Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics

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Abstract

Objective: Leptin receptor (LepR) deficiency is an autosomal-recessive endocrine disorder causing early-onset severe obesity, hyperphagia and pituitary hormone deficiencies. As effective pharmacological treatment has recently been developed, diagnosing LepR deficiency is urgent. However, recognition is challenging and prevalence is unknown. We aim to elucidate the clinical spectrum and to estimate the prevalence of LepR deficiency in Europe.

Design: Comprehensive epidemiologic analysis and systematic literature review.

Methods: We curated a list of *LEPR* variants described in patients and elaborately evaluated their phenotypes. Subsequently, we extracted allele frequencies from the Genome Aggregation Database (gnomAD), consisting of sequencing data of 77 165 European individuals. We then calculated the number of individuals with biallelic disease-causing *LEPR* variants.

Results: Worldwide, 86 patients with LepR deficiency are published. We add two new patients, bringing the total of published patients to 88, of which 21 are European. All patients had early-onset obesity; 96% had hyperphagia; 34% had one or more pituitary hormone deficiencies. Our calculation results in 998 predicted patients in Europe, corresponding to a prevalence of 1.34 per 1 million people (95% CI: 0.95–1.72).

Conclusions: This study shows that LepR deficiency is more prevalent in Europe ($n = 998$ predicted patients) than currently known ($n = 21$ patients), suggesting that LepR deficiency is underdiagnosed. An important cause for this could be lack of access to genetic testing. Another possible explanation is insufficient recognition, as only one-third of patients has pituitary hormone deficiencies. With novel highly effective treatment emerging, diagnosing LepR deficiency is more important than ever.

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Introduction

Obesity is one of the most urgent health problems of modern times because of its epidemical prevalence, high disease burden, and high mortality (1). In rare cases, obesity

is caused by genetic disorders in the leptin-melanocortin pathway, the hypothalamic system controlling energy expenditure and food intake. The anorexic hormone leptin is mainly secreted by adipose tissue and reflects the body's energy reserves. Hypothalamic leptin signaling

leads to activation of the melanocortin-4-receptor (MC4R), resulting in increased energy expenditure and satiety. When this signaling is disturbed, patients develop hyperphagia and early-onset obesity. A recent breakthrough for leptin-melanocortin pathway disorders is treatment with MC4R-agonist setmelanotide, which results in impressive weight loss (2). One of the endocrine disorders that now can be treated is leptin receptor (LepR) deficiency, a rare autosomal recessive disorder caused by pathogenic variants in the leptin receptor gene (*LEPR*). Adequate functioning of the leptin receptor is essential for maintaining body weight. Moreover, adequate leptin signaling is necessary for onset of puberty, pubertal growth spurt, and production of thyroid-releasing hormone (3, 4). Additionally, LepR-deficient rodents show decreased levels of pituitary growth hormone and stunted growth curves (5). When looking at the phenotype of LepR deficiency in humans, patients with LepR deficiency indeed can exhibit hypogonadotropic hypogonadism (HH), hypothyroidism, and/or growth hormone deficiency (GHD) in addition to extreme early-onset obesity and hyperphagia. It remains unclear why some patients only exhibit severe obesity, whereas others also have the associated pituitary hormonal disturbances. Residual receptor activity associated with specific *LEPR* mutations might partially explain this (4), but has not been investigated systematically. Other features reported in patients with LepR deficiency are frequent infections and hyperinsulinemia (3, 4), but to what extent they are part of the clinical spectrum of LepR deficiency is unknown. In some patients a lower CD4+ T-cell count and a compensatory higher B-cell count has been reported, which is in accordance with known effects of leptin on the immune system (4). It is hypothesized that this may contribute to early childhood death due to infections (4). Individuals affected by LepR deficiency have hyperinsulinemia to a degree consistent with the severity of their obesity (4), although it is suggested that these patients might be predisposed to develop insulin resistance and diabetes at an earlier age (3). The phenotype variability makes identification of LepR deficiency challenging. Recognition might be further hampered due to lack of awareness of possible rare underlying causes in routine obesity care. In obesity cohort studies, LepR deficiency prevalence of 0–3% is found (4, 6, 7, 8). Higher prevalence of up to 10% is reported in cohorts from consanguineous families (9). However, it is important to realize that these estimations only reflect prevalence of LepR deficiency in selected patient groups. The traditional approach to prevalence estimations of genetic diseases (counting the people diagnosed with the disease) greatly depends on local

availability and application of genetic testing. Nowadays, genetic data from large population databases can be used to better estimate general prevalence of genetic disorders.

