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Differentiating monogenic and syndromic obesities from polygenic obesity: Assessment, diagnosis, and management

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ABSTRACT

Background: Obesity is a multifactorial neurohormonal disease that results from dysfunction within energy regulation pathways and is associated with increased morbidity, mortality, and reduced quality of life. The most common form is polygenic obesity, which results from interactions between multiple gene variants and environmental factors. Highly penetrant monogenic and syndromic obesities result from rare genetic variants with minimal environmental influence and can be differentiated from polygenic obesity depending on key symptoms, including hyperphagia; early-onset, severe obesity; and suboptimal responses to nontargeted therapies. Timely diagnosis of monogenic or syndromic obesity is critical to inform management strategies and reduce disease burden. We outline the physiology of weight regulation, role of genetics in obesity, and differentiating characteristics between polygenic and rare genetic obesity to facilitate diagnosis and transition toward targeted therapies.

Methods: In this narrative review, we focused on case reports, case studies, and natural history studies of patients with monogenic and syndromic obesities and clinical trials examining the efficacy, safety, and quality of life impact of nontargeted and targeted therapies in these populations. We also provide comprehensive algorithms for diagnosis of patients with suspected rare genetic causes of obesity.

Results: Patients with monogenic and syndromic obesities commonly present with hyperphagia (ie, pathologic, insatiable hunger) and early-onset, severe obesity, and the presence of hallmark characteristics can inform genetic testing and diagnostic approach. Following diagnosis, specialized care teams can address complex symptoms, and hyperphagia is managed behaviorally. Various pharmacotherapies show promise in these patient populations, including setmelanotide and glucagon-like peptide-1 receptor agonists.

Conclusion: Understanding the pathophysiology and differentiating characteristics of monogenic and syndromic obesities can facilitate diagnosis and management and has led to development of targeted pharmacotherapies with demonstrated efficacy for reducing body weight and hunger in the affected populations.

1. Introduction

Obesity is a chronic, progressive, relapsing, and multifactorial neurohormonal disease resulting from impaired energy balance regulation and subsequent excess adiposity [1–3]. Because of the structural, physiologic, and functional abnormalities that result from excess adiposity, obesity can lead to increased morbidity, mortality, and diminished quality of life (QOL) [2]. The pathophysiology of obesity involves dysfunction in key regulatory pathways of energy balance, which can be impacted to varying degrees by both genetic and environmental factors [4]. Furthermore, differences in prevalence and outcomes among individuals with obesity exist along intersecting axes of race, ethnicity, socioeconomic status, and disability and may result from inequities in access to quality healthcare, employment opportunities, recreational spaces, community resources, and food security (Fig. 1) [5–8].

Globally, an estimated 13% of adults aged ≥18 years (11% of men and 15% of women) and 8% of boys and 6% of girls aged 5–19 years had

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obesity in 2016 [11,12]. In the United States, the prevalence of obesity from 2017 to 2020 was 41.9% in adults aged ≥20 years and 19.7% in pediatric patients aged 2–19 years [13]. Guidelines for characterizing obesity in adult and pediatric patients vary between organizations; however, the Lancet Commission on Diagnostic Criteria of Clinical Obesity began meeting in October 2022 with the aim to define diagnostic criteria for clinical obesity that will inform clinical decision-making, development of public health interventions, and insurance coverage of evidence-based treatments [14,15]. Generally, pediatric obesity is defined as ≥95th percentile of body mass index (BMI) based on age and sex [5]. Severe obesity in pediatric patients is subdivided into class 2 obesity (≥120% to <140% of the BMI 95th percentile, or BMI ≥35 to <39 kg/m^2, whichever is lower on the basis of age and sex) and class 3 obesity (≥140% of the BMI 95th percentile, or BMI ≥40 kg/m^2, whichever is lower on the basis of age and sex) [5,16]. In adults, obesity is defined as BMI ≥30 kg/m^2 and subdivided into class 1 obesity (BMI 30 to <35 kg/m^2), class 2 obesity (BMI 35 to <40 kg/m^2), and class 3 obesity (BMI ≥40 kg/m^2) [1,11,17].

Traditional weight management strategies for patients with obesity include lifestyle changes (eg, dietary changes, increased physical activity, behavior modification) that can be self-managed or administered under professional care, antiobesity medications, and metabolic and bariatric surgery (MBS) [1,5]. Additionally, 2 medical devices, Plenity® (oral superabsorbent hydrogel) and SmartByte® (Sensor Monitored Alimentary Restriction Therapy [SMART] device), are approved and cleared, respectively, by the United States Food and Drug Administration for weight management in individuals with overweight or obesity [18–20]. Critically, outcomes are variable, and traditional, nontargeted therapies are frequently inadequate in patients with highly penetrant obesity caused by rare genetic variants in key obesity pathogenesis pathways (ie, monogenic and syndromic obesities) [20–26]. Thus, identification and diagnosis of monogenic or syndromic obesity is necessary to ensure appropriate and timely care for these patients [27]. Here, we discuss these topics and considerations for clinical care of patients with rare genetic obesity phenotypes.

2. The physiology of weight regulation

Weight regulation is a complex process that involves both central and peripheral pathways and their interaction (Fig. 2). A comprehensive review of these processes is provided in a scientific statement by the Endocrine Society [4].

