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Original article

Rare genetic causes of obesity: diagnosis and management in clinical care Causes génétiques rares de l'obésité : diagnostic et prise en charge cliniques

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Abstract

Rare genetic forms of obesity are linked to impaired energy balance (i.e., eating behaviour and energy expenditure) involving hypothalamic pathways. More than 60 genes coding for proteins located in the hypothalamic leptin/melanocortin pathway contribute to the development of these rare forms of obesity. The ambition of the French National Protocol for the Diagnosis and Care (PNDS) of Obesity of Rare Causes was to establish practical recommendations for assessment and management at all ages. This report is available on the website of the French Health Authority (HAS).

In addition to severe obesity, patients often display obesity-related comorbidities and neuropsychological/psychiatric disorders. These complex conditions make clinical management particularly challenging. Early diagnosis is critical for the organization of coordinated specialized multidisciplinary care, with mandatory interaction between

caregivers, social partners and families. Strategies to prevent aggravation of obesity consist in limiting access to food, establishing a reassuring daily eating environment, and the practice of sustained adapted supervised daily physical activity. The implementation of genetic diagnosis in clinical practice now enables a personalized medicine approach with access to new drug therapies, and improves the analysis of the risk/benefit ratio of bariatric surgery.

Résumé

Certaines formes rares de l'obésité sont liées à une altération de l'équilibre énergétique (comportements alimentaires et dépenses énergétiques) impliquant les voies hypothalamiques. Il y a plus de 60 gènes qui codent pour des protéines localisées dans la voie leptine-mélanocortine qui contribuent au développement de ces formes rares. L'ambition du Protocole Nationale de Diagnostic et de Soins (PNDS) Générique Obésité de Causes Rares est d'établir des recommandations pratiques pour l'évaluation et la prise en charge à toute âge. Le rapport est disponible sur le site web de la Haute Autorité de Santé (HAS).

En association à l'obésité sévère, les patients présentent souvent des comorbidités et des troubles neuropsychologiques ou psychiatriques liés à l'obésité. Ces situations complexes représentent un défi pour la prise en charge clinique. Le diagnostic précoce est essentiel pour mettre en place une prise en charge pluridisciplinaire spécialisée et bien coordonnée, où l'interaction entre les professionnels de santé, les acteurs sociaux et les familles est fondamentale. Les stratégies pour prévenir l'aggravation de l'obésité consistent à limiter l'accès à la nourriture, à créer un environnement alimentaire quotidien qui est rassurant, et à mettre en place des activités physiques supervisées, soutenues et adaptées. L'intégration du diagnostic génétique dans la pratique clinique dorénavant permet d'adopter une approche de médecine personnalisée et améliore l'analyse du rapport risque / bénéfice de la chirurgie bariatrique.

Keywords

Syndromic obesity, monogenic obesity, hypothalamic obesity, leptin/melanocortin pathway

Mots-clés

Obésité syndromique, obésité monogénique, obésité hypothalamique, voie leptine-mélanocortine

1. Introduction

There is a continuum between polygenic obesity, which is the most common form of obesity, and rare, early-onset, severe forms of obesity caused by identified genetic variations. These genetic forms of obesity represent approximately 5 to 10% of childhood obesity and can sometimes be associated with neurodevelopmental disorders.

Conditions usually classified as syndromic obesity (such as Prader-Willi (PWS), X-Fragile, Bardet-Biedl (BBS), or 16p11.2 deletion) and as monogenic obesity involving pathogenic variants in genes of the hypothalamic leptin-melanocortin pathway. Indeed, the pathophysiological background of most of these clinical situations shows an alteration of the regulation of the energy balance by hypothalamic centres.

These conditions associating early-onset severe obesity with eating disorders have a strong neuroendocrine component that sometimes manifests with a neurodevelopmental disorder e.g. intellectual disability, autism spectrum disorder and/or psycho-behavioural disorder.