Aim of this study is to establish the prevalence of LepR deficiency in the general European population. To achieve this, we first performed a systematic literature review to identify all published cases and add unpublished cases from our obesity center. We use the *LEPR* variants from these cases to perform a prevalence estimation based on European allele frequencies. Our second aim is to gather clinical information from published LepR deficiency patients to describe the clinical spectrum.

Methods

Systematic literature search

A systematic literature search was performed in Embase, Medline (Ovid), Web of Science, Cochrane Library, and Google Scholar to identify all patients with LepR deficiency from its first report in 1998 up to May 2019. The complete search strategy is presented in the supplement (Supplementary file 1, see section on [supplementary materials](#) given at the end of this article). In short, the strategy consisted of the themes '*LEPR*/'LepR deficiency' or 'obesity genetic diagnostics'. We adopted a broad search strategy to not miss studies which sequenced *LEPR* as part of an obesity gene panel. Additionally, we searched for additional cases in ClinVar, the Human Gene Mutation Database, and the Decipher database (10, 11, 12). Finally, we performed a non-systematic search in Researchgate (www.researchgate.net; accessed 24-05-2019; search queries '*LEPR*', 'leptin receptor' and 'leptin receptor deficiency') to identify studies and conference abstracts that were not indexed in the mentioned databases.

Title and abstract of all identified studies were screened by two investigators (L K, O A); studies describing patients with LepR deficiency were included; duplicate studies were removed (Fig. 1). In case of disagreement over inclusion, a senior investigator (E v d A/M v H) served as adjudicator. Additionally, reference lists of included studies were screened for relevant articles. Follow-up studies on cases already described in literature were only used for phenotype assessment.

Data extraction from included articles

An overview of genetic aberrations and phenotype features of patients with LepR deficiency (early-onset obesity, hyperphagia, signs of hypopituitarism and

Figure 1

PRISMA flow diagram of systematic literature search. *LEPR*, leptin receptor gene, SNP, single nucleotide polymorphism.

frequent infections) was made. When standard deviation scores (SDS) were not originally reported for anthropometric data, we calculated these using WHO growth charts as external standard (13). In case insufficient clinical data were reported, we tried to contact corresponding authors to provide additional information.

Case presentation of Dutch patients with *LepR* deficiency

We present two novel cases of *LepR* deficiency identified in our obesity center. Written informed consent for publication of their clinical details was obtained from the patient and/or parents. For these two patients' anthropometric data, SDS are presented using Dutch growth charts as external standard (14).

Selection of variants in *LEPR*

We extracted disease-associated *LEPR* variants from published cases identified through our systematic

literature search and added in-house genetic data (Table 2). Additionally, we curated and added variants with a high likelihood of being pathogenic, that is, loss-of-function (LoF) variants that were proximal to the pathogenic variant p.S1090Wfs*6. This variant is the most distal pathogenic variant reported in a patient with *LepR* deficiency; hence, LoF variants located more proximally are very likely to cause *LepR* deficiency. For all selected *LEPR* variants, we extracted allele frequencies from the Genome Aggregation Database (gnomAD). The gnomAD database (<https://gnomad.broadinstitute.org/>; accessed 06-10-2019) is the largest freely accessible population-based database consisting of sequencing data from 77 165 Europeans. Individuals with known severe pediatric diseases and their first-degree relatives are removed from this database. We excluded variants that did not pass gnomAD's quality control. Because of their distinctive genetic background, Finnish individuals are often omitted from European population studies. However, by performing separate prevalence calculations for Finnish and Non-Finnish cases, we could aggregate the results and provide estimations for the whole European population. All selected *LEPR* variants were evaluated by a clinical laboratory geneticist according to the current international guideline for variant classification (15). All variants are aligned to the canonical transcript NM_002303.5.

