ untranslated region) to define the LEPR alleles segregation. Because no homozygous deletion was observed in the relatives’ DNA samples and classic sequencing cannot reveal large heterozygous deletion, DNA samples were further analyzed by MLPA (Figure 2E) and through a dual color qPCR screening (data not shown). In family 6, the Δexon6–8 variant (in allele1) was inherited from both parents, suggesting either consanguinity or coancestry between the father and the mother because they were nonconsanguineous to their knowledge. The grandfather did not carry the mutation, indicating inheritance from the grandmother (Figure 2B). In family 9, the mother was the only other family member available and was a carrier of the deleted allele (Figure 2C).

**Clinical and biological phenotypes in homozygous carriers of LEPR mutations**

We examined clinical and biological phenotypes of the subjects homozygous for a LEPR mutation (Table 2; data available for 11 subjects) and searched for differences between patients originating or not from Reunion Island.

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**Figure 1.** Pedigrees and segregation analysis of the LEPR gene alleles in four families not originating from Reunion Island. Squares and circles indicate men and women, respectively. The proband is indicated in each family by an arrow. Open symbols represent unaffected family members, filled gray symbols indicate family members with obesity (in adults, defined as a BMI between 30 and 39 kg/m²; in children, defined as a BMI Z-score [Zs] between 2 and 3 SD), and filled black symbols indicate family members with severe obesity (in adults, defined as a BMI of 40 kg/m² or more; in children, defined as a BMI Zs of 3 SD or more). A question mark represents family members with unknown BMI. A slash indicates a family member who has died. Age, BMI, and Zs, when they are known, are indicated below the individuals’ symbols along with the genotype. M, M1, M2 denote the mutated allele and N the wild-type (normal) allele. ND indicates the members with nondetermined genotype.
Figure 2. Characterization of the Δexon6–8 LEPR mutation. A—C, Pedigrees and segregation analysis of the LEPR gene alleles in three families originating from Reunion Island. Squares and circles indicate men and women, respectively. The proband is indicated in each family by an arrow. Open symbols represent unaffected family members, filled gray symbols indicate family members with obesity (in adults, defined as a BMI between 30 and 39 kg/m²; in children, defined as a BMI Z-score [Zs] between 2 and 3 SD), and filled black symbols indicate family members with severe obesity (in adults, defined as a BMI of 40 kg/m² or more; in children, defined as a BMI Zs of 3 SD or more). A question mark represents family members with unknown BMI. A slash indicates a family member who has died. Age, BMI, and Zs, when they are known, are indicated below the individuals’ symbols along with the genotype. M denotes the mutated allele, and N the wild-type (normal) allele. ND indicates the members with nondetermined genotype. Different alleles are identified based on common polymorphisms genotyped in the coding region of the LEPR gene. D, PCR amplification product of exons 5, 6, 7, 8, of the LEPR gene, of the proband in family 6 (6-III.9), and one control. These results show the
The mean age at genetic diagnosis was 18 years 6 months [4–36 years]. All subjects with LEPR mutations had normal birth weight. Severe obesity rapidly developed within the first months of life (mean age of obesity onset, 4.1 mo [1–6 mo]) (Figure 3, A and B). There was no history of neonatal hypotonia or mental retardation. At diagnosis, mean BMI was 49.6 kg/m² [34.9–62.9], corresponding to a mean BMI Z-score at 6.6 SD [5–12.3]. The mean percentage of fat mass was in accordance with the severity of obesity (51.9% [36.3–65%]). The mean resting energy expenditure (REE) measured by indirect calorimetry was 11% lower than the HB estimation (measured REE, 2103 ± 316 vs. 2362 ± 372 kcal by HB; P = .26, nonsignificant).

All subjects had severe hyperphagia during childhood and adulthood, and food impulsivity was present in eight of 11 cases (73%) at diagnosis. Mean circulating leptin measurement (100.3 ng/mL [36.4–162.4]) was around 1.5 times higher than expected for fat mass. No elevated circulating receptor was detected for the exon6–8 subjects, suggesting that this protein is not secreted (data not shown), unlike the first published case of LEPR mutation (8).

