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REVIEW

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Medical semiology of patients with monogenic obesity: A systematic review

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Summary

Patients with monogenic obesity display numerous medical features on top of hyperphagic obesity, but no study to date has provided an exhaustive description of their semiology. Two reviewers independently conducted a systematic review of MEDLINE, Embase, and Web of Science Core Collection databases from inception to January 2022 to identify studies that described symptoms of patients carrying pathogenic mutations in at least one of eight monogenic obesity genes (*ADCY3*, *LEP*, *LEPR*, *MC3R*, *MC4R*, *MRAP2*, *PCSK1*, and *POMC*). Of 5207 identified references, 269 were deemed eligible after title and abstract screening, full-text reading, and risk of bias and quality assessment. Data extraction included mutation spectrum and mode of inheritance, clinical presentation (e.g., anthropometry, energy intake and eating behaviors, digestive function, puberty and fertility, cognitive features, infectious diseases, morphological characteristics, chronic respiratory disease, and cardiovascular disease), biological characteristics (metabolic profile, endocrinology, hematology), radiological features, and treatments. The review provides an exhaustive description of mandatory, non-mandatory, and unique symptoms in heterozygous and homozygous carriers of mutation in eight monogenic obesity genes. This information is critical to help clinicians to orient genetic testing in subsets of patients with suspected monogenic obesity and provide actionable treatments (e.g., recombinant leptin and MC4R agonist).

KEYWORDS
medical semiology, monogenic obesity, systematic review

Abbreviations: ACG, anterior cingulate gyrus; ACTH, adrenocorticotropic hormone; ADCY3, adenylate cyclase 3; ADHD, attention deficit hyperactivity disorder; AMP, adenosine monophosphate; ARMS, amplification refractory mutation system; BMI, body mass index; CGH, comparative genomic hybridization; DHPLC, denaturing high performance liquid chromatography; FSH, follicle stimulating hormone; GH, growth hormone; GLP-1, Glucagon Like Peptide 1; GPCR, G-protein-coupled receptor; HRM, high resolution melt; IGF1, insulin growth factor 1; IGFBP3, insulin growth factor-binding protein; LEP, leptin; LEPR, leptin receptor; LH, luteinizing hormone; LOF, loss of function; MAF, minor allele frequency; MC3R, melanocortin 3 receptor; MC4R, melanocortin 4 receptor; MRAP2, melanocortin 2 receptor accessory protein 2; MRI, magnetic resonance imaging; MSH, melanocyte-stimulating hormone; NGS, next generation sequencing; NHLBI, National Heart, Lung, and Blood Institute; NK, natural killer; PCR, polymerase chain reaction; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; RLFP, restriction fragment length polymorphism analysis; RYGB, Roux-en-Y gastric bypass; SDS, standard deviation; SG, sleeve gastrectomy; SSCP, single strand conformation polymorphism; T2D, type 2 diabetes; TSH, thyroid stimulating hormone.

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1 | INTRODUCTION

Obesity is a global health concern that affected more than 650 million adult people worldwide in 2016 based on data from the World Health Organization. Furthermore, 380 million children and adolescents suffer from overweight and obesity at the global level. This disease is associated with multiple co-morbidities: depression, sleeping disorders, osteoarthritis, type 2 diabetes (T2D), fatty liver, hypertension, cardiovascular diseases, cancers, and COVID-19 complications.[1,2] Obesity results in decreased quality of life[3] and premature mortality.[4] Despite the availability of different treatments and major investments in health policy (diet and exercise, behavioral and cognitive therapy, medication, and bariatric surgery), there is no sign of slowing down in obesity prevalence at the global level.[5,6] In this context, research for better prediction, prevention, and care represents an important objective to decrease obesity prevalence worldwide.[7]

Obesity results from the interplay between biological (e.g., sex, age, preexisting diseases, fetal programming, gut microbiota, epigenetics, and genetics), societal (e.g., education, socio-economic status, and urbanization), and environmental (e.g., unhealthy diet, physical inactivity, stress, and pollution) factors.[8,9] Heritability studies estimate that 40–75% of body mass index (BMI) variation is explained by genetic factors.[10,11] Genetic forms of human obesity can be classified into a continuum: syndromic obesity (with neurodevelopment disorders), monogenic obesity, and polygenic obesity.[8] Up to date, mutations in eight genes involved in the leptin/melanocortin pathway have been linked to monogenic obesity in several independent studies (*LEP*,[12,13] *LEPR*,[14,15] *POMC*,[16,17] *PCSK1*,[18,19] *MC3R*,[20] *MC4R*,[21,22] *MRAP2*,[23,24] *ADCY3*[25,26]). The leptin/melanocortin pathway plays a central role in regulating mammalian food intake, energy expenditure, and body weight regulation.[27]

Leptin is a hormone encoded by the leptin (*LEP*) gene located on chromosome 7q32.1 and produced by white adipocytes. Leptin binds to long-form leptin receptors (LEPRs) in the arcuate nucleus of the hypothalamus. By binding to its receptor, leptin inhibits secretion of orexigenic neurotransmitters and increases anorexigenic hormones like alpha melanocyte-stimulating hormone (alpha-MSH), produced after POMC cleavage (by prohormone convertase PC1/3 encoded by the *PCSK1* gene). Alpha-MSH acts on the melanocortin 4 receptor (MC4R) to reduce energy intake and lead to satiety sensation. ADCY3 is an adenylate cyclase, co-localized in the primary cilia of the hypothalamus with MC4R implicated in the synthesis of cyclic AMP.[28] MRAP2, a G-protein-coupled receptor (GPCR) accessory protein, promotes primary cilia localization of MC4R and enhances signaling of MC4R in response to MC4R agonist.[24,29] MC3R is one of the 5 melanocortin receptors and is primarily expressed in the arcuate nucleus of the hypothalamus. MC3R plays crucial roles in the regulation of energy homeostasis by binding to ligands such as MSH and agouti-related peptide.[30]

These monogenic forms of obesity are especially relevant in the context of precision medicine: the biological cause is simple, the phenotypic consequence are striking, and actionable treatments (e.g., recombinant leptin and MC4R agonist) are already available for LEP, LEPR, and POMC complete deficiency.[31–33] One essential question prior to shift from conventional to precision medicine in obesity is to know whether all patients with obesity or well-phenotypically characterized subsets of patients may be sequenced to identify monogenic cases. Considering that targeted gene panel sequencing, whole-exome sequencing, and whole-genome sequencing are still costly, knowing precisely the medical semiology (i.e., combined symptoms including symptoms, somatic and laboratory signs, history taking, and physical examination) of patients with monogenic obesity may help the clinician to orient genetic testing and provide actionable treatments to the right subset of patients.

Prior to implementing a decision-making tree based on clinical and biological factors for the triage of patients with obesity, an exhaustive knowledge of these characteristics in patients with monogenic forms of obesity is needed. Narrative reviews on the topic exist, but no systematic review has been performed to date. This led us to complete a systematic review of the literature to describe the medical semiology of patients with monogenic non-syndromic forms of obesity in eight genes from the leptin-melanocortin pathway.

2 | METHODS

A protocol for this systematic review was registered on PROSPERO (CRD42023412167). Criteria for search methods, article eligibility, and factors associated with gene names, mutations, and obesity traits, were determined a priori. The PRISMA statement was used to guide reporting of this systematic review[34] (Table S1).

2.1 | Study inclusion/exclusion criteria

Any observational study evaluating the clinical and/or biological characteristics of patients with monogenic obesity caused by pathogenic mutations or likely pathogenic mutations (characterized by in silico, in vitro, and in vivo methods) with minor allele frequency (MAF) < 1% in at least one of the eight well-established genes (i.e., with 2 independent observations) from the leptin-melanocortin pathway (*LEP*,[12,13] *LEPR*,[14,15] *POMC*,[16,17] *PCSK1*,[18,19] *MC3R*,[20] *MC4R*,[21,22] *MRAP2*,[23,24] *ADCY3*[25,26]) was included. Coding synonymous mutations were not considered in this study. Studies were included independent of age, sex, or ethnicity of participants. Studies that used the same cohort for multiple publications were included, and we merged the clinical/biological information. Search results were limited to human studies published in English only. Animal studies and cellular studies were excluded. Review articles, commentaries without original data, and conference abstracts were also excluded.

2.2 | Electronic search strategy

Search strategies (Table S2) were developed in collaboration with the field expert (DM) to systematically search the MEDLINE, Embase, and

Web of Science Core Collection databases from the inception of the database to 24/01/2022. Search terms such as gene names, obesity-, and mutation-related terms were used with Boolean operators to identify studies on the semiology of carriers of pathogenic mutations in monogenic obesity genes. Works cited in eligible articles were hand-searched to ensure all pertinent studies were included in the current review.