2.1. Central regulation of body weight

The arcuate nucleus (ARC) of the hypothalamus contains 2 distinct neuronal populations that project to the downstream melanocortin-4 receptor (MC4R)–expressing neurons of the paraventricular nucleus of

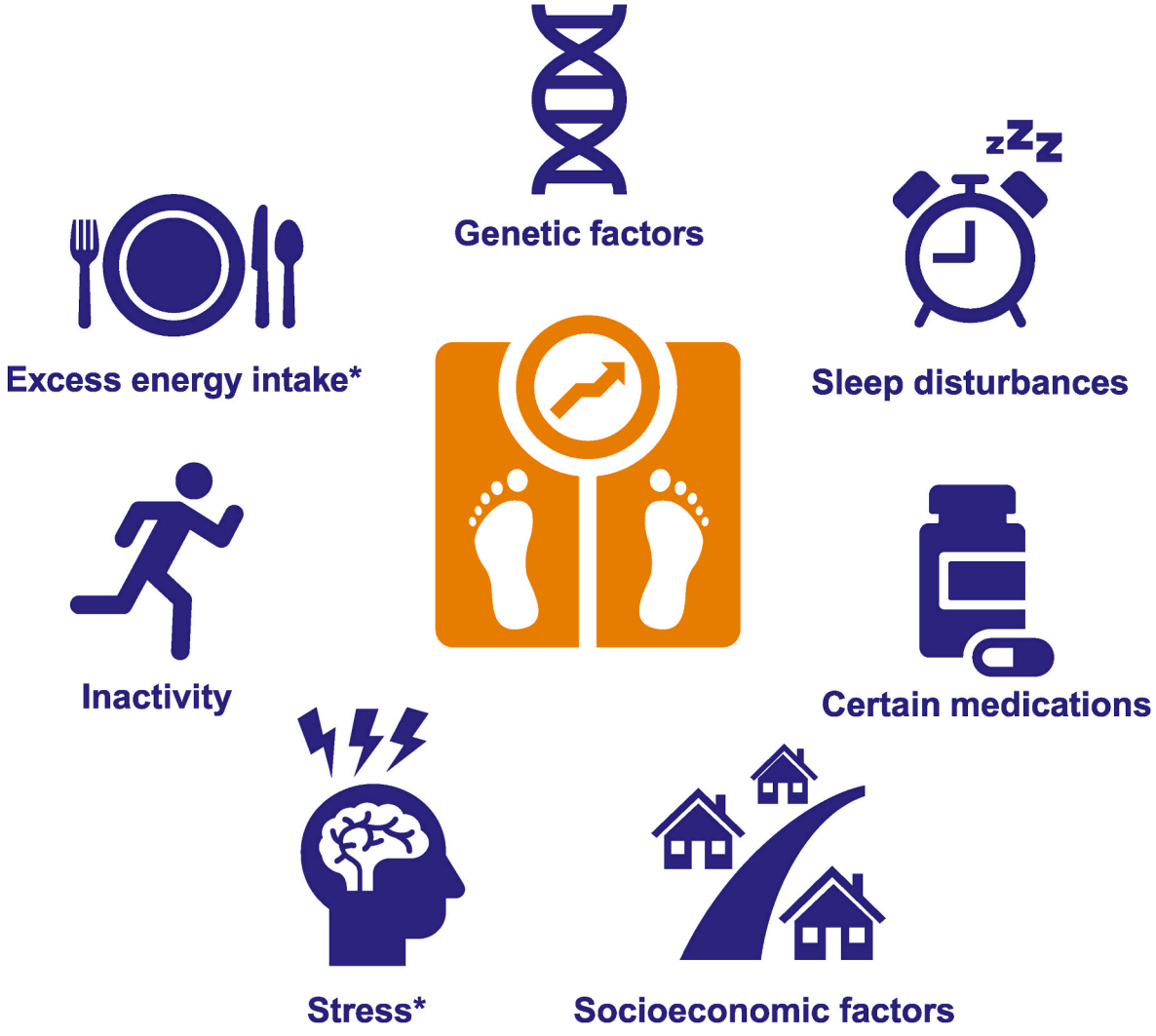

Fig. 1. Factors contributing or predisposing to development of obesity. *Through complex relationships between excess energy intake, endoplasmic reticulum stress, insulin resistance, and obesity (reviewed elsewhere [9,10]), evidence suggests that obesity may both contribute to and result from endoplasmic reticulum stress.