Hypogonadotropic hypogonadism was diagnosed in six of nine subjects (67%), and GH insufficiency in four of 11 cases (36%). Thyroid and adrenal axis were normal in all subjects, except for one subject with central hypothyroidism (subject 9-II.1). Most subjects had normal glucose concentrations, except for one subject with type 2 diabetes needing oral hypoglycemic medication (subject 11-III.1). Five subjects had an insulin resistance with a HOMA-IR index of more than 2. Fasting total lipids were within the normal range in all subjects.

In the six carriers of the exon6–8, although no specific phenotype was associated, endocrine abnormalities seemed to be more severe, with GH insufficiency noted in three of five subjects (60%).

Extremely controlled, restrictive diets and physical activity programs were transiently effective and led to later weight regain in almost all homozygous LEPR-mutated patients, except for patient 5-II.1 who had been on a re-
strictive control diet for several years (Figure 3, A and B). We compared the result of bariatric surgery procedures in patient 3-IV.2 (p.L786P mutation, gastroplasty) and patient 2-II.1 (p.C604G mutation, gastric bypass) to that of a previously published patient (14) who benefited from an adjustable gastroplasty (patient 1, p.N624KfsX21 mutation). As previously described, maintained weight loss was observed after 8 years of follow-up in this patient (14). In patient 3-IV.2, gastroplasty also led to significant initial weight loss (44% of weight loss after 9 mo). On the contrary, in patient 2-II.1, gastric bypass did not induce significant weight loss long term. Her weight was 162 kg (BMI 64.1 kg/m²) at the time of surgery. She had lost 45 kg (BMI 46.3 kg/m²) 17 months later, but then she progressively started to regain weight. Five years after surgery, her weight was 151 kg (BMI 59.7 kg/m²) corresponding to moderate weight loss (7%). No patient originating from Reunion Island underwent surgery.

Clinical and biological phenotypes in heterozygous LEPR mutation carriers from Reunion Island

In all subjects, the severity of obesity (BMI Z-score at diagnosis) was significantly higher in homozygous mutation carriers when compared to heterozygous and not mutated relatives ($P = .0002$) (Supplemental Figure 2). We compared the phenotype of heterozygous mutation carriers to homozygous subjects in the large family 6 bearing the Δexon6–8 (Table 3). Most of the heterozygous subjects were less obese (mean BMI 34.5 ± 7.1 kg/m²; mean BMI Z-score +3.3 ± 1.2 SD). In addition, obesity developed later in life during adulthood (mean age of obesity onset 24.5 y). Neither food impulsivity nor endocrine abnormalities were reported.

Discussion

We identified a novel deletion (Δexon6–8 LEPR gene) in half (six of 12) of the studied French subjects with early-
onset morbid obesity carrying new LEPR mutations. These six subjects originated from Reunion Island. We did not detect this deletion in 500 severely obese patients who were not from Reunion Island and 189 controls. The discovery of a cluster of six unrelated individuals with the same phenotype and carrying the same deletion in a specific geographic area raises the question of its origin from a common ancestor and suggests a founder effect.

Founder effect is a well-known pathophysiological mechanism described in rare genetic diseases (19). It has been described in Reunion Island in other metabolic diseases, such as severe lipodystrophy (20). Reunion Island is a French administrative department located in the Indian Ocean and was unoccupied until immigrants from Europe, Africa, and Asia settled there during the 17th century. The ethnic groups in the Reunion Island also include peoples of European, African, Malagasy, Indian, and Chinese origin as well as many of mixed origin. Its inhabitants constitute a genetically isolated population favoring a founder effect, but the fraction of people of each ethnicity in the Reunion Island is not known exactly.

Because we identified six homozygous and eight heterozygous carriers of this deletion among 49 subjects originated from Reunion Island screened for LEPR mutations, we could hypothesize that the frequency of the mutated allele would be around 20.4% [10.6–30.2]. So, frequency of homozygous LEPR mutation subjects would probably be far higher than its prevalence found in other specific populations (3%) (9, 11). To confirm the high frequency of the ∆exon6–8 LEPR gene in the Reunion Island population, we developed a qPCR assay to diagnose heterozygous carriers in the future, because obesity affects 20% of adults and children in this population. Our observation also raises the question of screening for LEPR mutations in other French overseas departments and territories also characterized by a high prevalence of obesity.