2.3 | Study selection

Two reviewers (ER and ATB) independently screened titles and abstracts of articles to determine eligibility after removing duplicate records. A sample of 100 abstracts was screened in triplicate by ER, ATB, and the field expert (DM) in a training exercise. An inter-rater reliability/kappa of a minimum of 0.81 had to be achieved between ER and ATB prior to reviewing all titles and abstracts.[35] The inter-rater agreement of reviewers was calculated using Cohen's kappa (κ) to ensure consistent interpretation of the inclusion and exclusion criteria. The equation used to calculate κ is as follows:

$$\kappa = {\Pr(a) - \Pr(e)}/{1 - \Pr(e)}$$

where Pr(a) is the observed agreement among raters and Pr(e) is the chance agreement. κ was calculated for the results of the complete title and abstract screening.[35] Articles that were declared relevant by either of the reviewers were selected for full-text review. Any disagreements at any stage of the process were resolved through consensus or consulting the field expert (DM), as required.

2.4 | Data extraction and management

Data were extracted in duplicate (ER and ATB) from studies satisfying the inclusion criteria using a standardized form. Information on study characteristics (author's name, year, title of the article; type of the study, e.g., cross-sectional, prospective, retrospective, case–control, case-only, case report, pedigree, general population), demographics of study participants in both comparator groups (ethnicity/geographic origin, sample size, male to female ratio, mean age with standard deviation), obesity status and anthropometric characteristics (method of BMI reported, the estimated value of BMI along with variability in the comparator groups, estimate effect as odds ratio, risk ratio or rate ratio [if reported]), and additional clinical and biological features were noted. Furthermore, genes, mutations, and their functional consequences were noted.

2.5 | Risk of bias and quality assessment

The risk of bias for rare variant genetic association studies with comparator group was assessed using the tool considering Q-Genie tool and ROBINS previously described by Qasim et al. and Ehtesham et al.[36,37] (Table S3): selection bias, bias because of confounding, bias in classification of exposure, bias in assessment of outcome, bias because of missing data, and bias in selection of reported results received rating of "low risk," "probably low risk," "probably high risk," and "high risk." Quality of studies (except for case reports) was assessed by the Study Assessment tools developed by NHLBI (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools): quality was qualified as good, fair, or poor. Quality of case reports or pedigree reports was considered as low in accordance with GRADE assessment.[38] Quality and risk of bias of included studies were assessed independently by two reviewers (ER and ATB). All conflicts were resolved by discussion with the field expert (DM).

3 | RESULTS

3.1 | Literature search

Our systematic search resulted in a total of 8430 relevant references (Figure 1). Then, 5207 titles and abstracts were independently screened by ER and ATB to determine eligibility after removing 3223 duplicates. Title and abstracts were screened in duplicate by ER and ATB. The inter-rate reliability was $\kappa = 0.9$ calculated for the entire screening with a percentage of agreement of 98.5%. In total, 402 references were selected for full-text review, of which 133 were excluded for one or more of the following reasons: (1) animal studies, (2) functional studies without clinical description, (3) polymorphism (MAF > 1%), (4) no clinical description, (5) no mutation identified in the list of genes, (6) review (Figure 1). A total of 269 articles (Table S4) were considered eligible for the literature review (77 case reports, 67 case series, 13 unique pedigrees, 4 pedigree series, 90 case–control studies, 3 comparative studies, 6 population-based studies, 5 clinical trials, 2 cohort studies, and 2 meta-analyses. Then, 143 publications (53.2%) concern only children, 93 (34.5%) only adults, and 33 (12.3%) adults and children.

The age of patients was comprised between 6 months and 69 years old. BMI *Z* score in children and adolescents were comprised between 1.56 and 18.8 standard deviation (SDS), whereas in adults, BMI values varied from 20.4 to 76.7 kg/m^2. In the group of obesity cases, 38.4% ($N = 376$) and 34% ($N = 334$) of mutations carriers are females and males, respectively (sex was not reported in 27.6% of carriers).

One-hundred thirty-six, 37, 34, 26, 26, 11, 5, and 5 publications focused on the *MC4R*, *LEP*, *POMC*, *LEPR*, *PCSK1*, *MC3R*, *MRAP2*, and *ADCY3* genes, respectively. The total number and type of mutations identified in each of the above mentioned genes are reported in Table 1. While 48% of mutations have been characterized in vitro, 22.5% have been characterized only with in silico prediction tools (Table 1). The functional characterization status was missing for 29.5% of the mutations.

Investigators used Sanger sequencing for 112 studies (41.6%), next generation sequencing (NGS) for 38 studies (14.1%), and 3 reports combined Sanger and NGS methods (1.1%). Twenty-five

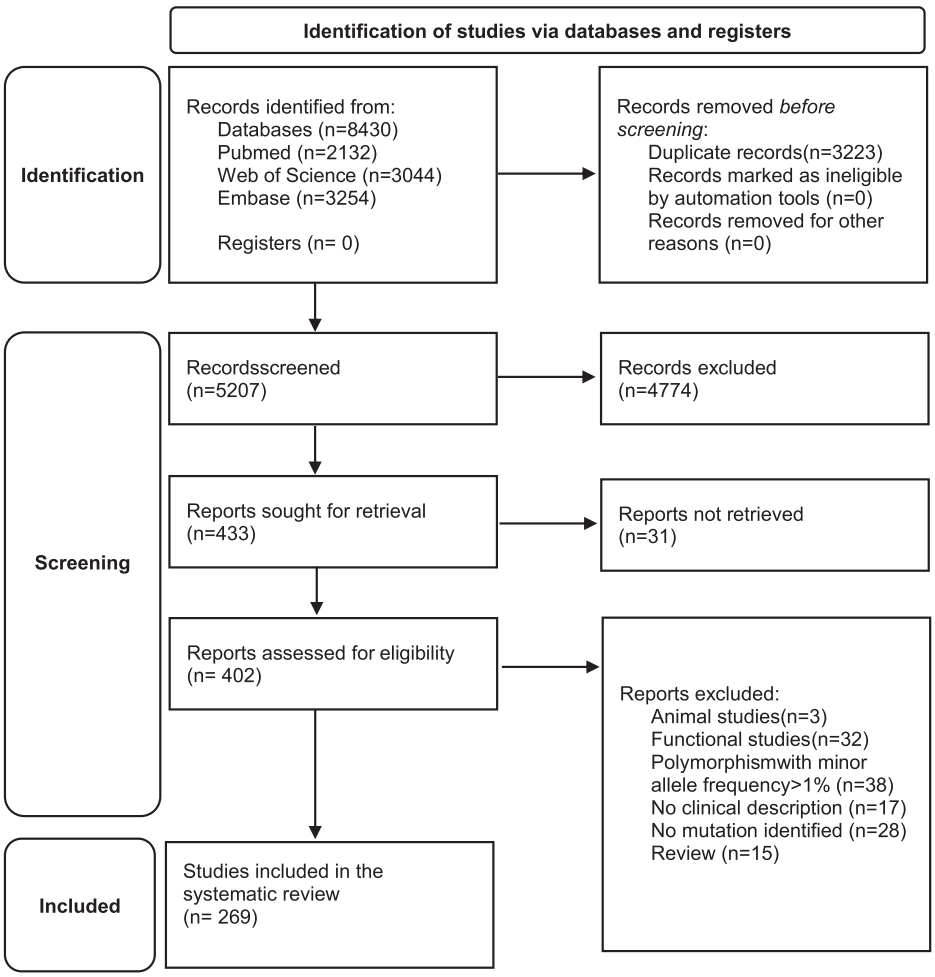

FIGURE 1 PRISMA 2020 flow diagram for the systematic review.

TABLE 1 Types and numbers of mutations identified in this systematic review for 8 monogenic obesity genes of the leptin melanocortin pathway.

Genes	Number of mutations	Missense	Frameshift	Deletion	Insertion	Non-sens	Splicing
LEP	24	14	6	1	0	2	0
LEPR	58	26	20	6 (2 entire gene deletion)	0	4	0
POMC	42	21	10	1 (deletion–insertion)	1	7	0
MC4R	198	144	30	6 (2 entire gene deletion)	1	17	0
MC3R	28	27	0	0	0	1	0
MRAP2	15	12	0	2	0	1	0
PCSK1	47	25	4	1		12	3
ADCY3	9	4	2	2	0	0	1

studies have used genotyping technology associated with Sanger sequencing (9.3%), whereas 12 reports used only genotyping without sequencing (4.5%). Genotyping technologies include single strand conformation polymorphism (SSCP) ($N = 13$), high resolution melt (HRM) ($N = 4$), denaturing high performance liquid chromatography (DHPLC) ($N = 9$), restriction fragment length polymorphism analysis (PCR-RLFP) ($N = 6$), TaqMan technology ($N = 4$), or amplification refractory mutation system (ARMS) ($N = 1$).