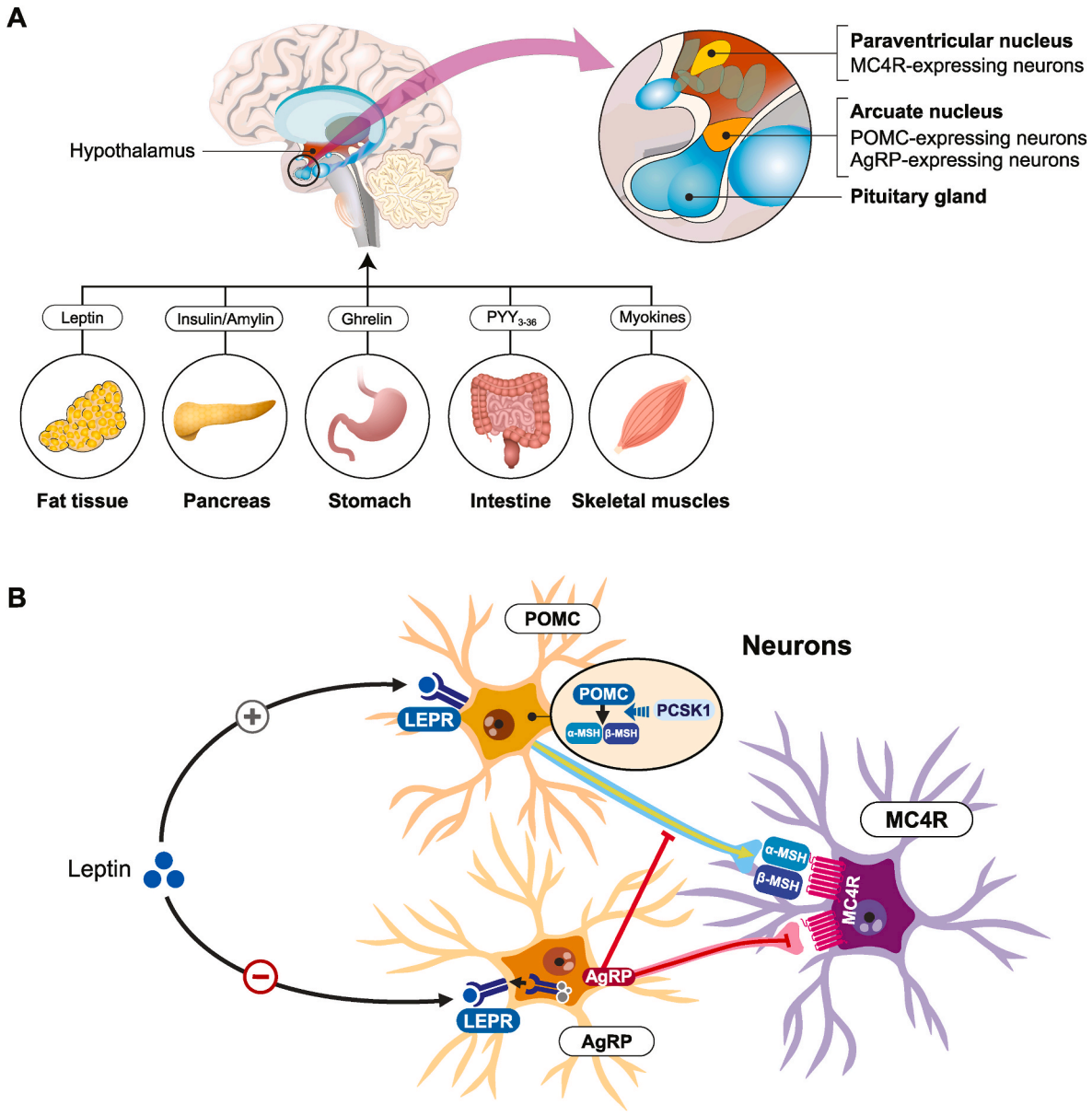

Fig. 2. Physiologic pathways underlying obesity. **(A)** Peripheral signaling to the hypothalamus involved in regulating weight and energy homeostasis. **(B)** The MC4R signaling pathway in the arcuate nucleus. AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PYY_{3-36}, peptide YY_{3-36}.

the hypothalamus and exert opposing influences on caloric intake and energy expenditure [28,29]. Neurons in the ARC that coexpress neuropeptide Y, agouti-related peptide (AgRP), and γ-aminobutyric acid are stimulated by caloric insufficiency and promote increased food intake, reduced energy expenditure, and weight gain via MC4R antagonism [28, 29]. In contrast, activation of proopiomelanocortin (POMC)–expressing ARC neurons leads to reduced food intake and increased energy expenditure in response to caloric sufficiency via MC4R activation [28, 29]. Rare variants in key genes within the MC4R pathway, including *POMC*, *PCSK1* (encodes proprotein convertase 1/3 [PC1/3]), *LEPR*, *MC4R*, *NCOA1* (encodes steroid receptor coactivator 1), *SH2B1*, *SIM1*, *ALMS1*, and genes associated with Bardet-Biedl syndrome (BBS), disrupt signaling in this pathway and can lead to early-onset, severe obesity [27, 30–33].

2.2. Peripheral regulation of body weight

Key contributors to peripherally mediated weight regulation include, but are not limited to, adipocytes, incretin hormones, leptin, and ghrelin (as described in this section), in addition to amylin, insulin, peptide YY, and myokines (see Fig. 2) [34,35].

2.2.1. Adipocytes

The 2 types of adipose tissue, white and brown, play important roles in peripheral regulation of body weight. White adipose tissue is the main cell type found in human fat and is composed of adipocytes, adipocyte precursors, endothelial cells, and immune cells, and stores excess calories as triglycerides and cholesterol esters; adipocytes in white adipose tissue synthesize adipokines (eg, leptin) [34,36,37]. White adipose tissue expansion contributes to obesity and obesity-related comorbidities [38]. Brown adipose tissue regulates energy expenditure through various forms of thermogenesis [39,40]. Brown adipose tissue deposition and function vary across age; whereas newborn infants have large interscapular and perirenal depots that maintain core body temperature, adults have smaller depots in cervical, supraclavicular, axillary, periaortic, paravertebral, and suprarenal regions that regulate energy

expenditure and body weight [41,42].

2.2.2. Incretin hormones

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide are released from cells in the small and large intestines in response to ingestion of glucose and other carbohydrates. These bind to their respective receptors in the pancreas and stimulate insulin secretion, thereby regulating glucose homeostasis [43]. In addition to the pancreas, GLP-1 acts in the central nervous system to reduce appetite and in the stomach to delay gastric emptying and may facilitate browning of adipose tissue [43].

2.2.3. Leptin and ghrelin

Leptin and ghrelin are peripheral hormones that are released in response to changes in nutritional status and adiposity, cross the blood-brain barrier, and lead to suppression or promotion of food intake via the hypothalamic MC4R pathway. In a fasted state, ghrelin secreted from the stomach binds to its receptors on ARC AgRP neurons and increases production of neuropeptide Y and AgRP; these peptides act as MC4R antagonists and increase food intake, energy conservation, and weight gain [31,44]. Excess adiposity or caloric sufficiency causes adipocytes to release leptin, which binds to leptin receptors (LEPRs) on ARC AgRP neurons and suppresses this pathway [31,44]. Leptin also binds to LEPRs on ARC POMC neurons, leading to increased production of POMC, which is cleaved by PC1/3 into α– and β–melanocyte-stimulating hormone (MSH). Activation of MC4R by α-MSH and β-MSH suppresses appetite and increases energy expenditure [31].

3. The role of genetics in polygenic, monogenic, and syndromic obesity

The evidence supporting the heritability of body weight is strong and has revealed varying degrees of genetic influence on the development of obesity [45]. The most common form of obesity is polygenic obesity, which results from the cumulative contribution of multiple gene variants interacting with behavioral and environmental factors (eg, eating behavior, physical activity, stress) [46–48]. Genome-wide association studies have identified >500 loci associated with BMI, with modest and varying effect size [46,49–54]. Identification of these variants enables prediction of an individual's risk for the development of obesity (ie, polygenic risk score) [49].