Thus, these conditions with combined severe obesity and neuropsychological or psychiatric disorders are complex. They can be associated with a myriad of comorbidities such as diabetes, alveolar hypoventilation, syndromic organic complications (scoliosis, visual impairment, etc.) and lead to many challenges to adapt the care. As such early diagnosis is key to organize comprehensive, multidisciplinary, and specialised treatment at any age, as well as access to novel innovative therapies developed over the last several years.

Here, we present the main features useful to identify these genetic forms of obesity and provide guidelines regarding genetic testing and care management. This summary is based on a complete report, The French *National Diagnosis and Care Programme (PNDS) for Rare Obesity* accessible online by physicians and caregivers (https://www.has-sante.fr/jcms/p_3280217/fr/generique-obesites-de-causes-rares).

2. Pathophysiology

Two separate entities have usually been described:

- **Syndromic obesity:** obesity is associated with other signs suggestive of a neurodevelopmental disorder (intellectual disability or autism spectrum disorder) and/or a congenital malformation syndrome (dysmorphic features, organ anomalies).
- **Non-syndromic monogenic obesity:** these forms are caused by pathogenic variants in genes coding for regulators within the hypothalamic leptin-melanocortin pathway (Figure 1).

Nevertheless, the common pathophysiological background led us revisit these entities as a global neuroendocrine disease, with a continuum of clinical conditions (Figure 2). Rare genetic forms of obesity are indeed due to alterations in the central regulation of the energy homeostasis. The genetic anomaly induces dysfunction of key hypothalamic neuronal networks, themselves connected not only to other centres controlling the eating behaviour (reward system or cortical regions) but also to metabolic alterations in peripheral organs. The leptin/ melanocortin pathway involving anorectic neurons (propiomelanocortin neurons or POMC) and orectic neurons (expressing the neuropeptide Y [NPY] and the agouti-related protein [AgRP]) is the crucial pathway in which functioning and regulation can be impaired (Figure 1) [1]. A resulting clinical consequence of hunger/satiety signals' impairment is severe hyperphagia with eating disorders, and alteration in energy expenditure, with a decrease in the basal metabolic rate leading to an increased body fat mass. This complex clinical phenotype include frequently neuropsychological disorders and sometimes endocrine (hypopituitarism including GH deficiency and hypogonadism), metabolic perturbations such as hyperinsulinism, and dysautonomia, with dysfunction of the autonomic nervous system.

There are more than 60 genes/syndromes with pathogenic variants contributing to hypothalamic dysfunction [2]. These are described in the *PNDS* report (https://docs.google.com/spreadsheets/d/1vQUcZna_vjpgVLLtylDKc1zIVRNvoSPOVITsixUdTWg/edit#gid=0).

In this review, we described some examples. Mutations in genes directly located in the leptin/melanocortin pathway have been described to lead to the dysfunction of neurons in the arcuate and paraventricular nuclei (Figure 1) [3]. They include leptin (*LEP*), its receptor (*LEPR*), proopiomelanocortin (*POMC*), prohormone convertase subtilisin/kexin 1 (*PCSK1*), melanocortin receptor type 4 (*MC4R*), SIM BHLH transcription factor 1 (*SIM-1*), brain-derived neurotrophic factor (*BDNF*), and, more recently, adenylate cyclase (*ADCY3*), dual-specific tyrosine phosphorylation-regulated kinase 1A (*DYRK1B*), kinase suppressor of ras 2 (*KSR2*), and melanocortin-2 receptor accessory protein 2 (*MRAP2*). Whereas pathogenic variants in those genes lead to these severe obesity forms (previously names monogenic obesity), anomalies in the regulation of the leptin/ melanocortin pathway were also described in syndromic obesities such as PWS [4]. Amongst them, abnormalities of POMC neurons and activation of AgRP orexigenic neurons [5] were reported in PWS together with an increase in the levels of ghrelin, an activating hormone of the arcuate nucleus orexigenic pathway [6]. Inactivation of the *MAGEL2* gene, located in the PWS genomic region (15q11-13), was shown to be responsible for a decrease in the density of axons in α -MSH neurons in a mouse model [7]. In BBS, belonging to the ciliopathies, the transport and localisation of LEPR at the ciliary membrane of POMC neurons is altered [8].