Comparative genomic hybridization (CGH) array was used in one study (0.4%) and epigenome-wide methylation analysis in another report (0.4%). Genetic methods used to identify mutations were not reported in 77 publications (28.6%).

Quality of studies included (at the exception of case reports) in this review is evaluated according to NHLBI study quality assessment tools and detailed in Table S5. Quality of studies was considered as poor for 43.5% ($N = 117$), fair for 44.6% ($N = 120$), and good for 11.9% ($N = 32$). The evaluation of risk of bias for studies with a comparator group is detailed in Table S6. The majority of studies with comparator groups are evaluated as "probably low risk" for the different risk of bias. The principal bias in the selected studies

is due to the lack of information regarding ethnicity or geographical origin of included patients.

3.2 | Leptin (*LEP*) gene

3.2.1 | Mutation spectrum and mode of inheritance

The first mutation was described in 1997[12] in 2 cousins of Pakistani origin with severe obesity; since then, 27 mutations have been described[39] with 133 homozygous and 20 heterozygous cases reported to date (Tables 1 and S7). Fifty seven percent ($n = 76/133$) of homozygous are from consanguineous families, with 28.6% of patients of Pakistani origin ($n = 38/133$) and 8.2% of Turkish origin ($n = 11/133$). The frequency of mutations in *LEP* varies from 1% to 5% in patients with obesity but is more frequent in patients with obesity from consanguineous populations (16.1% in Saeed et al.[40]). The mode of inheritance of monogenic obesity caused by LEP deficiency is habitually considered as autosomal recessive. However, the intermediate anthropometric phenotype observed in heterozygous mutation carriers suggests that the autosomal additive/semi-dominant inheritance model may also fit.

3.2.2 | Clinical presentation

Anthropometry

Children affected by congenital leptin deficiency present with a normal weight at birth (range 2820–3680 g) but show rapid weight gain in the first few months of life (during 6 first months in 71.4% of cases, $N = 20/28$ cases). BMI increases rapidly, with severe obesity frequently diagnosed in the first 2 years of life or before 6 years old.[41–44] Homozygous patients with *LEP* mutations suffer from severe obesity with a mean BMI of 8.45 SDS in children (min 2.46; max 21.9 SDS) and a mean BMI of 51.3 kg/m^2 in adults (min 37.8 kg/m^2; max 64.2 kg/m^2).[1]

Patients with congenital leptin deficiency show an excess of fat mass[12,45] (mean 52.4%, $N = 4$). Growth is normal or accelerated with obesity in a majority of cases,[46] but few cases of short stature have been reported.[13,47] Mean BMI of heterozygous adult patients reported in this review is 38.1 kg/m^2 (min 34/max 64.2 kg/m^2). In a Pakistani family (mutation c.398delG p.Gly133_VfsX14), 76% of heterozygous carriers were diagnosed with obesity, and they exhibited a higher percentage of fat mass at a given BMI than non-carrier counterparts.[48] Recently, heterozygous predicted loss-of-function variants in the *LEP* gene have been associated with higher BMI in a large-scale population-based exome sequencing study ($N = 640{,}000$).[49]

Energy intake and eating behaviors

Homozygous children are described as constantly hungry even after meals, with an aggressive food-seeking behavior.[13,40,47,50–53] This occurs rapidly after birth with crying babies, constantly looking for breastfeeding or milk.[44,50,54] Hyperphagia was confirmed with ad libidum test in a young boy of 2 years old with a caloric intake of 680 kCal in a rapid time.[54]

Puberty and fertility

Central hypogonadism represents the main endocrine manifestation of congenital leptin deficiency (mentioned in 67% of adults or pubescent adolescents $n = 6/9$), which can lead to pubertal delay,[41,45,55] primary or secondary amenorrhea,[13,45,47] or fertility troubles in adults. In males, hypogonadism and micropenis[56] can also be a manifestation of hypogonadotropic hypogonadism. Other endocrine manifestations have been rarely described, such as growth hormone (GH) deficiency[41] in one patient or central hypothyrodism[41,44,56] in three patients.

Cognitive features

Homozygous patients have normal neurologic development in a majority of cases, but three patients displayed delayed cognitive milestones.[41,57]

Infectious diseases

Homozygous patients report frequent infections (e.g., respiratory tract, ear, and urinary tract), particularly during childhood[44,50,54] (28.7%, $n = 43/150$). This sometimes results in childhood deaths by septic shock in siblings.[50]

Morphological characteristics

Patients with congenital leptin deficiency usually do not show morphologic abnormalities. Only one homozygous patient presented nail hypoplasia and clinodactyly.[47]

Chronic respiratory disease

A limited subset of patients with complete LEP deficiency suffer from asthma[42,44] (3%, $n = 4/150$), with an improvement observed after metreleptin treatment.[44]

3.2.3 | Biological characteristics

Metabolic profile

Patients with congenital leptin deficiency display very low levels (less than 2 ng/ml) or undetectable levels of circulating leptin despite high level of fat mass (median 0.19 ng/ml, min 0, max 83 ng/ml). Nevertheless, leptin levels can be normal because of biologically inactive leptin with defect of binding to its receptor[54,58] (mutation p.Asp100Tyr). Metabolic complications that are usually secondary to morbid obesity can be observed in homozygous patients such as T2D (1.5%, $N = 2$),[13,55] hyperinsulinemia (9%, $n = 12/133$, but 67% of pubescent adolescents and adults are hyperinsulinemic),[40,44,45,54,55,59] dyslipidemia[44] (4.5%, $n = 6/133$, but 55.5% of pubescent adolescents and adults are dyslipidemic),[13,41,44,47,56,60] and fatty liver (2.2%; $n = 3$).[43,56,61] Fatty liver was reported in children before 3 years old.[43,56]

Endocrinology

Central hypogonadism represents the main endocrine manifestation of congenital leptin deficiency (mentioned in 67% of adults or pubescent adolescents $n = 6/9$) with low follicle stimulating hormone [FSH], luteinizing hormone [LH], testosterone andestradiol). Concerning GH axis, low insulin growth factor 1 (IGF1) and insulin growth factor-binding protein (IGF1/IGFBP3) molar ratios were also reported in leptin-deficient patients.[46]

Hematology

On blood cell count, congenital leptin deficiency can be associated with reduced circulating CD4(+) T cells and impaired T cell proliferation and cytokine release.[33] One child shows regularly elevated white cell count without obvious signs of infection.[44] In some cases, no abnormalities are observed.[41,54]

3.2.4 | Radiological features

Low bone mass density has been described in two patients with congenital leptin deficiency.[45,55]

3.2.5 | Treatments

Patients with severe obesity secondary to congenital leptin deficiency usually show difficulties in controlling weight gain with ineffective conventional treatments (e.g., low-caloric diet, physical activity, and behavioral therapy), mainly due to intense hyperphagia. Bariatric surgery is not efficient in treating severe obesity secondary to congenital leptin deficiency, as rapid post-operative weight gain is observed after sleeve gastrectomy (SG).[47] A treatment with recombinant leptin (metreleptin) is available for patients with congenital leptin deficiency,[44,46,55,62] which not only permits substantial weight loss but is also associated with increased physical activity, reduced caloric intake, and beneficial changes in endocrine function (hypogonadism resolution,[55] thyroid improvement[33]) and immune regulation[33] (improvement of immunophenotype and T cell responsiveness). Treatment with recombinant leptin has been associated with an increase of the gray matter tissue concentration in the area involved in food intake of the brain (anterior cingulate gyrus [ACG], cerebellum, and inferior parietal lobule, areas involved in food intake),[63,64] highlighting the role of leptin in neurogenesis, neuronal growth, and viability.

3.3 | Leptin receptor gene (*LEPR*)

3.3.1 | Mutation spectrum and mode of inheritance

First described in 1998,[14] more than 50 mutations have been reported in the literature (Tables 1 and S8). The mode of inheritance of monogenic obesity caused by LEPR deficiency is autosomal recessive, and so is particularly frequent in consanguineous population.[57,59] While heterozygous mutation carriers have similar BMI values than homozygous wild-type participants,[49] they display a higher absolute percentage of fat mass.[15] Recently, heterozygous predicted loss-of-function variants in the *LEPR* gene have been associated with higher BMI in a large-scale population-based exome sequencing study ($N = 640{,}000$).[49] Heterozygous *LEPR* mutation carriers with obesity have been reported in literature,[65,66] but it is challenging to assess causality.