Prevalence calculation

We extracted European population size from the 2019 United Nations World Population Prospects report, which estimates a population size of 747.183 million Europeans, of which 5.532 Finnish Europeans (<https://population.un.org/wpp/Download/Standard/Population/>; accessed 28-09-2019). We estimated the number of individuals with biallelic (homozygous or compound heterozygous) pathogenic *LEPR* variants by calculating the probability of homozygosity or compound heterozygosity for each possible combination of our selected variants. We assumed that the population was in Hardy-Weinberg equilibrium and that random mating between individuals with and without obesity occurred. We did not correct for specific genetically isolated consanguineous populations in Europe. The CI of our prevalence estimation was calculated using derived variances (16). We adapted the formulas to allow derivation based on the sum of independent random variables.

Results

Systematic literature search and overview of published cases

In total, 5175 records were screened (Fig. 1), of which 24 records presented unique patients with LepR deficiency and were eligible for inclusion (2, 4, 5, 7, 9, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35). From these 24 records, we identified $n=86$ unique patients with LepR deficiency from 57 different families. We add two new unrelated cases with LepR deficiency (Box 1). Including these two new cases, 88 patients have now been described worldwide (Table 1), harboring 45 distinct *LEPR* variants (Table 2). Twenty-one of these patients are from European ancestry. To gain more insight in the clinical spectrum of the disease, the phenotypes are summarized in Table 1 and presented on individual level in Supplementary Table 1. Consanguinity was reported in 65/88 (74%) patients. Of the 84 patients in which sex was reported, 42 (50%) were female. Median age at description was 8.0 years (IQR: 3.0–15.2 years). Eighteen (22%) out of the 83 patients in which age was reported were adults, the three oldest of which were 39, 41, and 55 years old. Median BMI was 39.6 kg/m² (IQR: 34.1–49.1 kg/m²). Mean BMI SDS was +5.2 (SD 2.0) and was not significantly different between males and females

($P=0.39$). Interestingly, three patients (Dehghani III:9 and III:10, Kakar VII:6) did not have obesity at presentation. A large inter-individual variation was seen with respect to height SDS (mean +0.3 SDS, s.d. 2.1; reported in 49/88 patients): 11/49 (22%) patients had a tall stature (height SDS >2), whereas 8/49 (16%) patients had a short stature (height SDS <−2). Early-onset obesity (<age 5 years) and hyperphagia were the most common phenotypic features (Table 1). In 21 cases, exact age of onset of obesity was reported; when aggregated, median age of onset was 0.3 years (IQR 0.2–0.4). Pituitary hormone disturbances were present in 24 patients (Table 1). In the majority of these patients (15/24, 63%), only one pituitary hormone disturbance was present. Three patients had both HH and GHD; one patient had HH and central hypothyroidism; one patient had GHD and central hypothyroidism. Three patients had HH, GHD as well as central hypothyroidism.

Known and likely pathogenic *LEPR* variants

Of the 45 distinct variants described in patients with LepR deficiency, only eight variants were present in the global gnomAD population, and seven were present in the European population of the gnomAD database (Table 2). Additionally, 20 LoF variants with a high likelihood of being pathogenic were identified in