The phenotype of patients with the ∆exon6–8 LEPR mutation did not differ markedly from other LEPR mutations carriers. Patients share common characteristics with early-onset morbid obesity, severe hyperphagia, and inconsistent hypogonadotropic hypogonadism (8, 9). The variability of hypogonadism (Table 2) and the recent description of normal spontaneous pregnancy in one LEPR-deficient woman (21) call into question the role of leptin in reproductive function (22, 23). The control of pubertal maturation results in synergistic action, besides leptin, of peripheral and central hormones acting on the reproductive axis, such as ghrelin and insulin as well as other epigenetic or genetic mechanisms (24, 25). The interruption of the leptin signal due to LEPR deficiency may thus be counteracted in some individuals with time.

Usual care management (controlled restrictive diets and physical activity programs) for LEPR-deficient patients is poorly and transiently effective in most cases, particularly in regions with a strong obesogenic environment such as in Reunion Island. Severe hyperphagia and uncontrolled weight gain are observed in all patients with the ∆exon6–8 LEPR mutation. However, the fact that hyperphagia can be controlled in some other mutation carriers suggests the determinant effect of the patient (familial) environment and/or the possibility that voluntary caloric restriction may sometimes counteract the consequence of lacking leptin signal (patient 5-II and Ref. 26).

Table 3. Body Composition and Biological and Hormonal Characteristics in Family 6 Carrying the ∆exon6–8 LEPR Mutation

<table>
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<tr>
<th>Subject</th>
<th>II-2</th>
<th>II-3</th>
<th>II-4</th>
<th>II-5</th>
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<td>20 ND</td>
<td>ND M/N</td>
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<td>30 ND</td>
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<td>No No</td>
<td>ND No</td>
<td>No No</td>
<td>ND No</td>
<td>No No</td>
<td>No No</td>
<td>No No</td>
<td>No No</td>
<td>No No</td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.4</td>
<td>4.8</td>
<td>4.8</td>
<td>6.2</td>
<td>ND</td>
<td>5.3</td>
<td>5.4</td>
<td>ND</td>
<td>4.6</td>
<td>4.8</td>
<td>4.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.7</td>
<td>6.2</td>
<td>4.6</td>
<td>5.4</td>
<td>ND</td>
<td>5.2</td>
<td>4.1</td>
<td>ND</td>
<td>5.9</td>
<td>6.2</td>
<td>4.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2</td>
<td>1.1</td>
<td>1</td>
<td>2.3</td>
<td>ND</td>
<td>1.1</td>
<td>0.8</td>
<td>ND</td>
<td>1.7</td>
<td>1.7</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>TSH, mU/L</td>
<td>1.7</td>
<td>1</td>
<td>5.7</td>
<td>1.6</td>
<td>ND</td>
<td>1.6</td>
<td>0.5</td>
<td>ND</td>
<td>2.5</td>
<td>1.2</td>
<td>1.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Abbreviations: M/M, homozygous mutated subject; M/N, heterozygous subject; N/N, not mutated subject; ND, not determined.
described in heterozygous subjects at discrepancy from homozygous carriers. This variability of BMI in heterozygous subjects is also described for other genes of the leptin/melanocortin pathway (27–31). As described for the MC4R or POMC genes, the penetrance of obesity due to the loss of one copy of the LEPR functional gene can be incomplete, with variable clinical expression depending on the localization and type of mutations and on the role of the environment and other potentially modulating genetic factors (32, 33). Cumulative mutation heterozygosity at several genes implicated in energy homeostasis with relatively subtle effects on gene expression and function may also be a common mechanism for obesity (34). New molecular approaches such as whole-exome sequencing could probably be helpful in identifying these interactions of heterozygous mutations and in making progress toward understanding the genetics of human obesity.

In conclusion, we describe a novel mutation (Δexon6–8 LEPR gene) in a cluster of six severely obese patients apparently unrelated but all originating from Reunion Island, suggesting a founder effect. Systematic mutation screening of this specific population, in whom obesity frequency is particularly high, may be necessary to evaluate the impact of heterozygous LEPR mutations on obesity predisposition.

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References