3.3.2 | Clinical presentation

Anthropometry

Homozygous carriers of *LEPR* mutations show normal birth weight with a rapid weight gain during the first years of life, leading to early-onset obesity.[14,67–72] Mean BMI is 9.9 SDS (min 4.48; max 26 SDS) in childhood and 52.6 kg/m^2 (min 39.9 kg/m^2; max 65.5 kg/m^2) in adulthood with excessive body fat.[14,57,59,68,71–73] Accelerated growth velocity, due to the severity of obesity, is usually observed.[74–76]

Energy intake and eating behavior

Patients exhibit severe hyperphagia since the first months of life, with abnormal compulsive food-seeking behavior.[14,59,67,69,77–80] Hyperphagia has been confirmed by ad libidum test, with a caloric consumption three times higher than controls.[15]

Puberty and fertility

Central hypogonadism is reported in 22.7% ($N = 22/97$) of homozygous carriers of mutations and is present in 65.6% ($N = 21/32$) of homozygous carriers older than 12 years old). As a result, homozygous carriers present absent or delayed puberty,[14,74,80] primary or secondary amenorrhea in girls,[81] or infertility.[82] A spontaneous pregnancy has been reported in a woman with a homozygous mutation of *LEPR*.[83]

Cognitive features

Mild developmental delays (language, motor function) have been reported in 7.2% ($N = 8/97$) of homozygous cases.[57,67,74,79] Rare cases of depression or anxiety are also reported.[72,84]

Infectious diseases

Recurrent infections are reported in 16.5% ($N = 16/97$) of homozygous carriers, particularly respiratory tract infections,[57,76,82,85] and recurrent diarrheas.[72,85] Infections may be less severe in males than in females.[82]

Morphological characteristics

Patients with congenital LEPR deficiency most often do not display morphologic abnormalities. However, some morphological particularities have been individually reported, such as round face and mild brachydactily[79] and almond-shaped eyes and tapering fingers.[68]

Chronic respiratory disease

Asthma and obstructive sleep apnea are reported in rare cases.[74,86]

Others symptoms

A diagnosis of acromegaly in a context of empty sella was made in one patient with LEPR deficiency (possibly the consequence of the LEPR deficiency on the GH regulation).[84]

3.3.3 | Biological characteristics

Metabolic profile

Leptin level is classically within normal range and correlated to BMI[15,57,67,87] but can be elevated (superior to 100 ng/ml[14,57,59,80,88]). In homozygous mutation carriers, mean leptin level is 92.1 ng/ml (min 10; max 670 ng/ml). Hyperinsulinemia[67,79,89] and T2D[65,74,84] are frequent complications of obesity secondary to *LEPR* mutations, which could be already present in infancy.[74,87] Dyslipidemia that starts sometimes in childhood has been documented in homozygous carriers of *LEPR* mutations, especially in patients who display severe obesity[67,87] and hepatic steatosis.[72,74]

Endocrinology

The main endocrine characteristics of homozygous patients are central hypogonadism with low LH and FSH and low estradiol or testosterone[14,74,82,88] (22.7% of homozygous cases [$N = 22/97$], 65.6% [$N = 21/32$] of homozygous carriers older than 12 years old). Central hypothyroidism with low T4 and inadequate TSH is also described in 4.1% of cases[14,67,68] ($N = 4/97$). GH deficiency is reported in 7.2% of cases[14,80] ($N = 7/97$). In contrast, no alteration of adrenal function was reported.

Hematology

Regarding blood cell phenotypes, one case reported low CD4+ T lymphocytes and increased CD8+ T lymphocytes that resulted in a low CD4/CD8 T-cell ratio and number NK (Natural Killer) lymphocytes higher than normal.[79]

3.3.4 | Radiological features

Increased bone mass density has been reported in one publication.[90]

3.3.5 | Treatments

Obesity due to *LEPR* mutations is resistant to lifestyle modification interventions. Bariatric surgery (SG,[72] gastric banding,[72] vertical ring gastroplasty,[80] or gastric bypass[83]) results in initial weight loss but is followed by rapid weight regain due to persistent hyperphagia.[72,80,83] MC4R agonist (setmelanotide) has demonstrated its efficiency in the treatment of patients with severe obesity due to homozygous *LEPR* mutations.[32,91] After 1 year of treatment, a mean percentage change in BMI of −13.1% was observed in treated patients with bi-allelic *LEPR* mutation, with a decrease of mean most hunger score of 43.7%.[32]

3.4 | Proopiomelanocortin (POMC)

3.4.1 | Mutation spectrum and mode of inheritance

Homozygous pathogenic mutations in the *POMC* gene lead to congenital POMC deficiency, characterized by severe early-onset obesity with central adrenal insufficiency, red hair, and pale skin in patients of European ancestry. First described in 1998,[16] 22 patients with POMC deficiency have been reported in the literature. More than 40 mutations have been described (Tables 1 and S9),which can be localized on POMC-derived peptides alpha and beta-MSH.[92] The mode of inheritance of monogenic obesity caused by *POMC* mutations is autosomal additive/semi-dominant; that is to say, a more severe phenotype in homozygous patients is observed compared with heterozygous.[69,93–95] Only 23% of cases ($n = 5/22$) are from consanguineous families.

3.4.2 | Clinical presentation

Anthropometry

Patients who suffer from congenital POMC deficiency show normal birth weight, with a rapid weight gain during the first months of life.[96–99] Mean BMI of children with homozygous mutation is 5.8SDS[17,99,100] (min 1.2 SDS; max 14.3 SDS). In adults, the BMI of homozygous mutation carriers is superior to 50 kg/m^2[91,101] (mean 50.8 kg/m^2, min 49.8; max 52.8 kg/m^2). In patients with heterozygous mutations of POMC, BMI varies between 2.5 and 4.9 SDS (mean 3.58 SDS)[66,69,93,95] in children and between 32 and 70 kg/m^2 in adults (mean 47.8 kg/m^2).[69,102–105] Accelerated growth velocity is observed with tall stature in prepubertal children.[94,98,106–108]

Energy intake and eating behaviors

Early and severe hyperphagia is reported in homozygous[17,98,108,109] (45.5%, $n = 10/22$) and less often in heterozygous mutation carriers of POMC[66,69,94,106] (12.5%, $n = 6/48$). In one case (homozygous mutation carrier), no appetite increase was noted.[107]

Puberty and fertility

Delayed puberty has been reported in two homozygous carriers of *POMC* mutations[101,110] (9%, $n = 2/22$). In the majority of cases, puberty progresses normally. No alteration in fertility has been reported.

Cognitive features

Cognitive and motor delay have been reported in 27.3% ($n = 6/22$) of patients with homozygous mutations.[100,101,108–111] Autism associated with macrocephaly has been reported in one patient with a heterozygous *POMC* mutation.[69]

Infectious diseases

No recurrent infection is observed in cases with *POMC* mutations. Only one septic shock has been reported in a case with *POMC* mutations[100] and recurrent respiratory tract infections in another case.[109]

Morphological characteristics

The main phenotypical characteristic of patients with homozygous *POMC* mutation is red hair coloration and pale skin[16,97–101,111] reported in 41% of cases ($n = 9/22$). Nevertheless, this feature is more visible in populations of European ancestry and is not observed in patients with dark or brown skin, to the exception of red hair roots (18.2%, $n = 4/22$).[17,101,108,110]

Others symptoms

Depression is mentioned in two cases[69,104] with heterozygous mutations.

3.4.3 | Biological characteristics

Metabolic profile

Leptin levels are in accordance with BMI and body fat mass.[93,103,106,112] Metabolic complications of severe obesity are frequently present during childhood, such as hyperinsulinemia[102,106,112] and non-alcoholic steatohepatitis.[109,110] Dyslipidemia are rarely described.[113]

Endocrinology

Common endocrine manifestation of complete POMC deficiency is adrenal insufficiency (by ACTH deficiency) described in 82% of cases reported ($n = 18/22$), mostly revealed by neonatal hypoglycemia and prolonged jaundice.[16,96–98,101,107,109–111,114] Central hypothyroidism has been reported in 22.7% ($n = 5/22$) of cases.[96,109,110] Central hypogonadism has been reported in two cases (9%).[97,101] GH deficiency was described in one patient with compound heterozygous mutations.[110] In heterozygous carriers, adrenal and thyroid axis are normal.[93,102,106] Type 1 diabetes has been reported in 3 patients with homozygous or compound heterozygous mutations[99,107,110] (13.6%).

3.4.4 | Radiological features

Patients with POMC deficiency present an excess of body fat.[94,115]

3.4.5 | Treatments

Obesity secondary to POMC mutation is difficult to treat with dietary measures and physical activity, mainly due to intense hyperphagia. Bariatric surgery with Roux-en-X gastric bypass and SG results in similar weight loss to non-mutated carriers.[69,116]

POMC complete deficiency in homozygous patients is an indication for setmelanotide treatment, which has demonstrated its efficiency in weight loss and satiety control[32] with a BMI reduction of −27.8% after 1 year of treatment and a concomitant reduction of the hunger score.

