

REVIEW

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# Monogenic forms of childhood obesity due to mutations in the leptin gene

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## Abstract

Congenital leptin deficiency is a rare autosomal recessive monogenic obesity syndrome caused by mutations in the leptin gene. This review describes the molecular and cellular characteristics of the eight distinct mutations found so far in humans.

**Keywords:** Leptin deficiency; Leptin mutation; Leptin secretion; Obesity; Bioinactive hormone

## Introduction

During the last four decades, the prevalence of obesity in childhood has increased dramatically and obesity has become an epidemic disease with more than 5% of all children affected in developed countries [1]. Changes in living conditions may act on children's behavior and favor the development of obesity due to individual genetic susceptibility [1].

In the vast majority of obese children, no syndromal or monogenic cause for the obese state can be diagnosed and therefore a polygenic cause is suggested. Generally, monogenic forms of childhood obesity are very rare [2]. Mutations in only a few genes are known to cause the development of severe obesity in early childhood [2]. Most of these genes are involved in the central nervous regulation of hunger and satiety where the leptin/leptin receptor system plays a pivotal role [3]. Of all monogenic forms of obesity, the only one causally treatable is congenital leptin deficiency caused by homozygous mutations of the leptin gene [4]. Leptin is a protein secreted mainly by adipocytes, and its circulating levels correlate positively with the body mass index and the body fat mass. By central as well as peripheral action, leptin impacts diverse physiological processes including energy balance, metabolism, endocrine regulation, and immune function [3]. One of the main functions of leptin is to control the body fat mass by inhibiting food intake via the central nervous system. Recombinant human

leptin (metreleptin) can be administered to patients with congenital leptin deficiency to compensate the lack of leptin [5].

Current clinical recommendations suggest that children with a normal birth weight but rapid weight gain in the first few months of life leading to extreme obesity should be tested for congenital leptin deficiency when they show impaired satiety, intense hyperphagia, and food-seeking behavior (see Clinical phenotype of patients with congenital leptin deficiency) [6,7]. Most patients described up to now had consanguine parents. Patients usually develop metabolic and hormonal alterations including hyperinsulinemia, insulin resistance, severe liver steatosis, dyslipidemia, as well as hypogonadotropic hypogonadism (see Clinical phenotype of patients with congenital leptin deficiency) [7,8]. Furthermore, some patients display immunological alterations in early childhood that manifest in recurrent severe bacterial infections possibly resulting in death in childhood (see Clinical phenotype of patients with congenital leptin deficiency) [4]. Upon substitution therapy with recombinant human leptin applied by daily subcutaneous injections, patients lose weight, the body fat mass is reduced, and the metabolic, hormonal, and immunological abnormalities are normalized [4,8,9].

## Clinical phenotype of patients with congenital leptin deficiency

Normal birth weight  
Rapid weight gain after birth  
Severe early-onset obesity  
Impaired satiety

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Intensive hyperphagia  
 Constant food-seeking behavior  
 Recurrent severe and possibly lethal bacterial infections in early childhood (some patients)  
 Development of hyperinsulinemia  
 Development of severe liver steatosis  
 Development of dyslipidemia  
 Hypogonadotropic hypogonadism

In humans, eight distinct leptin mutations have been described in the literature, which lead to congenital leptin deficiency when present in the homozygous state. On the cellular level, these mutations result in defects in the synthesis and/or secretion of leptin. In the following paragraphs, we have summarized the molecular and cellular characteristics of these mutations.