Box 1: Presentation of two new cases with LepR deficiency

The first patient is a 3-year-old boy, referred at age 13 months because of increased linear growth, obesity and hyperphagia. He was born at a gestational age of 36 + 6 weeks with normal birth weight (3840 g, +0.9 SDS). Parents did not report consanguinity, but their families lived in the same small Dutch municipality. There was no history of frequent infections. On presentation at age 13 months, height was 83.2 cm (+1.9 SDS), weight 17 kg (+4.9 SDS), and BMI 24.6 kg/m² (+4.4 SDS). Laboratory testing showed a central hypothyroidism. A growth hormone test was performed because of height deceleration, which confirmed GHD. Thyroid and growth hormone supplementation were started. Adrenal insufficiency was excluded by a high-dose ACTH test. MRI cerebrum revealed no anatomic abnormalities in the pituitary region. Obesity gene panel analysis (described in detail elsewhere (6)) revealed a homozygous variant of uncertain significance (VUS) in *LEPR*: c.3414dup p.(Ala1139Cysfs*16). This variant is located in the C terminal domain of the transcript. Since this is a frameshift near the end of the protein, replacing the last 27 amino acids with 15 alternative amino acids, the clinical relevance remains uncertain. However, the typical clinical phenotype (including hormonal disturbances) in the absence of other plausible explanations, makes this homozygous variant the most probable cause of the LepR deficiency phenotype.

The second patient is a 15-year-old girl referred to our obesity center at age 14 years for personalized treatment advice. She was born at a gestational age of 42 weeks with normal birth weight (3400 g, −0.1 SDS). At age 3.5 years, she was referred to a pediatric endocrinologist for evaluation of hyperphagia and obesity. There was no history of frequent infections. Height was 97 cm (−1.2 SDS), weight 23.1 kg (+3.0 SDS), BMI 24.6 kg/m² (+4.4 SDS). Laboratory testing showed no signs of hypopituitarism. During clinical follow-up, she had spontaneous start and progression of puberty and menarche at age 12.5 years. Whole-exome sequencing analysis revealed compound heterozygosity for two known pathogenic variants in the *LEPR* gene: c.1835G>A (p.Arg612His), c.2051A>C (p.His684Pro). Previously reported functional studies confirmed impaired functionality of the His684Pro variant, whereas the Arg612His variant has some residual function (4).

the European population of the gnomAD database (Supplementary Table 2). As expected, no (likely) pathogenic variants were present in a homozygous state in gnomAD.

Prevalence calculation

The calculated number of individuals with LepR deficiency (caused by biallelic disease-causing variants in the *LEPR* gene) in Europe is 998 patients (95% CI 708–1288). This would indicate that only 21/998 (2.1%) European cases with LepR deficiency are currently described in literature. The prevalence of LepR deficiency based on published European patients would be 0.03 per 1 million people. However, our calculated ‘genetic prevalence’ of LepR deficiency in Europe is 1.34 per 1 million people (95% CI 0.95–1.72 per 1 million people).

Discussion

Leptin receptor deficiency is a rare endocrine disease, but our population genetics-based analysis shows that it

is much more prevalent in Europe than expected based on literature. Assuming that most patients with LepR deficiency have been published, as is demonstrated by the ongoing reports of new cases in the past years, this suggests underdiagnosis. This is especially problematic since diagnosing LepR deficiency now has therapeutic consequences: pharmacological treatment aimed at restoring the leptin-melanocortin pathway has recently shown impressive results in terms of weight loss, satiety, and improvement of metabolic parameters (2).

Genetic testing for obesity disorders, including LepR deficiency, is recommended in patients with extreme early-onset (before age 5 years) and clinical features of a genetic obesity disorder and/or a positive family history for extreme obesity (36). However, a recent review from the United States reports that only 8% of patients in whom genetic testing would be indicated had undergone genetic testing (37). An important reason for underdiagnosing might be limited access to genetic diagnostics. Although *LEPR* sequencing has become available in clinical practice in the last decade, it is not yet part of routine care in many countries. Indeed, all published European LepR deficiency cases

Table 1 Summarized overview of clinical characteristics of all 88 currently known patients with LepR deficiency.