3.5 | PCSK1

3.5.1 | Mutation spectrum and mode of inheritance

Congenital PCSK1 deficiency is characterized by neonatal diarrhea, obesity, alteration of glucose metabolism, and diverse endocrine deficiencies. First described in 1997,[18] 34 cases of congenital PCSK1 deficiency (homozygous or compound heterozygous mutation carriers) and more than 40 mutations have been reported (Table 1 and S10) (of which, 15 mutations are reported only in heterozygous patients). Congenital PCSK1 deficiency is frequent in the consanguineous population (63% of cases, $n = 21/34$), with 36.4% from Turkish families ($n = 9/34$). Heterozygous carriers of mutation have an increased risk of obesity, meaning that monogenic obesity caused by *PCSK1* mutations follows an autosomal additive/semi-dominant inheritance.

3.5.2 | Clinical presentation

Anthropometry

Affected homozygous patients are frequently born with normal birth weight,[117–120] but in some cases, birth weight is superior to 4 kg.[121,122] Weight gain only appears from 2 years of life and onward, probably because of neonatal diarrhea. The extent of obesity is variable in children (63% of children have a BMI > 2SDS before 3 years old, 80% after 3 years old), and obesity is usually severe in adults. In homozygous children, the mean BMI is 2.24 SDS (min −5.63; max 10.3), and after 3 years old, mean BMI is 3.12 SDS (min − 2.1; max 10.3). In homozygous adults, the mean BMI is 39.9 kg/m^2 (min 38.3; max 41.5 kg/m^2) ($N = 2$). In heterozygous adults, the mean BMI is 46.3 kg/m^2 (min 31.2; max 50.75 kg/m^2) ($N = 6$). In contrast with accelerated growth usually observed in cases with obesity, slower growth is observed in these children with height frequently under the mean for age (mean for height in children −1 SDS, min −2.8; max 0.79 SDS). Some cases of growth delay have been reported.[119,121,123]

Energy intake and eating behaviors

Hyperphagia is described in some cases of *PCSK1* mutation carriers (3 homozygous [9%], 1 heterozygous).[113,120,124,125]

Digestive function

Neonatal diarrhea secondary to small-intestinal absorptive dysfunction[126] is one of the main symptoms of patients with complete PSCK1 deficiency (homozygous mutation carriers)[117,119,121,122,127,128] and is

present in 82% of cases ($n = 28/34$), requiring parenteral nutrition in a majority of cases. Heterozygous carriers of mutations do not present intestinal dysfunction.

Puberty and fertility

Only few data have been reported in patients with PCSK1 deficiency regarding puberty. Three cases with micropenis[121,122,129] (8.8%) and 1 with cryptorchism[123] have been described.

In heterozygous mutation carriers, an adolescent girl with polycystic ovarian syndrome has been reported in the context of metabolic syndrome.[130] A girl with obesity and precocious puberty[69] has also been described.

Cognitive features

To the exception of an heterozygous patient with attention deficit hyperactivity disorder (ADHD),[69] no specific cognitive feature has been reported in *PCSK1* mutation carriers.

Morphological characteristics

Morphologic features have been reported in one homozygous patient: frontal bossing, midface hypoplasia, depressed nasal bridge, macroglossia, and bilateral clinodactyly of the fourth and fifth toes.[122] Otherwise, no specific morphologic feature has been reported in *PCSK1* mutation carriers.

3.5.3 | Biological characteristics

Metabolic profile

Hypoglycemia (neonatal[120,122] or post-prandial[18,119,127]) are present in 38.2% of cases of PCSK1 deficiency. This is secondary to altered cleavage of proinsulin and its elevated circulating level (mean level 561.8 pmol/L, min 45.8; max 1255 pmol/L). One homozygous patient presents with T2D at 14 years old.[117]

Endocrinology

Multiple endocrinological deficiencies are described in patients with PCSK1 deficiency. Polyuria and polydipsia are reported in 58.9% of cases ($n = 20/34$), with insipidus diabetes confirmed in 35.3% of cases ($n = 12/34$).[119,121,122,129,131] Central hypoadrenalism is reported in 47% of cases ($n = 16/34$).[119,121,122,125,126,131–133] Central hypothyroidism is reported in 44% of cases ($n = 15/34$).[119,122,125,128,129,131,132] GH deficiency is reported in 26.4% of cases ($n = 9/34$).[119,121,122] Hypogonadotropic hypogonadism is reported in 11.8% ($n = 4/34$).[18,122,123,129] Heterozygous carriers of mutations do not present any endocrine deficiency.

3.5.4 | Radiological features

Anterior and posterior pituitary gland morphology assessed by magnetic resonance imaging (MRI) is normal.[122]

3.5.5 | Treatments

The principal treatment is correction of deshydratation and parenteral nutrition in case of severe neonatal diarrhea (reported in 52.9% of cases, $n = 18/34$).[119,121,125,126,128] Hormonal supplementations are necessary for multiple pituitary deficiencies (levothyroxine, hydrocortisone, GH, desmopressin). For obesity, conventional treatments are dietary measures, physical activity, and psychological therapy. Bariatric surgery (Roux-en-Y bypass [RYGB]) shows the same weight loss response in patients with PSCK1 deficiency than controls after 2 years.[116] Setmelanotide treatment over 1 year resulted in weight loss of 2.4% in one homozygous child.[134]

3.6 | MC3R

3.6.1 | Mutation spectrum and mode of inheritance

To date, 13 mutations have been reported in children and adults with overweight and obesity (26 heterozygous and 1 homozygous[135] [Table 1 and S11]), with a functional characterization of partial or complete loss of function (LOF) for 100% of them. A recent meta-analysis showed a 3.1-fold increased risk of obesity in heterozygous children and adults who carry rare coding partial/complete LOF mutations in *MC3R*.[37] More recently, a homozygous LOF mutation was described in a 40-year-old man with a BMI of 40.4 kg/m^2.[135] These data suggest an autosomal additive/semi-dominant mode of inheritance of monogenic obesity conferred by *MC3R* mutations.

3.6.2 | Clinical presentation

Anthropometry

In children, the mean BMI in heterozygous *MC3R* mutation carriers is 4.9 SDS (min 1.8; max 16.7 SDS), and in adults, mean BMI is 42.5 kg/m^2 (min 33.1; max 52 kg/m^2). Early-onset obesity (before 6 years old) is reported in 71% of cases ($n = 10/14$). Few data are available for growth (height reported in 5 cases [11.4%], mean 0.25 SDS, min −2.95 SDS, max 2.75 SDS).[135–137] An adult man who carried a homozygous loss-of-function mutation p.G240W in *MC3R* displayed a short stature (−2.95 SDS).[135] In the same study, a gene mutation burden score for *MC3R* was associated with shorter childhood and adult stature and lower sitting height. P.F45S and p.R220S mutations are associated with reduced growth.

Energy intake and eating behaviors

Eating behavior is reported in 7 patients (16%). Hyperphagia is present in 3 patients (42.8%),[69,136] and normal food intake in 4 patients (57.1%).[20,138]

Puberty and fertility

Few data are available regarding puberty and fertility. One heterozygous case reported irregular menses (secondary to polycystic ovarian

syndrome).[20] A homozygous man has delayed puberty (at 20 years old).[135] Moreover, females carrying *MC3R* rare mutations display a 4.7-month delay in age at menarche compared with non-carriers (delayed is more important for female with p.F45S heterozygous mutation with 5.16-month delay).[135]

Cognitive features

The need for special education has been reported in only one case.[87]

3.6.3 | Biological characteristics

Metabolic profile

Altered glucose metabolism is reported in 7 patients (13.6%, whom 4 with T2D [9%],[20,135,138,139] and 3 with insulin resistance [6.8%][136–138,140]). Hypercholesterolemia is only described in one 15-year-old boy.[137] Leptin level is correlated with BMI when measured.[20,139]

Endocrinology

One case of Addison disease[69] and one case of auto-immune thyroiditis[138] were reported in heterozygous patients. One homozygous mutation carrier displayed low IGF1 level, and a gene mutation burden score for *MC3R* was associated with lower IGF1 level.[135]

3.6.4 | Radiological features

Mean fat mass is 45.9% (median 44%; min 35.8%; max 71%). Accelerated bone age is reported in two cases.[136]

3.6.5 | Treatments

No specific treatment is available. Lifestyle modification (dietary habits and physical activity) remains the main intervention for *MC3R* mutation-induced obesity.