Conversely, monogenic and syndromic obesities are caused by rare variants in as few as 1 gene (and/or deletions of chromosomal regions encompassing genes) involved in key obesity pathogenesis pathways leading to early-onset, severe obesity [55,56]. For the purposes of this narrative review, monogenic and syndromic obesities are differentiated by the presence (syndromic obesity) or absence (monogenic obesity) of neurodevelopmental delay and additional multisystem disease-specific phenotypes [55]. Thus, monogenic obesity refers to obesity caused by single gene variants primarily within the hypothalamic MC4R pathway, whereas syndromic obesity refers to severe obesity associated with neurodevelopmental delay, endocrine abnormalities, sensory impairment, and dysmorphic features [55]. Of note, these obesities are sometimes defined as nonsyndromic monogenic obesity and syndromic monogenic obesity because some forms of syndromic obesity (eg, Alström syndrome) are caused by single gene variants [26]. The phenotypes associated with specific monogenic and syndromic obesities are detailed later.

There is also evidence to support a role of prenatal and developmental epigenetic modifications (ie, heritable changes in gene expression in response to environmental conditions that lead to phenotype variation but do not change the coding sequence) in the pathogenesis of obesity [4,57–61]. For example, animal studies have shown increased risk of obesity and metabolic abnormalities in offspring following maternal undernutrition [57,62]. Additionally, a genome-wide methylation study showed that epigenetic profiles of individuals with obesity differ from individuals with normal weight, and this variance predicted obesity status [63].

4. Morbidity, mortality, and QOL in individuals with obesity

Polygenic obesity is most commonly associated with the development of type 2 diabetes, cardiovascular disease (eg, hypertension), thrombosis, dyslipidemia, obstructive sleep apnea, increased cancer risk, anxiety and depression, polycystic ovary syndrome, bone and joint issues, and nonalcoholic fatty liver disease [64–68]. Critically, the risks of obesity-related comorbidities, obesity in adulthood, and premature death increase with earlier onset and increased severity of obesity, and therefore may be amplified in monogenic and syndromic obesities, which are characterized by early-onset, severe obesity [5,65,69–74]. Obesity onset during young adulthood can also increase the risk of cardiovascular comorbidities and mortality later in life [75]. In a study examining BMI changes from young to middle adulthood in 36,051 individuals, development of obesity during young adulthood was associated with a 22% higher risk of mortality and 49% higher risk of cardiovascular disease–related mortality during a mean follow-up period of 12.3 years [75].

In addition to increased morbidity and mortality, obesity has substantial negative impacts on QOL. A systematic review of the relationship between obesity and health-related QOL (HRQOL) in various contexts (ie, before or in the absence of treatment, following weight loss) found that obesity was associated with significantly reduced general and obesity-specific HRQOL across all contexts [76]. Furthermore, in qualitative studies of individuals with overweight or obesity, including those seeking help with weight management at the time of the study or those who previously underwent MBS, patients reported shame related to prior unsuccessful attempts to lose weight, constant preoccupation with weight, weight-related stigma and discrimination, social isolation, and impaired relationships related to obesity [77–80]. For patients with monogenic and syndromic obesities, QOL is affected by obesity and obesity-related complications, as well as the burden of insatiable hunger (ie, hyperphagia) associated with these diseases. In-depth qualitative interviews with patients and caregivers of patients with POMC deficiency, LEPR deficiency, and BBS revealed serious consequences of hyperphagia on patient and caregiver QOL, including impaired social relationships and family dynamics, inability to focus and complete tasks at school or work, and feelings of frustration, sadness, and failure [81,82].

5. Differentiating characteristics of polygenic, monogenic, and syndromic obesity

Several key factors differentiate polygenic obesity from monogenic and syndromic obesities, including etiology, prevalence, age of onset, and response to available treatments (Table 1).

As described previously, polygenic obesity arises from interactions between multiple gene variants and an environment that may facilitate development of obesity, whereas highly penetrant monogenic and syndromic obesities are caused by variants with a strong effect in as few as 1 gene and/or chromosomal region deletions with negligible environmental influence [26,55,56,83,84]. Whereas a substantial proportion of the global population has polygenic obesity, monogenic and syndromic obesities are rare, with some variants affecting only hundreds of people [27,108,109]. Of note, prevalence estimates of monogenic and syndromic obesities are likely low because genetic testing is not often considered in individuals with obesity [110]. Additionally, polygenic obesity is diagnosed on the basis of BMI, whereas monogenic and syndromic obesities typically require genotyping and analysis of genetic variants for diagnosis [11,27]. One exception is BBS, which is diagnosed using clinical presentation and may subsequently be genetically confirmed [111].

Monogenic and syndromic obesities are also unique in that patients

Table 1
Differentiating characteristics of polygenic obesity from monogenic and syndromic obesities.

	Polygenic obesity	Monogenic and syndromic obesities
Etiology	• Cumulative effects of multiple genetic variants interact with environmental factors that may facilitate development of obesity [48,83,84]	• Variants in ≥1 gene and/or chromosomal deletion with a strong effect [56,85–90]
Primary cause(s) of obesity	• Multifactorial o Diet [91] o Physical activity [91] o Aging [91] o Pregnancy [91] o Abstinence from substance use [91] o Medications [91] o Stress [91] o Circadian disruption [91] o Microbiome [91]	• Genetic variants [27]
Age of obesity onset	• Any age [92,93]	• Early in life (before 5 years of age) [56,89,90,94–96]
Feeding behavior	• Phenotypic variability (eg, poor satiety, increased hunger) [97]	• Hyperphagia [56,86–89,98,99] • Negative impact on patient and caregiver quality of life [81,82,100,101]
Efficacy of lifestyle-based management strategies	• Partially effective; recommended to be used with pharmacotherapy [92,102]	• Not effective; strategies do not target underlying hyperphagia [22,23,89,96,97]
Response to medical or surgical management strategies	• Heterogeneous responses [24,25]	• Limited research and long-term efficacy for traditional pharmacologic agents, GLP-1R agonists, and MBS; strategies do not target hyperphagia [21–23,96,103–105] • Efficacious therapy with MC4R agonism in patients with POMC deficiency, LEPR deficiency, or BBS [106,107]