## Review

### Leptin gene and protein structure

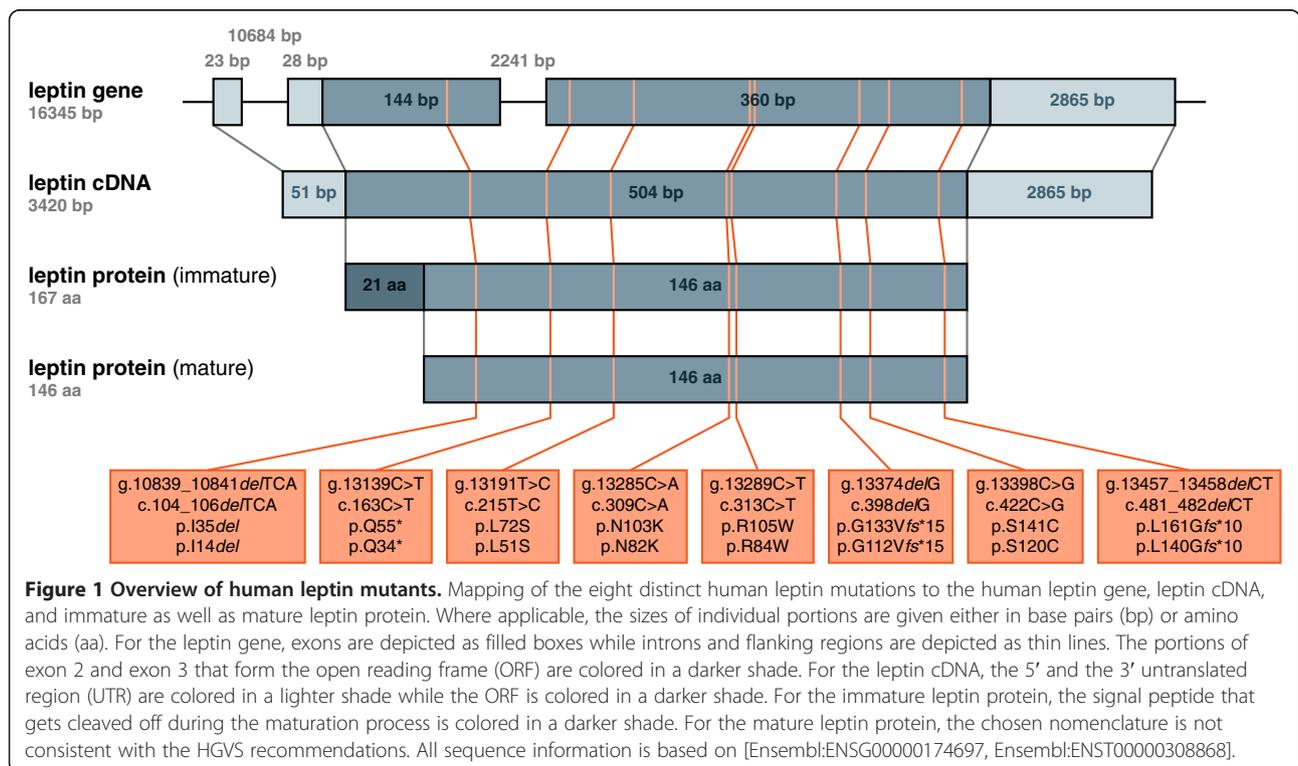
The gene encoding leptin (*LEP* or *OB*) was discovered by positional cloning in 1994 [10]. The *LEP* gene is located on chromosome 7q31.3 and consists of three exons separated by two introns [11] [Ensembl:ENSG00000174697].

Leptin is a type I cytokine and member of the family of long-chain helical cytokines which also includes interleukin 6 (IL-6), granulocyte colony-stimulating factor (G-CSF), and growth hormone (GH) [12]. It is synthesized as an immature 167-amino acid protein encompassing an N-terminal 21-amino acid signal peptide [10]

[Ensembl:ENST00000308868]. Cleavage of the signal peptide yields a non-glycosylated, mature 146-amino acid protein [10] [Ensembl:ENST00000308868]. Its structure features four major  $\alpha$  helices A to D as well as a distorted minor  $\alpha$  helix E, localized in the loop connecting helices C and D [12]. Assuming an up-up-down-down orientation, the helices A to D form a four-helix bundle which is stabilized by a single intramolecular disulfide bond spanning from the beginning of the loop between helices C and D to the C-terminus of the protein [12].