3.7 | MC4R

3.7.1 | Mutation spectrum and mode of inheritance

Since the first reports in 1998,[21,22] about 200 *MC4R* mutations have been described in association with obesity in more than 1000 patients ($N = 1098$) (Tables 1 and S12). Mode of inheritance was initially proposed as autosomal dominant with co-dominance effect, that is to say, a more severe phenotype in homozygous or compound heterozygous mutation carriers.[141] However, the description of patterns of incomplete penetrance of obesity in heterozygous *MC4R* carriers suggests that an autosomal additive/semi dominant mode of inheritance of obesity is more adequate.[40,142,143] The frequency of *MC4R* mutations is variable according the geographical origin of patients, from 0.5% to 5.8%.[141,144] In Europe, the frequency of *MC4R* pathogenic mutations in Caucasian patients with obesity was estimated at 1.72%, with a penetrance of 40% in MC4R-deficient adults aged >52 years, 60% in 18- to 52-year-old adults, and 79% in children.[142] Nevertheless, according to geographical origin, prevalence can vary in European population, with 1.9% in German,[145] 0.2% in Greek,[143] and under 0.5% in Italian populations.[146] In North American, the frequency of *MC4R* mutation in a large cohort of American Caucasian adults is 2.25%[147] and higher in African American (2.6%[148]). In parallel, a high frequency of homozygous *MC4R* mutations is observed in Pakistani population (3.2%), secondary to the high rate of consanguineous unions in this population.[40] In Asian population, prevalence of MC4R mutation is estimated to 1.3%,[149] but *MC4R* mutations are rarely reported in Japanese population.[150,151] Private mutations have been identified in Pima Indians, not found in other population.[152]

3.7.2 | Clinical presentation

Anthropometry

Bi-allelic MC4R mutation carriers (homozygous or compound heterozygous) display early-onset severe obesity: children's mean BMI is 9.8 SDS (min 5.2; max 24.4 SDS), and in adults, mean BMI is 51.2 kg/m^2 (min 40.3; max 71 kg/m^2). In heterozygous carriers, degree of severity of obesity is variable: children mean BMI is 5.5 SDS (min 2.2; max 15.9), and in adults, mean BMI is 42.7 kg/m^2 (min 27.8; max 62 kg/m^2). In children, BMI of heterozygous mutation carriers is similar than wild-type children with obesity.[153,154] In contrast, in adults, heterozygous carriers' BMI is superior than wild type patients with obesity.[153,155] A gender effect has been demonstrated with an excess of BMI superior to 9.5 kg/m^2 in middle age women and 4 kg/m^2 in middle-aged men compared with wild type patients.[142,156] When information is available ($n = 104$), mean age of obesity onset is 1.2 years old (min 0.25; max 10) in homozygous and 3.8 years old (min 0.16; max 18) in heterozygous mutation carriers. Children with *MC4R* mutations show accelerated growth (mean height SDS in heterozygous patients: 1.86 SDS [min −2; max 4.62 SDS]; in homozygous patients: 2.58 SDS [min 1.37; max 3.41]) ($n = 27$). Accelerated growth during childhood has been confirmed in *MC4R* mutation carriers compared with obese controls in independent studies.[144,157–159] Adult final height is within normal values: mean height −0.38 SDS (min −1.66; max 1.38 SDS) (in homozygous mean −0.145 SDS [$n = 2$], in heterozygous mean −0.348 [$n = 8$]). Martinelli et al. show that final height in MC4R deficient patients is greater than in controls.[159]

Energy intake and eating behaviors

Hyperphagia is a common characteristic of patients with *MC4R* mutations. When described ($n = 175$), hyperphagia is present in 95% of cases (100% in homozygous patients $n = 14/14$, 95.1% in heterozygous patients [$n = 153/161$]). This has been confirmed with an ad libitum meal 3 times superior for children with *MC4R mutations* (heterozygous [$n = 23$] and homozygous $n = 6$) than their

non-affected siblings, with a less hyperphagic comportment observed in older children (11–15 years old).[157] Patients with MC4R deficiency present an increased preference for high-fat, but a significantly reduced preference for high-sucrose food, compared with lean and weight-matched controls.[160] A meta-analysis of 49 *MC4R* mutation carriers and 1471 non-carriers with obesity did not detect an association between LOF mutations and binge-eating disorder.[36]

Puberty and fertility

No specific puberty and fertility phenotype was observed in patients with *MC4R* mutations, to the exception of three cases with precocious puberty[148,161,162] and one case with precocious pubarche.[136] In contrast, one case of delayed puberty secondary to hypogonadotropic hypogonadism has been reported in one patient with a homozygous *MC4R* mutation.[163] Another case of hypogonadism is reported in a compound heterozygous man.[69]

Cognitive features

Data about cognitive function are reported in 30 cases; 9 of them (30%) reported mild disability[69,84,148,151,164–166] (e.g., speech delay, motor retardation, and mild mental retardation).

ADHDs are described in 3 children with heterozygous MC4R mutations.[167–169] ADHD symptoms have been observed in 80% of *MC4R*p.C271R homozygous mutation carriers.[167] Autism is described in 2 patients (one with a homozygous MC4R mutation).[69]

Morphological characteristics

Macrocephaly is described in 2 patients.[69,170]

Acanthosis nigricans is frequently described in *MC4R* mutation carriers. It is reported in 20 patients, 6 with bi-allelic mutations (31.6%), and in 9 children (45%).[148,161,162,167,171–176] The youngest patient with *acanthosis nigricans* is a 3-year-old girl.[177]

Chronic respiratory disease

Asthma ($n = 7$, 3 homozygous and 4 heterozygous mutations carriers),[65,148,169,176,178,179] obstructive sleep apnea ($n = 5$, homozygous children),[99,149,176,178,179] and pulmonary hypertension ($n = 2$, homozygous children[167,179]) are sometimes reported.

Cardiovascular disease

High blood pressure has been reported in 17 cases (6 homozygous and 11 heterozygous, 8 children whom 5 are homozygous [62.5%], youngest is a 23-month girl with homozygous mutations). MC4R deficiency (with heterozygous or homozygous LOF mutations) has been associated with decreased systolic blood pressure before the age of 20.[152] Greenfield et al. evidenced that heterozygous carriers of LOF MC4R mutation present significantly lower blood-pressure level than obese controls.[180] Lower resting muscle sympathetic nerve activity, diastolic blood pressure, and heart rate have been observed in heterozygous *MC4R* mutation carriers,[181] suggesting an important role of MC4R in the regulation of sympathetic nerve activity in humans.

3.7.3 | Biological characteristics

Metabolic profile

Data about glucose metabolism are available for 148 patients, including 89 children. Fasting hyperinsulinemia is observed in 41.2% ($n = 61/148$) of mutation carriers; 29.5% are homozygous ($n = 18$). In children, hyperinsulinemia is reported in 55% of carriers ($n = 49/89$), whom 32% ($n = 16/49$) are homozygous (the youngest children is a 7-month girl, homozygous).[40] In adults, hyperinsulinemia is reported in 20.3% of mutation carriers ($n = 12/59$), whom 16.7% ($n = 2/12$) are homozygous.

T2D is reported in 16.9% of carriers ($n = 25/148$). In children, T2D is reported in 6 patients (6.7%), whom 50% are homozygous carriers ($n = 3/6$) (youngest is a 7-year-old girl).[148] In adults, T2D is reported in 37.2% of carriers ($n = 22/59$), whom 9% are homozygous ($N = 2/22$).

In total, 58% of mutation carriers ($n = 86/148$) present an alteration of glucose metabolism (hyperinsulinemia or T2D), 61.8% of children ($n = 55/89$), and 57.6% of adults ($n = 34/59$). In the Mexican population, the *MC4R* p.Ile269Asn founder mutation is associated with T2D, with a genotype by sex interaction (association is restricted to men).[182]

Data about lipid profile are available for 60 patients (37 children). Dyslipidemia is reported in 33% of mutation carriers ($n = 20/60$) (32% of children [$n = 12/37$] and 34.8% of adults [$n = 8/23$]).

Non-alcoholic hepatitis steatosis is also reported in some patients ($n = 20$).[66,136,162,163,183–185]

Leptin level is adapted to BMI and fat mass (mean 43 ng/L, median 39, min 3.7, max 100 ng/ml; $n = 60$) with a mean leptin/BMI ratio of 106%.

Endocrinology

MC4R mutation carriers do not display a specific endocrine profile. One case of GH deficiency,[164] 2 cases of hypogonadism,[69,163] 2 with hypothyroidism,[84,172] 1 with adrenal insufficiency (in association with hypothyroidism),[172] and 1 with hypercorticism[124] have been reported among mutation carriers.