Features	n patients with available data (out of 88)	Interpretation
Early-onset obesity	87	Present in 87 (100%) patients: <ul style="list-style-type: none"> • 51 (59%) onset before age 2 years • 7 (8%) in (early) infancy • 5 (6%) onset between age 2–6 years • 1 (1%) onset before age 13–14 years • 23 (26%) not further specified
Hyperphagia	84	Present in 81 (96%) patients
Pituitary hormone disturbances	70	Present in 24 (34%) patients
Central hypothyroidism	64	Present in 8 (13%) patients
Growth hormone deficiency*	64	Present in 8 (13%) patients
Hypogonadotropic hypogonadism	39	Additionally: <ul style="list-style-type: none"> • 3 (6%) IGF-1 values below reference range reported • 1 (2%) patients short stature reported Present in 22 (56%) patients Additionally: <ul style="list-style-type: none"> • 1 (3%) inconclusive due to young age but low gonadotrophins reported
Hyperinsulinemia	61	Present in 24 (39%) patients Additionally: <ul style="list-style-type: none"> • 10 (16%) inconclusive because no reference range for insulin values was reported
Frequent infections	44	Present in 23 (52%) patients, of which 3 died due to infections in childhood Additionally: <ul style="list-style-type: none"> • 2 (5%) lowered CD4+ T cell count reported • 1 (2%) alterations in immune function reported

*Formal diagnosis of growth hormone deficiency by appropriate GH provocation tests.
CD4, cluster of differentiation 4; IGF-1, insulin-like growth factor 1.

Table 2 Mutations in the *LEPR* gene described in patients with LepR deficiency.

Reference	n	Nationality	Zygosity	Variant in coding DNA	Aberration on protein level (NM_002303.5)	Functional analysis	Allele frequency European non-Finnish population in gnomAD
(35)	1	N.R.	Hom	N.A.	p.M1?	N.R.	8.80E-06
(4)	3	Southern European	Hom	N.A.	p.W31*	N.A.	Not present
(26)	1	Turkish	Hom	c.461dupA	p.N154Kfs*3	<i>In silico</i>	Not present
(29)	9	Iranian	Hom	c.461T>G	p.Y155*	<i>In silico</i>	Not present
(22)	2	Sudanese	Hom	c.479delA	p.H160Lfs*10	<i>In silico</i>	Not present
(22)	1	Guinean	Hom	c.556delT	p.C186Afs*28	<i>In silico</i>	Not present
(17)	2	Egyptian	Hom	c.946C>A	p.P316T	<i>In silico</i>	1.76E-05
(18),(26)	2	Turkmen; Turkish	Hom	c.946C>A; c. 1938G>T (both hom)	p.P316T and p.W646C (both hom)	<i>In silico</i>	Not present
(4)	1	Turkish	Hom	c.1226C>A	p.A409E	<i>In vitro</i>	Not present
(24)	2	French	Comp het	c.1264T>C and c.2131dup	p.Y422H and p.T711Nfs*18	<i>In silico</i>	Not present
(32)	1	N.R.	Hom	c.1285+1G>A	p.? (splicing defect)	<i>In silico</i>	Not present
(31)	1	Turkish	Hom	c.1603+2T>C	p.? (splicing defect)	<i>In silico</i>	Not present
(21)	5	Pakistani	Hom	c.1603+5G>C	p.R468Sfs*33	<i>In silico</i>	Not present
(25)	1	Dutch	Hom	c.1604-8A>G	p.K536Sfs*34 and p.V535Dfs*3 (two transcripts)	<i>In silico</i> , Sanger, RNA analysis	8.92E-06
(24)	1	French (Reunion)	Comp het	c.1604-1G>A and del exon 6-8	p.? (splicing defect) and p.?	<i>In silico</i>	Not present
(23), (9)	2	Pakistani	Hom	c.1675G>A	p.W558*	<i>In silico</i> , Sanger	Not present
(25)	1	Dutch	Comp het	c.1753-1dupG and c.2168C>T	p.M585Dfs*2 and p.S723F	<i>In silico</i> , Sanger, RNA analysis	Not present
(24)	1	French	Hom	c.1810T>G	p.C604G	<i>In silico</i>	Not present
(9)	2	Pakistani	Hom	c.1810T>A	p.C604S	<i>In silico</i>	Not present
This publication	1	Dutch	Comp het	c.1835G>A and c.2051A>C	p.R612H and p.H684P	<i>In silico</i>	Not present
(4)	1	UK	Comp het	c.N.A. (1-bp deletion in codon 15) and c.1835G>A	p.F15Lfs*4 and p.R612H	<i>In vitro</i> (p.R612H)	Not present
(28)	1	Spanish	Hom	c.1835G>A	p.R612H	<i>In vitro</i>	4.88E-04
(35)	1	N.R.	Hom	c.1871dupA	p.N624Kfs*21	<i>In silico</i>	Not present
(26)	1	German	Comp het	c.1874G>A and c.2051A>C	p.W625* and p.H684P	<i>In silico</i> , <i>In vitro</i> (p.H684P)	Not present
(34)	3	Middle-eastern	Hom	c.1916C>T	p.P639L	<i>In silico</i>	Not present
(27)	1	Dutch	Comp het	c.1985T>C and c.2168C>T	p.L662S and p.S723F	<i>In silico</i>	Not present
(4)	1	Norwegian	Hom	N.A.	p.W664R	<i>In vitro</i>	5.31E-05
(4), (26)	2	UK; German	Hom	c.2051A>C	p.H684P	<i>In vitro</i>	3.87E-05
(7)	1	Dutch	Comp het	c.2051A>C and c.2627C>A	p.H684P and p.P876Q	<i>In silico</i>	Not present
(26)	1	German	Comp het	c.2227T>C and c.2598-3_2607delTAGAATGAAAAAG	p.S743P and p.Q865_K870	<i>In silico</i>	Not present
(24), (2)	2	Portuguese	Hom	c.2357T>C	p.L786P	<i>In silico</i>	8.82E-06
(23), (9)	4	Pakistani	Hom	c.2396-1G>T	p.? (splicing defect)	<i>In silico</i>	Not present
(24)	1	Turkish	Hom	c.2491G>A	p.H800_N831del (splicing defect)	<i>In silico</i>	Not present
(5)	3	Algerian	Hom	c.2597+1G>A	p.? (splicing defect)	PCR and sequencing	Not present
(30)	1	Pakistani	Hom	c.2675C>G	p.P892R	<i>In silico</i>	Not present
(30)	4	Pakistani	Hom	c.3268_3269del	p.S1090Wfs*6	<i>In silico</i>	Not present