BBS, Bardet-Biedl syndrome; GLP-1R, glucagon-like peptide-1 receptor; LEPR, leptin receptor; MBS, metabolic and bariatric surgery; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

commonly present with early-onset, severe obesity (ie, ≥120% of the BMI 95th percentile before the age of 5 years) and hyperphagia [5,73,74]. Hyperphagia refers to pathologic, insatiable hunger that can be identified by symptoms associated with an extreme unsatisfiable drive to consume food (ie, food-seeking behaviors) [112,113]. Examples of food-seeking behaviors can include eating quickly, negotiating for more food than provided, and sneaking, stealing, or hiding the type and/or amount of food being eaten [81,82,113]. Hyperphagia may be extreme and constant, manifesting as prolonged time to satiation, shortened duration of satiety, prolonged feelings of hunger, preoccupation with food, distress if denied food, and/or eating more than optimal quantities of food [112,113]. Thus, hyperphagia is associated with substantial negative consequences for patients and caregivers [81,82].

Notably, hyperphagia in patients with obesity caused by rare genetic variants in the MC4R pathway complicates traditional methods to lose weight because patients with these diseases typically do not achieve sustained weight loss with nontargeted therapies [21–23,89,96,97,103,114]. For example, case reports and natural history studies describe multiple unsuccessful attempts to lose weight through dietary modifications, physical training, traditional antiobesity pharmacotherapies, outpatient and inpatient treatment, and MBS before diagnosis [23,89,96,99]. Furthermore, case reports of patients with highly penetrant monogenic or syndromic obesity who underwent MBS show that any initial postoperative weight lost is frequently regained [22,23,103]. Studies examining the efficacy of lifestyle interventions for treatment of monogenic or syndromic obesity are relatively limited. One study of 514 patients aged 5–16 years with overweight or obesity showed that a 1-year lifestyle intervention program (ie, exercise, behavioral therapy, and nutrition education under the care of pediatricians, exercise physiologists, psychologists, and dietitians) led to similar weight loss in both patients with and without pathogenic *MC4R* variants, but this weight loss was not maintained in the former group [115]. In addition, a study of 1209 pediatric patients aged 2–19 years showed that an ~1-year lifestyle intervention program consisting of education and counseling to support changes in diet, exercise, and sleep did not lead to significant weight loss in patients who had pathogenic *MC4R* variants compared with those who did not have *MC4R* variants [116].

6. Clinical assessment and management of monogenic and syndromic obesities

6.1. Clinical assessment

Considering the high disease burden and need for specialized care of patients with monogenic and syndromic obesities, early diagnosis is critical to inform disease management strategies and alleviate some of the anxiety and/or stigma patients and their families commonly experience [74]. Current clinical practice guidelines recommend genetic testing in children with severe obesity (ie, ≥120% of the BMI 95th percentile) occurring before the age of 5 years, hyperphagia, and/or a family history of severe obesity [5,74].

The presence of hallmark clinical characteristics (Table 2) can further inform genetic testing and diagnostic approach.

Patients with monogenic obesity demonstrate rapid weight gain from an early age along with disease-specific features. For example, altered immune function and delayed puberty are indicative of LEPR deficiency, fair skin and red hair are indicative of POMC deficiency caused by biallelic variants in *POMC*, and hypoglycemia and diarrhea suggest deficiency in PC1/3 protein caused by biallelic variants in *PCSK1* [30,90,123,125,152]. Syndromic obesity frequently presents with developmental delay along with additional multisystem disease-specific phenotypes. For example, patients with BBS may present with retinitis pigmentosa, rod-cone dystrophy, polydactyly, hypogonadism, and renal dysfunction; patients with Prader-Willi syndrome (PWS) may present with low birth weight, neonatal hypotonia and feeding difficulties, and behavioral disorders; and patients with Alström syndrome may present with neurosensory deafness, hepatic dysfunction, and dilated cardiomyopathy [111,113,139,143,145]. In case studies of patients who received a diagnosis of monogenic or syndromic obesity in adulthood, common clinical features included a history of early-onset, severe obesity, hyperphagia, ineffectiveness of traditional obesity management strategies, endocrine abnormalities, and short stature [89,96,153,154]. Patients presenting with current, personal, or family history of hallmark features of monogenic or syndromic obesity should undergo sequencing of the genes believed to be involved in the associated phenotype (Fig. 3) [74,155].

Next-generation sequencing, including gene panels (ie, sequencing of specific genes associated with patient phenotype), whole-exome

Table 2
Hallmark clinical characteristics of monogenic and syndromic obesity diseases.