Martinelli et al. show that mean GH concentrations were significantly higher in MC4R-deficient patients than in the obese control subjects, with no difference observed regarding IGF1 and IGFBP3 levels.[159]

3.7.4 | Radiological features

The mean fat mass percentage in *MC4R* mutation carriers is 43.5% (min 14.3; max 74.4%; $N = 26$). In children, the mean percentage of fat mass is 39.7% ($n = 15$), 41.6% in homozygous children ($n = 3$), and 39.19% in heterozygous children ($n = 12$). In adults, the mean percentage of fat mass is 48.9% (48.8% in heterozygous carriers [all female] $n = 9$; 49.6% in a homozygous male carrier $n = 1$). Others have confirmed this with a higher percentage of fat mass in homozygous mutation carriers[157] and by a positive association between fat mass and *MC4R* LOF mutations.[186]

Bone age advancement is reported in 12 children (mean 2.75 years old, min 0.9 years old; max 5.9years old; mean 2.38 years

old in heterozygous [$n = 10$]; mean 4.45 years old in homozygous children [$n = 2$])[136,161,170,177,187,188] and confirmed by Martinelli et al. in a group of 153 MC4R deficient patients.[159]

Greater bone mineral density has been described in a few cases[151,189] and confirmed by Wade et al. with 84% of MC4R deficiency patients with a bone mineral density superior to 1 *Z* score.[186]

3.7.5 | Treatments

The first line of treatment in patients with *MC4R* mutations is to decrease caloric food intake and increase physical activity.[190] In children with deleterious *MC4R* mutations, lifestyle intervention (based on physical exercise, nutrition education, and behavior therapy) is associated with a similar reduction of overweight after 1 year but with a failure to maintain this weight loss 2 years later compared with wild type patients with obesity.[190] Bariatric surgery in MC4R mutation carriers results in weight loss comparable with controls in the short-term, but weight regain is frequently observed in the long-term.[176,183,191–195] A case control study has shown that weight loss was greater with RYGB in comparison with SG, but long-term weight regain has been reported, highlighting the need for a pro-active lifelong management.[191] Response to bariatric surgery is reduced in homozygous *MC4R* mutation carriers compared with heterozygous.[196,197] Three mutations (p.V95I, p.I137T, and p.L250Q) have been associated with reduced weight loss after bariatric surgery in heterozygous carriers.[193] In *MC4R* heterozygous carriers, setmelanotide treatment leads to modest, but significant weight loss (on average 0.6 kg/week), without increasing heart rate or blood pressure.[31] Daily Glucagon Like Peptide 1 (GLP-1) analogs (liraglutide) lead to comparable weight loss after 16 weeks of treatment in patient with pathogenic *MC4R* mutations and patients with common obesity and also improve glycemia.[198,199]

3.8 | MRAP2

3.8.1 | Mutation spectrum and mode of inheritance

Heterozygous mutations in the Melanocortin 2 receptor accessory protein 2 (*MRAP2*) gene have been first described in 2013 in patients with obesity.[24] Since then, 15 mutations have been reported (Tables 1 and S13). Its mode of inheritance on obesity is autosomal dominant with incomplete penetrance. No homozygous mutation carrier has been reported to date.

3.8.2 | Clinical presentation

Anthropometry

The degree of obesity is variable with a mean BMI of 5.5 SDS in children ($N = 7$) (min 3.3; max 8.7 SDS) ($N = 7$) and in adults ($N = 11$) a mean BMI of 35.9 kg/m^2 (min 23.9 [in a patient after gastric restriction],[105] max 49.6 kg/m^2) with an onset during childhood.[23] Early onset obesity (<3 years old) is reported in children.[104,200] No information is available regarding the growth or final height in these patients.

Energy intake and eating behaviors

Overeating, snaking, and bulimia are reported in some patients (4 adults and 2 children, 33.3% of cases).[23]

Cognitive features

One patient is described with intellectual disability and a Prader–Willi like syndrome.[201]

Cardiovascular disease

High blood pressure is reported in 38.9% of mutation carriers ($N = 7/18$), of whom 63.6% of adults ($N = 7/11$).[23]

3.8.3 | Biological characteristics

Metabolic profile

T2D is reported in 3 adult cases (25%) ($N = 3/12$ patients with biological data reported) and hyperinsulinemia in 7 patients (58.3%) ($N = 7/12$; 4 adults and 3 children).[23,105]

Hypercholesterolemia (total cholesterol >2 g/L) is present in 70% of cases ($N = 7/10$ patients with biological data reported), hypertriglyceridemia (total TG > 1.5 g/L) in 50% of cases ($N = 5/10$).[23,104]

Endocrinology

No dysfunction of the hypothalamic–pituitary–adrenal axis has been identified in mutation carriers.[23]

3.8.4 | Radiological features

Percentage of body fat is reported in 2 patients (mean 38.2%).[105]

3.9 | ADCY3

3.9.1 | Mutation spectrum and mode of inheritance

Mutations in *ADCY3* confer severe obesity and were first described in 2018.[25,26] To date, only 7 mutations in 194 patients (15 homozygous and 179 heterozygous) have been described in the literature (Tables 1 and S14). The mode of transmission of monogenic obesity caused by *ADCY3* mutations is autosomal recessive (the autosomal additive model is excluded in analyses), despite the fact that rare cases of heterozygous patients with obesity have been reported.[105,202]

3.9.2 | Clinical presentation

3.9.3 | Anthropometry

In homozygous carriers, the mean BMI in children is 5.5 SDS (median 6.5; min 3.5; max 6.7). Adult homozygous carriers of the mutation c.2433-1G>A ($N = 7$) had a 7.3 kg/m^2 higher BMI.[26] In heterozygous carriers, only one child is reported with a BMI of 4.8 SDS,[202] and 7 adults are reported with a mean BMI of 36.5 kg/m^2 (median 37.4; min 23; max 48 kg/m^2). Data about growth are reported only in 4 homozygous children with a mean height SDS of 2.41 SDS (min −2.21; max 5.29 SDS).[25]

Puberty and fertility

Amenorrhea is reported in a 15-year-old girl.[57]

Cognitive features

Slight to moderate intellectual disability is reported in 5 children with homozygous mutations (33.3%, $N = 5/15$).

Others symptoms

Anosmia is reported in 6 homozygous children (40%, $N = 6/15$). Asthma and depression are reported in one heterozygous carrier.[202]

3.9.4 | Biological characteristics

Metabolic profile

T2D is observed in 3 of 7 homozygous mutation carriersc.2433-1G>A identified in the Greenlandic cohort.[26] The association is still significant after adjustment with BMI. In parallel, the same team shows an enrichment of rare *ADCY3* loss-of-function variants among T2D patients in trans-ethnic cohorts.[26] Fasting insulin level is normal in homozygous children.[25,57] Leptin level is adapted to BMI[25,57] (mean 20 ng/ml; min 11; max 30 ng/ml).

Endocrinology

Cortisol level is within normal values in homozygous carriers.[25,57]

3.9.5 | Radiological features

In 7 homozygous carriers of the mutation c.2433-1G>A, the percentage of body fat is 8.1% points higher than controls.[26]

4 | DISCUSSION

4.1 | Summary of the review

This is the first systematic review that synthesizes clinical, biological, and radiological features related to mutations in eight genes from the leptin-melanocortin pathway (Table 2). Hyperphagia is the main symptom of mutation carriers and is associated with the development of obesity, to a few exceptions. Endocrine, immune, digestive, morphologic, and respiratory manifestations are frequently observed, depending on the gene mutated and the mode of inheritance.

4.2 | Lessons of the review

Clinical characteristics related to mutations in monogenic genes from the leptin-melanocortin pathway can be divided into three categories: obligatory symptoms (present in all mutation carriers), non-obligatory symptoms (present in a subset of mutation carriers), and unique observations (only one case or one pedigree reported in literature). Several explanations can be proposed for non-obligatory phenotypes: variable environmental exposures,[142] age-dependence (e.g., no manifestation of hypogonadotropic hypogonadism reported in cases of *LEP* or *LEPR* mutations in pre-pubertal girls), mutation functional consequences (e.g., increased leptin level observed in case of mutation p.Asp100Tyr in *LEP* gene[52]), epigenetic modifications,[203] transgenerational gene amplifications,[204] and modifying genes.[205] In contrast, it is very challenging to distinguish between coincidence and causality for unique clinical observations in monogenic mutation carriers. As most of homozygous mutation carriers are from consanguineous unions, these unique observations are likely to be secondary to other autosomal recessive mutations or chromosomal abnormalities.[206] Therefore, one may not consider unique observations as relevant in clinical practice unless it is confirmed in independent reports.[207] In addition, some of the "non mandatory symptoms" may be a direct consequence of the genetic defect but also an indirect consequence/comorbidity of severe obesity (e.g., asthma or ADHD in *MC4R* mutation carriers).