### Molecular and cellular characteristics of human leptin mutants

The notation used to describe the position and character of human leptin mutations has been inconsistent up to now [13-23]. Therefore, we provide a consistent notation and overview of the eight distinct leptin mutations described in humans so far (Figure 1) mapped to the human leptin gene, transcribed leptin mRNA (here cDNA), and translated immature and processed mature leptin protein. In the text of this review, the given position of amino acids in the leptin protein uniformly refers to their position in the unprocessed, immature protein. Moreover, we have summarized information about the eight known leptin mutations in humans, including the number of patients reported to carry these mutations (Table 1). Unless otherwise indicated, the chosen nomenclature adheres to the recommendations of the Human Genome Variation Society (HGVS).



**Table 1 Summary of patients reported to carry leptin mutations**

Mutation	Reported patients	Serum leptin level	Reference
g.13374delG	30		
c.398delG	Female, 8 years	0.1 to 1.0 ng/ml (close to detection limit)	Montague et al. [13]
p.G133Vfs*15	Male, 2 years	0.4 to 0.7 ng/ml (close to detection limit)	
p.G112Vfs*15	Male, 3 years	Below detection limit	Farooqi et al. [5]
	Female, 5 years	Below detection limit	Gibson et al. [24]
	Gender and age not specified	Not reported	Farooqi [25]
	Gender and age not specified	Not reported	
	Gender and age not specified	Not reported	
	Female, 5 months	Below detection limit	Fatima et al. [21]
	Female, 2 years	0.1 ng/ml	
	Female, 2 years	Below detection limit	
	Female, age not specified	Below detection limit	
	Female, age not specified	Below detection limit	
	Male, 1 year	0.5 ng/ml	
	Male, 7 years	Below detection limit	
	Male, 7 years	Below detection limit	
	Male, 12 years	Below detection limit	
	Female, 8 months	0.8 ng/ml	Saeed et al. [22]
	Female, 8 months	1.0 ng/ml	
	Female, 8 months	Below detection limit	
	Female, 2 years	Below detection limit	
	Male, 8 months	Below detection limit	
	Male, 1 year	0.5 ng/ml	
	Male, 1 year 5 months	0.7 ng/ml	
	Male, 3 years 4 months	0.7 ng/ml	
	Male, 7 years	0.9 ng/ml	
	Female, age not specified	Below detection limit	Saeed et al. [26]
	Female, age not specified	Below detection limit	
	Female, age not specified	Below detection limit	
	Female, age not specified	Below detection limit	
	Male, age not specified	Below detection limit	
g.13289C>T	5		
c.313C>T	Female, 6 years	1.1 ng/ml	Strobel et al. [15]
p.R105W	Female, 34 years	1.3 to 1.6 ng/ml	
p.R84W	Male, 22 years	0.9 to 1.2 ng/ml	
	Female, 30 years	0.6 ng/ml	Ozata et al. [27]
	Male, 5 years 1 month	Not reported	Paz-Filho et al. [28]
g.13398C>G	2		
c.422C>G	Gender and age not specified	Not reported	Chekhranova et al. [17]
p.S141C	Gender and age not specified	Not reported	
p.S120C	Gender and age not specified	Not reported	
g.13285C>A	2		
c.309C>A	Female, 7 years	1.3 ng/ml	Mazen et al. [18]
p.N103K	Male, 3 years	1.1 ng/ml	
p.N82K			

**Table 1 Summary of patients reported to carry leptin mutations (Continued)**

g.13191T>C c.215T>C p.L72S p.L51S	1 Female, 14 years	0.4 ng/ml (at detection limit)	Fischer-Posovszky et al. [20]
g.10839_10841delTCA c.104_106delTCA p.I35del p.I14del	1 to 2 (probable overlap) Female, 7 months Female, 1 year 6 months	3.6 ng/ml Below detection limit	Fatima et al. [21] Saeed et al. [22]
g.13457_13458delCT c.481_482delCT p.L161Gfs*10 p.L140Gfs*10	1 Male, 1 year 6 months	0.2 ng/ml	Fatima et al. [21]
g.13139C>T c.163C>T p.Q55* p.Q34*	1 Female, 8 years	<0.6 ng/ml	Thakur et al. [23]

For the mature leptin protein, the chosen nomenclature is not consistent with the HGVS recommendations. All sequence information is based on [Ensembl:ENSG00000174697, Ensembl:ENST00000308868].