Disease	Mode of inheritance	Early-onset obesity	Hyperphagia	Growth	Endocrine abnormalities	Other clinical characteristics
LEP deficiency [26,117–121]	AR	✓	✓	Normal linear growth with reduced adult height due to absence of pubertal growth spurt	Hypogonadotropic hypogonadism, hypothyroidism	Frequent childhood infections related to abnormal T-cell count and function
LEPR deficiency [26,94,118,122,123]	AR	✓	✓	Normal linear growth with reduced adult height due to absence of pubertal growth spurt	Hypogonadotropic hypogonadism, hypothyroidism	Frequent childhood infections due to impaired T-cell immunity
MC4R deficiency [26,88,124]	AD or AR	✓	✓	Increased lean body mass and accelerated linear growth	Hyperinsulinemia	May have low blood pressure
POMC deficiency [26,90,99,125–127]	AR	✓	✓	Accelerated childhood growth	ACTH deficiency, mild hypothyroidism	Red/Orange hair, fair skin in non-Hispanic or non-Latino white patients
Deficient PC1/3 protein caused by biallelic variants in *PCSK1* [26,128–131]	AD or AR	✓	✓	Failure to thrive in early infancy	Hypoglycemia, hypothyroidism, ACTH deficiency	Intestinal malabsorption, diarrhea in early infancy
SRC1 deficiency [33,86]	NR	✓	✓	NR	Impaired leptin-induced POMC expression, PCOS, low testosterone and gonadotropin levels	Previous fractures from minor incidents, liver fibrosis, diabetes/insulin resistance
Loss-of-function *ADCY3* variants [132]	AR	✓	✓	Normal	Insulin resistance	Anosmia
Albright's hereditary osteodystrophy [26,133–138]	AD	✓[a]	✓[b]	Short stature	Pseudohypoparathyroidism, elevated parathyroid hormone levels	Hypocalcemia, subcutaneous ossifications and other skeletal anomalies, developmental anomalies
Alström syndrome [26,139–143]	AR	✓	✓	Short stature	Insulin resistance, T2D, hypothyroidism, hyperandrogenism in females, hypogonadism	Vision and hearing impairment, renal failure, hepatic dysfunction, cardiomyopathy
BBS [26,82,95,101,111,144]	AR	✓	✓	Rapid weight gain in early childhood sustained through adolescence	Hypogonadism	Visual impairment, cognitive disabilities, polydactyly, renal dysfunction
Prader-Willi syndrome [26,113,145]	Varies	✓	✓	Poor feeding, failure to thrive, and hypotonia in early infancy; short stature later in life	Hypogonadism	Dysmorphia, intellectual disability, behavioral disorders
SIM1 deficiency [26,146,147]	NR	✓	✓	Neonatal hypotonia and feeding difficulty	Hypogonadism	Developmental delay, facial dysmorphism
SH2B1 deficiency [26,87]	NR	✓	✓	Reduced adult height	Insulin resistance	Delayed speech and language development
16p11.2 deletion [27,56]	AD	✓	✓	NR	Hyperinsulinemia	Developmental delay, intellectual disability, communication and socialization difficulties
Smith-Magenis syndrome [26,148–151]	NA	✓	✓[c]	Failure to thrive, hypotonia in infancy	Hypothyroidism	Self-injurious behavior, developmental and speech delay, dental anomalies, deep/hoarse voice

ACTH, adrenocorticotropic hormone; AD, autosomal dominant; AR, autosomal recessive; BBS, Bardet-Biedl syndrome; LEP, leptin; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; NR, not reported; PC1/3, proprotein convertase 1/3; PCOS, polycystic ovary syndrome; POMC, proopiomelanocortin; SH2B1, SH2B adaptor protein 1; SIM1, single-minded homolog 1; SRC1, steroid receptor coactivator 1; T2D, type 2 diabetes.

[a] Early-onset obesity has been reported in patients with Albright's hereditary osteodystrophy who have pseudohypoparathyroidism types 1A and 1C.

[b] Evidence of hyperphagia in patients with Albright's hereditary osteodystrophy is inconsistent, with some reports showing hyperphagia in patients with pseudohypoparathyroidism types 1A and 1C, and other reports showing hunger in patients with pseudohypoparathyroidism type 1A that does not differ from patients with polygenic obesity.

[c] Retinoic acid induced protein 1 knockout mice, a model of Smith-Magenis syndrome, showed hyperphagic eating behaviors compared with their wild-type littermates.

sequencing (ie, sequencing of coding and adjacent intronic regions of the genome), and whole-genome sequencing (ie, sequencing of >90% of the genome), can be used for diagnosis of monogenic and syndromic obesities, with improved throughput, cost, and accuracy compared with Sanger (ie, first-generation) sequencing [31,156,157]. Diagnostic gene panels are well suited for patients presenting with distinct phenotypes suggestive of a specific genetic disease, whereas whole-exome and whole-genome sequencing provide a broad approach that is applicable for patients with complex phenotypes, genetic heterogeneity, atypical phenotype onset and course, and/or nondiagnostic results on previous focused testing [156]. Additionally, multiplexed assays of variant effects enable sequencing of thousands of variants and assaying for functional effects simultaneously [31,158].

6.2. *Multidisciplinary care*

Management strategies for polygenic obesity have been extensively researched [159,160]. Here, we focus on the treatment of monogenic or syndromic obesity. Management of monogenic and syndromic obesity diseases typically involves specialized, multidisciplinary teams (eg,