Table 2 Continued.

Reference	n	Nationality	Zygosity	Variant in coding DNA	Aberration on protein level (NM_002303.5)	Functional analysis	Allele frequency European non-Finnish population in gnomAD
(33)	5	Indian	Hom	c.3268_3269dup	p.S1090Rfs*6	<i>In silico</i>	Not present
This publication	1	Dutch	Hom	c.3414dup	p.A1139Cfs*16	<i>In silico</i>	Not present
(19)	1	N.R.	Hom	deletion <i>DNAJC6</i> and parts of <i>LEPR</i>	p.?	PCR, MPLC	Not present
(9)	1	Pakistani	Hom	1.3 kb and 58.8 kb deletions	p.?	<i>In silico</i>	Not present
(26)	1	Turkish	Hom	deletion exon 4–20	p.?	N.A.	Not present
(4)	3	Bangladeshi	Hom	N.A. (4-bp deletion codon 22)	N.A.	<i>In silico</i>	Not present
(4)	2	Turkish	Hom	N.A. (11-bp deletion codon 70)	N.A.	<i>In silico</i>	Not present
(24)	5	French (Reunion)	Hom	deletion exon 6–8	p.?	<i>In silico</i> , PCR	Not present
(4)	1	Iranian	Hom	N.A. (66-bp deletion codon 514)	N.A.	<i>In silico</i>	Not present

bp, base pair; Comp het, compound heterozygous; del, deletion; gnomAD, Genome Aggregation database; Hom, homozygous; MPLC, multiplex polymerase chain reaction/liquid chromatography; n, number of patients; N.A., not applicable; N.R., not reported; PCR, polymerase chain reaction; UK, United Kingdom.

are from high-income countries with well-established diagnostic genetic facilities. Another explanation why patients with LepR deficiency are not identified, is that the clinical phenotype is not sufficiently recognized. Our systematic literature search shows that the majority of patients do not have pituitary hormonal disturbances. It is hypothesized that there might be a genotype–phenotype correlation reflecting residual leptin receptor function in those cases (3), but the amount of patients is too small to draw conclusions. Thus, LepR deficiency should be suspected in all cases of severe early-onset obesity and hyperphagia, even without signs of hypopituitarism, especially in the case of consanguinity. In the most common monogenic obesity disorder, *MC4R* deficiency, segregation studies have shown incomplete expressivity and penetrance for the obesity phenotype (38). However, this is not likely for LepR deficiency, as there are no individuals present with biallelic pathogenic *LEPR* variants in gnomAD nor in large control cohorts without obesity (6, 39).