The first mutation found to result in congenital leptin deficiency in humans was originally described in 1997 in two children from a consanguineous Pakistani pedigree [13]. A deletion of the guanine at position 13374 of the leptin gene (g.13374delG) corresponding to position 398 of the transcript (c.398delG) led to a frameshift mutation of the protein. This changed the glycine at position 133 to a valine and inserted additional 13 subsequent aberrant amino acids before coming to a stop (p.G133Vfs\*15) [13]. In both patients, the serum leptin levels as measured by a radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) were close to the detection limit (1.0 and 0.7 ng/ml by RIA as well as 0.1 and 0.4 ng/ml by ELISA, respectively) [13]. Furthermore, in one of the patients, no leptin could be detected in the serum by Western blot [13]. Transfecting CHO cells with a plasmid encoding p.G133Vfs\*15 leptin showed that p.G133Vfs\*15 leptin is synthesized, but not secreted to the cell culture supernatant [13]. Montague et al. proposed two mechanisms responsible for the low serum leptin levels observed in the patients [13]. First, the introduction of a premature stop codon into the transcript might cause nonsense-mediated mRNA decay (NMD) [13]. Second, the introduction of an aberrant stretch of amino acids into the protein might cause improper intracellular transport and secretion [13]. A subsequent detailed study using CHO and COS-7 cells revealed that p.G133Vfs\*15 leptin indeed exhibits an improper intracellular transport, aggregates and accumulates in the ER, and subsequently undergoes degradation by the proteasome [14].

In 1998, a second mutation conferring a congenital deficiency in leptin was described in three individuals from a consanguineous Turkish pedigree [15]. A transition of the cytosine at position 13289 of the leptin gene to a thymine (g.13289C>T) corresponding to position 313

of the transcript (c.313C>T) led to a missense mutation of the protein, changing the arginine at position 105 to a tryptophan (p.R105W) [15]. The serum leptin levels as assessed by two different immunoassays were very low in all three patients (1.6, 0.9, and 1.1 ng/ml by the first assay as well as 1.3, 1.2, and 1.1 ng/ml by the second assay, respectively) [15]. Transfecting COS-1 cells, Strobel et al. showed that like p.G133Vfs\*15 leptin, p.R105W leptin is synthesized but not secreted [15]. They consequently assumed that the mutant leptin displays a normal synthesis and stability, but aberrant intracellular transport and impaired secretion [15]. Two subsequent studies employing *in vitro*-differentiated PAZ6 adipocytes, primary rat adipocytes, as well as CHO and COS-1 cells confirmed that p.R105W leptin indeed misfolds, aggregates, and accumulates intracellularly [14,16]. In wild-type leptin, p.R105 is surrounded by negatively charged amino acids and forms salt bridges with p.D76 and p.E102 [16]. Boute et al. proposed that the p.R105W mutation might induce protein misfolding by disrupting the formation of these salt bridges [16]. Transfecting COS-1 cells and *in vitro*-differentiated PAZ6 adipocytes with plasmids encoding p.C117S, p.C167S, or p.C117S/C167S leptin, these authors were furthermore able to demonstrate that the correct formation of the intramolecular disulfide bond is a prerequisite for the proper folding, intracellular transport, and secretion of leptin [16]. Boute et al. consequently proposed that the p.R105W mutation might alternatively induce protein misfolding by sterically interfering with the proper formation of this intramolecular disulfide bond [16].