This study highlights the diversity of symptoms associated with gene mutations from leptin-melanocortin pathway, on top of the typical hyperphagic obesity phenotype. Assessing these symptoms in routine clinical practice may guide the decision to perform a genetic test.

Genes from the leptin-melanocortin pathway are generally referred as non-syndromic monogenic obesity genes. The classical separation between syndromic and non-syndromic obesity is mainly based on the presence of neurodevelopmental disorders, dysmorphic features, and organ-specific abnormalities in mutation carriers. However, a genetic syndrome is defined as a collection of signs and symptoms known to appear together frequently.[208] This study shows that mutation carriers, especially homozygotes, show a spectrum of clinical and biological manifestations that could be qualified as syndromic (e.g., PCSK1 deficiency with neonatal diarrhea, multiple endocrine deficiency and obesity, POMC deficiency with obesity, adrenal insufficiency, and red hair), as recently highlighted in literature.[209] So, the term "monogenic obesity" has been chosen to describe Mendelian forms of obesity due to mutations in the leptin melanocortin pathway, in opposition to syndromic obesity with neurodevelopmental disorders.

TABLE 2 Summary of mandatory and non-mandatory clinical, biological, and radiological phenotypes of patients with mutations in 8 monogenic obesity genes of the leptin-melanocortin pathway.

Gene **Mode of inheritance**	***LEP*** **AR**	***LEPR*** **AR**	***MC4R*** **AA**	***MC3R*** **AD**	***POMC*** **AA**	***ADCY3*** **AR**	***MRAP2*** **AD**	***PCSK1*** **AA**
Mandatory phenotypes								
Auxological								
BMI	Severe early onset obesity (>3 SDS)	Severe early onset obesity (>3 SDS)	Early onset obesity	Early onset obesity (variable severity)	Severe early onset obesity (>3 SDS)	Severe early onset obesity (>3 *z* scores)	Obesity during childhood	Early onset obesity (variable severity)
Growth	Normal		Accelerated, normal adult final height	Variable	Normal (accelerated growth velocity)	Normal		No accelerated growth
Fat mass/Lean mass	Fat mass excess	Fat mass excess	Fat mass excess	Fat mass excess	Fat mass excess	Fat mass excess		
Eating behavior	Intense hyperphagia	Intense hyperphagia	Hyperphagia	Reduced, normal, hyperphagia possible	Intense hyperphagia	Hyperphagia	Overeating snacking	/
Digestive function	/	/	/		/	/		Severe neonatal diarrhea
Puberty/ fertility	Delayed puberty, primary amenorrhea, micropenile	Delayed puberty, primary amenorrhea, micropenile	/	Delayed puberty possible	/	Amenorrhea		
Cognitive features	Normal	Normal	/	/	Developmental delay (cognitive and/or motor)	Slight to moderate cognitive impairment possible		
Immune function	Recurrent infection (respiratory tract, ear, urinary)	Recurrent infection (respiratory tract)	/	/	/	/		
Morphological features	/		/	/	Red hair, pale skin frequent	/		
Others symptoms			/	/		Anosmia	HTA	
Biological:				/				
Leptin	Low (<2 ng/ml)	Leptin within normal range	Normal		Normal	Normal		

TABLE 2 (Continued)

Gene Mode of inheritance	*LEP* AR	*LEPR* AR	*MC4R* AA	*MC3R* AD	*POMC* AA	*ADCY3* AR	*MRAP2* AD	*PCSK1* AA
Metabolic syndrome	Associated with severity of obesity	Hyperinsulinemia	Hyperinsulinemia, type 2 diabetes, fatty liver		Hyperinsulinemia Fatty liver	Higher frequency of type 2 diabetes	Hyperinsulinemia, type 2 diabetes Hypercholesterolemia, hypertriglyceridemia	Elevated pro-insulin (>3 fold normal value) Hypoglycemia
Endocrine	Hypogonadotropic hypogonadism	Hypogonadotropic hypogonadism			Central adrenal insufficiency (ACTH deficiency) Central hypothyroidism possible		/	Frequent: PUPD, insipidus diabetes Central adrenal insufficiency Central hypothyroidism GH deficiency
Immune	Low LT4							
Paraclinic								
Bone age	/		Bone age advancement		/			
Bone densitometry	Osteopenia		Greater bone mass					
Non mandatory phenotypes								
Clinical	Short stature Developmental delay Asthma	Developmental delay	Asthma, obstructive apnea Mild intellectual disability ADHD, autism		Dark hair (red roots) Depression Autism Macrocephaly		Prader Willi like syndrome	Normal BMI (young age)
Biological							/	
Leptin	Elevated (biologically inactive leptin)	Elevated (> 30 ng/ml)			/			
Endocrine	GH deficiency Central hypothyroidism	GH deficiency Central hypothyroidism			GH deficiency			
Specific treatment	Recombinant leptin (metreleptin)	MC4R agonist (setmelanotide)	MC4R agonist (setmelanotide)		MC4R agonist (setmelanotide)		/	MC4R agonist (setmelanotide)

Abbreviations: AA, autosomal additive; AD, autosomal dominant; ADHD, attention deficit hyperactivity disorder; AR, autosomal recessive; BMI, body mass index; GH, growth hormone; HTA, hypertension; PUPD, polyuria polydispisa; SDS, standard deviation.

4.3 | Utility of the review

This study represents an important prerequisite to design a standardized "triage" protocol of patients with obesity who are suspected of carrying monogenic mutations in genes from leptin-melanocortin pathway. Indeed, these mutations can affect about 5–50% of patients with obesity, depending on their ethnicity.[40,57,69,93,116,210]

Genetic testing is all the more relevant than several personalized treatments are now available for a subset of patients with obesity. These treatments include recombinant leptin (metreleptin)[44,46,55,62] for homozygous *LEP* mutation carriers on the one hand and MC4R agonist (setmelanotide) for homozygous *LEPR*, *POMC*, and *PCSK1* mutation carriers on the other hand.[32,91] In addition, ongoing clinical trials are evaluating the efficacy of setmelanotide in other genes and in *LEPR* and *POMC* heterozygous mutation carriers. Even in the absence of personalized treatment available for a subset of monogenic obesity mutation carriers, the precise knowledge of clinical and biological characteristics could inform practitioners to afford better medical care while using conventional treatments.

This review evidences that the clinical presentation of several recently identified monogenic obesity genes (e.g., *ADCY3* and *MRAP2*) deserves further "deep phenotyping" investigation by the biomedical community. This work also opens new avenues of clinical research to confirm specific phenotypes reported in few or unique patients and assess gene causality (e.g., asthma or ADHD in *MC4R* mutation carriers and depression in *POMC* mutation carriers) or to systematically investigate functions rarely evaluated (e.g., respiratory, cardiac and cognitive functions, and psychological/psychiatric status).

4.4 | Strengths and limitations

This systematic review is the first to synthesize the medical semiology of patients with mutations in leptin-melanocortin pathway genes, from well-known symptoms to rare or unique observations, based on 25 years of research in the field. It follows gold-standard guidelines in knowledge synthesis, with a recording protocol in PROSPERO, a double-blind screening performed in three databases, and an evaluation of risk of bias and study quality. It has been handled by experts both in the scientific (DM) and medical (ER and ATB) fields.

This review also presents some limitations. Firstly, the number of studies can greatly differ according to the genes studied, and the seniority of the discovery (e.g., *MC4R* vs. *ADCY3*). Additional monogenic obesity genes have yet to be discovered[49,211] (as the recent description of *ASIP* duplication[212]), so this is not a definitive review, and updates will be warranted in the future. A common flaw we acknowledge in all systematic reviews is the possibility to miss relevant references. We chose to include all reported mutations with clinical or biological descriptions and not only mutations with a demonstration of partial or complete LOF (e.g., in vitro or in silico characterization). Some limitations are inherent to the included studies: phenotypes could be reported only if measured. Clinical and biological description can greatly vary between studies, explaining the presence or absence of certain phenotypic categories depending on the gene studied (e.g., absence of pubertal information in *MRAP2* mutation carriers). We chose to focus on monogenic non-syndromic obesity genes from the leptin melanocortin pathway, so we excluded other syndromic forms of obesity (79 syndromes associated with obesity previously reported).[208] Furthermore, the quality of included studies is typically low because of the scarcity of monogenic obesity gene mutations (many included studies are case reports or case series without control groups).

4.5 | Conclusion and perspectives

In conclusion, this review is a useful addition to guide clinicians to triage subsets of patients with obesity for genetic testing and precision medicine and open new perspectives of biomedical research in the field of monogenic obesity.

AUTHOR CONTRIBUTIONS

DM formulated the study design. ER and DM created the literature search. ER and ATB collected data. ER and DM contributed to data interpretation. ER and ATB conducted the quality assessment. ER and DM wrote the manuscript and prepared the figures and tables. ATB edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

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