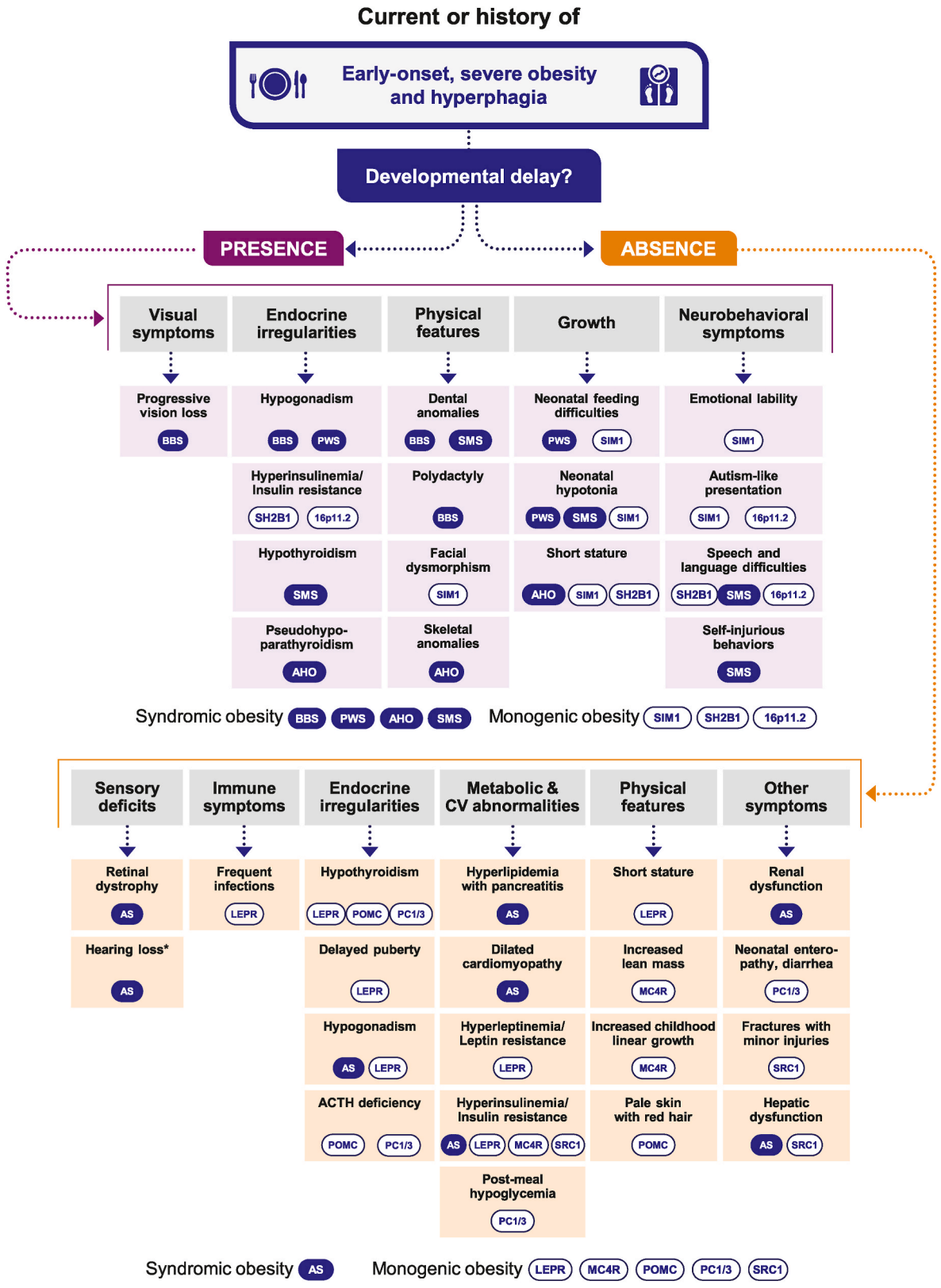

Fig. 3. Diagnostic algorithm for patients with suspected monogenic or syndromic obesity. 16p11.2, 16p11.2 chromosomal deletion; AHO, Albright's hereditary osteodystrophy; AS, Alström syndrome; BBS, Bardet-Biedl syndrome; CV, cardiovascular; LEPR, leptin receptor deficiency caused by biallelic variants in *LEPR*; MC4R, melanocortin-4 receptor deficiency caused by biallelic variants in *MC4R*; PC1/3, deficient proprotein convertase 1/3 protein caused by biallelic variants in *PCSK1*; POMC, proopiomelanocortin deficiency caused by biallelic variants in *POMC*; PWS, Prader-Willi syndrome; SH2B1, SH2B adaptor protein 1 deficiency caused by variants in *SH2B1*; SIM1, single-minded homolog 1 deficiency caused by variants in *SIM1*; SMS, Smith-Magenis syndrome; SRC1, steroid receptor coactivator 1 deficiency caused by variants in *NCOA1*. *Despite hearing and vision deficits in patients with Alström syndrome, most have normal intelligence.

healthcare providers who oversee weight and nutrition management, physical activity, developmental and psychomotor skills development, and hormone replacement therapy) and starts in childhood if diagnosed early [21]. These specialized care teams can address the complex features of monogenic and syndromic obesities, including endocrine, digestive, sensory, and behavioral abnormalities [21,161]. Hyperphagia associated with monogenic and syndromic obesities is managed behaviorally, and no standard treatment for hyperphagia is currently available [82,162]. Behavioral strategies used for hyperphagia may include managing expectations of what is available to eat and when it will be served, controlling access to food via refrigerator and pantry locks, and supervising food consumption (ie, preventing excess intake) [113].

6.3. MBS

Research supporting the efficacy of MBS in patients with monogenic or syndromic obesity is limited and consists primarily of case studies showing variable outcomes and lacking long-term follow-up [21,23,96,103,163,164]. One retrospective analysis of patients with monogenic obesity caused by biallelic variants in *LEPR*, *POMC*, or *MC4R* showed variable weight loss following MBS (maximum time since surgery: 19 years), followed by substantial (ie, ≥50% of maximum weight lost) weight regain in all patients [22]. One patient with POMC deficiency continued to show weight regain after the third surgery [22]. Additionally, in a retrospective analysis of 150 individuals who previously underwent Roux-en-Y gastric bypass, patients with heterozygous variants in the MC4R pathway showed significantly lower maximum weight loss and significantly greater weight regain at 10 and 15 years after surgery compared with matched participants without MC4R pathway variants [114].

6.4. Targeted pharmacotherapy

6.4.1. Metreleptin

Understanding the etiology and pathophysiology of monogenic and syndromic obesities has led to the development and approval of targeted pharmacotherapies for these diseases. Metreleptin was approved by the United States Food and Drug Administration in 2014 as a replacement therapy to treat the complications of leptin deficiency [165]. In patients with congenital leptin deficiency, subcutaneous injection of human recombinant leptin leads to reduced food intake, fat mass, and body weight, as well as improved hyperinsulinemia, hyperlipidemia, liver steatosis, and hypogonadism [166–169]. Notably, leptin supplementation is ineffective in patients with LEPR deficiency, as dysfunctional LEPRs preclude the ability of increased leptin to activate the MC4R pathway [27].