A third mutation was described in 2008 in two individuals from a population inhabiting a small Turkmenian mountain village [17]. A transversion of the cytosine at position 13398 of the leptin gene to a guanine

(g.13398C>G) corresponding to position 422 of the transcript (c.422C>G) led to a missense mutation of the protein, changing the serine at position 141 to a cysteine (p.S141C) [17]. No measurement of serum leptin levels was reported in these patients [17]. Chekhranova et al. proposed that the p.S141C mutation might result in protein misfolding and/or loss of biological activity by introducing a third cysteine into the protein, interfering with the correct formation of the intramolecular disulfide bond [17]. To our best knowledge, no study investigating the synthesis or secretion of this mutant has been published yet.

In 2009, a fourth mutation was described in two children from a consanguineous Egyptian pedigree [18]. Here, a transversion of the cytosine at position 13285 of the leptin gene to an adenine (g.13285C>A) corresponding to position 309 of the transcript (c.309C>A) led to a missense mutation of the protein, changing the asparagine at position 103 to a lysine (p.N103K) [18]. The serum leptin levels were very low in both patients (1.1 and 1.3 ng/ml) [18]. Mazen et al. did not explicitly hypothesize about how the p.N103K mutation might impact the synthesis, secretion, or biological activity of the protein [18]. Also in this case, no study examining the synthesis or secretion of this mutant has been published up to now. Notably though, the biological activity of this mutant was nonetheless addressed by an *in vitro* study performed by Niv-Spector et al. [19]. They made use of a prokaryotic expression system to produce p.N103K leptin and demonstrated that the p.N103K mutation drastically reduces the biological activity of the protein [19]. While they do not provide insight into the mechanisms underlying the defective synthesis and/or secretion of the mutant protein, they claim that not only the very serum levels but also the biological inactivity of the p.N103K leptin may contribute to the phenotype observed in affected patients [19].

A fifth mutation was described by our group in 2010 in a child from an Austrian pedigree without known consanguinity [20]. A transition of the thymine at position 13191 of the leptin gene to cytosine (g.13191T>C) corresponding to position 215 of the transcript (c.215T>C) led to a missense mutation of the protein, changing the leucine at position 72 to a serine (p.L72S) [20]. In this patient, the serum leptin levels as measured by an RIA were at the detection limit (0.4 ng/ml) [20]. Moreover, no leptin could be detected in the serum of this patient by immunoprecipitation and subsequent Western blot [20]. Analyzing patient-derived adipose tissue, expression of the mutant protein could be detected in adipocytes by qRT-PCR, Western blot, as well as immunohistochemistry [20]. Furthermore, *in vitro*-differentiated patient-derived adipocytes showed expression of the mutant protein [20]. Transfecting HEK293 cells confirmed that p.L72S leptin

indeed is synthesized, but not secreted [20]. By generating plasmids encoding p.L72A, p.L72I, p.L72V, or p.L72T leptin and transfecting these plasmids into HEK293 cells, our group was able to determine the lack of side chain hydrophobicity at position 72 of the protein as the main cause for the lack of secretion [20].

A sixth and a seventh mutation were originally described in 2011 in individuals stemming from consanguineous Pakistani pedigrees [21]. In a child, a deletion of a thymine-cytosine-adenine triplet at positions 10839 to 10841 of the leptin gene (g.10839\_10841delTCA) corresponding to positions 104 to 106 of the transcript, respectively, (c.104\_106delTCA) was detected [21]. This in turn resulted in the deletion of the isoleucine at position 35 of the protein (p.I35del) [21]. In this patient, Fatima et al. originally observed low, but still detectable serum leptin levels as measured by an ELISA (3.6 ng/ml) [21]. In a later publication, Saeed et al. also reported a child with a p.I35del mutation, probably the very same patient, in which they could not detect any leptin in the serum using an ELISA [22]. Fatima et al. hypothesized that the deletion of this highly conserved isoleucine at position 35 of the protein and thus resulting loss of hydrophobicity in the N-terminal region of the protein might result in defective intracellular transport and secretion [21]. Furthermore, these authors proposed that the p.I35del mutation might also result in a loss of the biological activity of the secreted protein as the N-terminal region of leptin has been proposed to be involved in the binding of leptin to the leptin receptor [21].