A more daunting possible cause of the discrepancy between amount of described patients versus predicted patients is mortality. Young age of known patients and absence of adult LepR deficiency patients in several large adult cohorts with early-onset obesity (6, 7, 8) could suggest that these patients die before they are identified. This may occur due to the consequences of their severe obesity, but mortality in early childhood due to infections has also been reported (4, 29). Long-term follow-up studies of the clinical course of LepR deficiency have however not yet been performed. These studies are also needed because in some cases, improvement of the endocrine phenotype after puberty has been reported (Supplementary Table 1), however, without a clear explanation. Le Beyec *et al.* reported resolving of central hypothyroidism from age 16 years onward and hypogonadism from age 19 years onward in a male patient (20). Dehghani *et al.* reported that two affected males in a consanguineous family showed BMI normalization from puberty onset onward, in contrast to the affected females in this family who did not show improvement of BMI nor hypogonadotropic hypogonadism, suggesting a sex-specific effect might be present (29). However, Nizard *et al.* reported resolving of hypogonadotropic hypogonadism in a female patient from age 18 years onward and occurrence of natural pregnancy 2 years after gastric bypass surgery (40), which challenges the assumption that hormonal disturbances only resolve in male patients. However, the number of patients is too low to draw conclusions on this phenomenon.

Strengths and limitations

To the best of our knowledge, this is the first systematic literature overview of LepR deficiency cases. We identified 86 published cases, compared to the 57 cases in a previous, non-systematic overview from 2018 (3). A strength of this study is that we could add clinical information from 26/86 (30%) known LepR deficiency cases by contacting authors. Another strength is our stringent variant selection. There is always an insecurity regarding the pathogenicity of variants when functional tests have not been performed. This is even the case for variants identified in patients with clear LepR deficiency phenotypes, such as the male patient described earlier. In 2018, Ayers *et al.* presented a prevalence calculation for LepR deficiency in the United States (41). However, they estimated prevalence using a far less stringent method by adding variants predicted to be pathogenic solely on the basis of *in silico* prediction tools. It is known that these tools are not specific, leading to high false-positive rates (42). When we would use their method, this would lead to a prevalence estimation of 8953 patients (95% CI: 7880–10 027 patients). This would be a significant overestimation, whereas our calculation would rather yield an underestimation of actual number of patients. An important limitation of our study is that only 7/45 distinct pathogenic variants identified in patients with LepR deficiency were present in the European gnomAD population. Therefore, when sample size of sequencing data in population databases expands, prevalence calculations might yield a higher number of patients. Another limitation of our calculation is that first-degree relatives from patients with severe pediatric diseases, such as LepR deficiency, are removed from gnomAD, which could have led to a lower allele frequency of pathogenic *LEPR* variants. Moreover, we are aware that it is possible that some diagnosed patients have not been described in literature yet. This could lead to a higher prevalence calculation if these patients have novel *LEPR* variants. Thus, our current prevalence calculation should be seen as a minimum estimation.

Conclusion

LepR deficiency is an endocrine obesity disorder for which encouraging treatment options recently became available. Genetic testing in patients with early-onset obesity, hyperphagia, and/or LepR-associated hormone disturbances is therefore more important than ever. By using large population-based genetic data, we estimated the prevalence of this rare disease in Europe. Our data

suggest that the majority of patients with LepR deficiency in Europe are currently not recognized. Improving awareness and availability of genetic testing for early-onset obesity is needed to help these patients gain access to newly developed effective treatment.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0678>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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