6.4.2. Setmelanotide

Because many genetic variants underlying monogenic and syndromic obesities prevent downstream MC4R activation, MC4R agonists were hypothesized to be a valuable therapeutic option for these diseases [166]. The MC4R agonist setmelanotide has demonstrated efficacy and safety for reducing weight and hunger in patients with POMC deficiency caused by biallelic variants in *POMC* or *PCSK1*, LEPR deficiency caused by biallelic variants in *LEPR*, and BBS [106,107]. Two Phase 3 trials showed that 8 of 10 patients with POMC deficiency (80%) and 5 of 11 patients with LEPR deficiency (45%) met the primary endpoint of ≥10% body weight reduction from baseline after ~1 year of setmelanotide treatment. Setmelanotide also led to significant reductions in body weight, BMI, and hunger [106]. Additionally, in a Phase 3 trial of setmelanotide in patients with obesity and BBS or Alström syndrome, 32.3% of patients aged ≥12 years reached the primary endpoint of ≥10% weight loss after 52 weeks of setmelanotide treatment; all patients achieving the primary endpoint were those with BBS [107]. Setmelanotide also led to clinically meaningful reductions in age-appropriate weight-related parameters and significant improvement in hunger in patients with BBS, although results were inconclusive for patients with Alström syndrome [107]. Setmelanotide was generally well tolerated across the 3 trials [106,107].

6.4.3. Available literature on nonapproved therapies

GLP-1 receptor (GLP-1R) agonists have led to significant weight reduction in patients with polygenic obesity [166,170–173]; however, randomized, controlled trials investigating the efficacy of GLP-1R agonists in patients with monogenic or syndromic obesity are lacking, and evidence is mostly limited to case reports or open-label studies in patients with PWS, *MC4R* variants, or BBS. A systematic literature review of 10 publications including 23 patients with PWS aged 13–37 years found that treatment with GLP-1R agonists (range, 14 weeks to 4 years) showed potential benefit, but there were evidence gaps, substantial heterogeneity among case studies, and a lack of randomized controlled trials performed in this population [105]. One randomized, placebo-controlled, Phase 3 trial of liraglutide in 55 patients aged ≥6 to <18 years with genetically confirmed PWS who received dietary and physical activity counseling demonstrated no significant group differences in BMI standard deviation (SD) score change or the proportion of patients who achieved ≥5% BMI reduction from baseline to Week 52 in either children (aged ≥6 to <12 years) or adolescent (aged ≥12–18 years) patients despite significantly larger decreases in hyperphagia from baseline to Week 52 in adolescent patients [174]. In a 16-week, open-label, Phase 2 trial of patients aged >18 to <65 years with pathogenic *MC4R* variants (mean [SD] BMI, 37.5 [1.8] kg/m^2; n = 14) or matched control participants (mean [SD] BMI, 36.8 [0.9] kg/m^2; n = 28), once-daily treatment with 3.0 mg of liraglutide was associated with reductions from baseline to Week 16 in weight (122.4 [6.7] vs 115.6 [6.7] kg; −6.8 [1.8]–kg difference; $P = 0.003$) and BMI (37.5 [1.8] vs 35.4 [1.9] kg/m^2; −2.0 [0.5]–kg/m^2 difference; $P = 0.001$) in patients with pathogenic *MC4R* variants. Similar weight changes were reported in control participants, with no significant group differences [104]. Larger-scale randomized controlled trials are needed to determine if GLP-1R agonists are efficacious for weight and hunger improvement in this population [104]. Evidence for GLP-1 treatment in BBS is limited to a case report that assessed liraglutide and semaglutide for weight management in an adult patient with BBS. BMI was reduced relative to baseline after 5 months of treatment with liraglutide (37.9 kg/m^2 at baseline vs 33.5 kg/m^2 at month 5). When the patient was transitioned to semaglutide treatment, BMI was further reduced after 19 months (nadir of 24.3 kg/m^2) [175]. There is also growing interest in unimolecular polypharmacology, wherein 1 drug targets multiple pathways [166]. The dual GLP-1R and glucose-dependent insulinotropic polypeptide receptor agonist tirzepatide showed significant weight loss in patients with polygenic obesity but evidence of its efficacy and safety in monogenic or syndromic obesity has not been demonstrated [166,176].

7. Conclusions and future directions

Obesity is not a uniform disease, and timely recognition of the underlying etiology and subsequent differentiation of monogenic or syndromic obesity from polygenic obesity are critical to initiate appropriate management of weight and associated obesity-related comorbidities [5,27,74,177]. Early identification of monogenic or syndromic obesity enables initiation of multidisciplinary care and targeted pharmacotherapies that have demonstrated efficacy for weight loss, hunger reduction, and QOL improvement in these patient populations [27,100,101,106,107]. Moreover, additional research is needed on the long-term efficacy of targeted pharmacotherapy and MBS in patients with monogenic and syndromic obesities. Limitations of this review are its narrative rather than systematic design and focus on select forms of monogenic and syndromic obesities associated with early-onset obesity and hyperphagia. Considering the structural inequities that confer disparities in healthcare access and outcomes among individuals with

obesity, future research should investigate the role of socioeconomic inequities and weight-related stigma in delayed or insufficient management of obesity and strategies for mitigating this shortcoming [5].

Key takeaway clinical messages

- Highly penetrant monogenic and syndromic obesities result from rare genetic variants with minimal environmental influences and can be differentiated from the more common polygenic obesity depending on key symptoms, including hyperphagia (pathologic, insatiable hunger); early-onset, severe obesity; and suboptimal responses to nontargeted therapies
- Patients with monogenic or syndromic obesity commonly present with hyperphagia and severe obesity before the age of 5 years
- Early diagnosis of monogenic or syndromic obesity and differentiation from polygenic obesity are crucial to direct disease management strategies and lessen anxiety and stigma for patients and their families

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Ethical review

This manuscript represents the original work of the authors and all referenced studies reviewed herein have been cited appropriately.

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