In another child, a deletion of a cytosine-thymine doublet at positions 13457 and 13458 of the leptin gene (g.13457\_13458delCT) corresponding to positions 481 and 482 of the transcript (c.481\_482delCT) led to a frameshift mutation of the protein, changing the leucine at position 161 of the protein to a glycine and inserting additional eight subsequent aberrant amino acids before coming to a stop (p.L161Gfs\*10) [21]. In this patient, the serum leptin level as measured by an ELISA was very low (0.2 ng/ml) [21]. Fatima et al. proposed that in the case of the p.L161Gfs\*10 mutation, the loss of the C-terminal p.C167 and thus resulting loss of the intramolecular disulfide bond as well as the introduction of an aberrant stretch of amino acids might result in misfolding, impaired intracellular transport and secretion, as well as a loss of the biological activity of the secreted protein [21]. No study examining the synthesis or secretion of either the p.I35del or the p.L161Gfs\*10 mutant has been published up to now.

Only recently, in 2013, an eighth mutation was described in a child from a consanguineous Indian pedigree [23]. Here, a transition of the cytosine at position 13139 of the leptin gene to thymine (g.13139C>T) corresponding to position 163 of the transcript (c.163C>T)

led to a nonsense mutation of the protein, converting the glutamine at position 55 to a stop (p.Q55\*) [23]. The serum leptin levels in this patient were very low (<0.6 ng/ml) [23]. Thakur et al. did not explicitly hypothesize about how the introduction of an early premature stop codon into the mutant transcript might impact the synthesis, secretion, or biological activity of the protein [23]. As with the p.G133Vfs\*15 and p.L161Gfs\*10 mutants, NMD should definitely be considered as a possible mechanism causative of the very low serum leptin levels observed with this mutant. Again, to our best knowledge, no study investigating the synthesis or secretion of this mutant has been published as of now.

#### **Existence of novel biologically inactive human leptin mutants veiled by unsuspecting serum leptin levels**

As presented in the preceding paragraphs, the serum leptin levels reported in the patients carrying homozygous leptin mutations have been close to undetectable or very low and thus out of proportion to the body fat mass found in these patients, making these patients severely leptin deficient [13,15,18,20-23].

A comparable situation is observed in leptin-deficient *obese (ob/ob)* mouse strains, in which leptin was originally discovered in 1994 [10,29]. In the *ob<sup>1j</sup>* strain, a transition of the cytosine at position 12850 of the leptin gene to thymine (g.12850C>T) corresponding to position 313 of the transcript (c.313C>T) leads to a nonsense mutation of the protein, converting the arginine at position 105 to a stop (p.R105\*) [10] [Ensembl:ENSMUSG00000059201, Ensembl:ENSMUST00000069789]. In this strain, the abundance of the leptin transcript in adipose tissue is drastically increased, while no corresponding leptin protein can be found in the serum, arguing for the synthesis of a mutant protein affected by an impaired intracellular transport and secretion [10,30]. In contrast, in the *ob<sup>2j</sup>* strain, the insertion of a retroviral-like transposon featuring several splice acceptor and polyadenylation sites into the first intron of the leptin gene results in the generation of chimeric transcripts and consequently no leptin protein synthesis at all [10,29].

Most strikingly, by far, not all known murine leptin mutants exhibit a defective leptin synthesis and/or secretion.

*N*-ethyl-*N*-nitrosourea (ENU)-driven mutagenesis led to the generation of a leptin-mutant mouse strain displaying a coexistence of high serum leptin levels and a phenotype very similar to that of the *obese* mouse strains [30]. In this strain, a missense mutation of the leptin protein changing the valine at position 145 to a glutamate (p.V145E) was detected, which was caused by a transversion of the thymine at position 12971 of the leptin gene to an adenine (g.12971T>A) corresponding to position 434 of the transcript (c.434T>A) [30]

[Ensembl:ENSMUSG00000059201, Ensembl:ENSMUST00000069789].

In two extensive *in vitro* studies, Peelman et al. and Iserentant et al. generated a large number of distinct murine leptin mutants featuring either single or multiple amino acid changes, essentially covering the whole surface of the leptin protein [31,32]. Interestingly, using COS-1 cells as a eukaryotic expression system, all mutants except for those targeting p.L34 were found to be synthesized and secreted to the cell supernatant, from which they could be purified for further experiments [31,32]. Several of these mutants showed pronounced changes in their capacity to bind and/or activate the leptin receptor, essentially proving that mutations rendering murine leptin biologically inactive do not necessarily have to affect leptin synthesis and/or secretion [31,32].

This raises the question whether forms of human congenital leptin deficiency exist, in which the production of biologically inactive leptin is veiled by the presence of unsuspecting or even elevated serum leptin levels.

Referring to current clinical recommendations, a sequencing of the leptin gene in patients with extreme early-onset obesity is suggested only in the presence of undetectable or very low serum leptin levels [6]. Therefore, it cannot be excluded that cases of congenital leptin deficiency with clearly detectable levels but bioinactive hormone exist in humans.

Diseases caused by bioinactive hormones are very rare, but still existent. For example, cases of biologically inactive protein have been reported for hormones like ACTH, TSH, as well as the leptin-related GH [33-36]. Therefore, the existence of congenital leptin dysfunction should definitely be considered.

#### **Conclusions**

Congenital leptin deficiency caused by homozygous mutations in the leptin gene results in impaired satiety, intense hyperphagia, and extreme early-onset obesity accompanied by multiple metabolic, hormonal, and immunological abnormalities. In humans, eight distinct leptin mutations characterized by undetectable to low serum leptin levels have been identified so far. Mechanistically, defects in the synthesis and/or secretion of the hormone have been proposed and demonstrated for some of these mutations. Affected patients can be successfully treated with recombinant human leptin. Current clinical recommendations suggest sequencing of the leptin gene in cases of extreme early childhood obesity preferably in the presence of undetectable to low serum leptin levels. Thus, a change in practice might be necessary to identify novel leptin mutations not showing defects in the synthesis and secretion but in the biological activity of the hormone.

## Abbreviations

ACTH: adrenocorticotropic hormone; aa: amino acid; bp: base pair; CHO: Chinese hamster ovary cell line; COS-1, COS-7: CV-1 origin SV40 cell lines 1 and 7; ELISA: enzyme-linked immunosorbent assay; ENU: *N*-ethyl-*N*-nitrosourea; G-CSF: granulocyte colony-stimulating factor; GH: growth hormone; HEK293: human embryonic kidney 293 cell line; HGVS: Human Genome Variation Society; IL-6: interleukin 6; LBD: leptin-binding domain; *LEP*, *OB*: human leptin (*obese*) gene; NMD: nonsense-mediated mRNA decay; *ob/ob*: obese mouse strain; *ob<sup>1</sup>*, *ob<sup>2</sup>*: obese mouse strain variants; ORF: open reading frame; RIA: radioimmunoassay; TSH: thyroid-stimulating hormone; UTR: untranslated region.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

J-BF prepared the figures, analyzed the literature, and wrote the manuscript. JvS analyzed the literature and critically revised the manuscript. BL critically revised the manuscript. GL analyzed the literature, supervised the correct usage of the HGVS nomenclature, and critically revised the manuscript. K-MD critically revised the manuscript. PF-P analyzed the literature and wrote the manuscript. MW analyzed the literature and wrote the manuscript. All authors read and approved the final manuscript.

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