3. Clinical pictures

Early-onset severe obesity

The common phenotype is early childhood obesity, often severe (BMI Z score > +3 SD) and usually resistant to medical management based on lifestyle modifications (diet/physical activity). This severe condition associates with eating disorders characterised by difficulties in voluntarily controlling food intake (uncontrollable hyperphagia with altered perception of the physiologic signals of hunger and satiety and food impulsivity).

For obesity associated with a neurodevelopmental disorder, the age of onset depends on the related aetiology: very early for some syndromes (e.g. before two years of age for pseudohypoparathyroidism, around three years old for PWS, and between two and five years old for BBS), and at later age for other syndromes (between 5 and 10 years old for X Fragile syndrome, from 9 years onwards for the

16p11.2 deletion, and at the onset of puberty for Angelman or Smith Magenis syndromes). It is however admitted that obesity development occurs in the vast majority of cases before or during puberty.

Homozygous or heterozygous composite pathogenic variants of *LEP*, *LEPR*, and *POMC* are associated with obesity starting from the first months of life. Children with obesity due to leptin or *LEPR* deficiency have a BMI $> 27 \text{ kg/m}^2$ at two years of age and $> 33 \text{ kg/m}^2$ at five years of age corresponding to a BMI Z-score $> + 4 \text{ SDS}$ [9]. Children who are homozygous or composite heterozygous carriers of a *LEPR* variant are generally obese before six years of age [10].

For heterozygous variants in the *LEP*, *LEPR*, *POMC*, or *PCSK1* genes, scarce data have been reported. In a cohort of French patients with early and/or severe obesity, the age at onset of obesity for children carrying these variants in an heterozygous state was very early (on average 1.5 ± 1.3 years). In adults, although weight gain was slightly less early, with an age at onset of 5.4 ± 4.3 years, 74% were nevertheless obese before the age of 12 years [11]. For children with heterozygous *MC4R* variants, obesity has been reported to start between two and five years of age [9, 12].

However, these rare forms of obesity show phenotypic heterogeneity probably due to factors such as ethnicity, gender, family and social environment, and genetic, allelic, or epigenetic heterogeneity. Thus, for the genes upstream of *MC4R*, such as *LEPR* or *POMC*, subjects carrying homozygous or heterozygous composite variants have an obligatory obesity phenotype that is only slightly dependent on the environment and much more severe and early than in heterozygous subjects, whose phenotype depends, in part, on the environment and the combination with other rare variants located in other genes or a polygenic background [13]. Interestingly, subjects carrying the same pathogenic variant of *MC4R* have a different BMI depending on their polygenic score, with a difference of 14 kgs for an identical height depending on whether the score is high or low [14].

Eating disorders

A common feature observed in rare genetic forms of obesity is a defect in hunger/fullness/satiety signals and the presence of food impulsivity. The degree of loss of control in the food intake however

varies depending on the age, clinical and environmental context (e.g., parental/educational guidance), ranging from simple compulsion to severe binge eating. This defect in hunger and satiety signals leads to hyperphagia, defined as an amount of food ingested that surpasses physiological needs, and can start at a very early age.

This generic term “hyperphagia” however does not fully cover the complex variety of eating disorders found in rare genetic forms of obesity. Indeed, many forms of eating disorders, from more-or-less compulsive snacking to severe binge eating, can be observed, and should be systematically scrutinized.

The wide dimension of eating behaviour in patients with PWS is also illustrative. It resembles to food addiction, which includes an obsession and persistent preoccupation with food (active foraging, stealing and hoarding, food-related behaviours, behavioural disturbances or psychological distress when access to food is prevented or in relation to food-related themes), eating in the absence of hunger, or manipulation/negotiation with peers [15]. In other syndromes, such as 22q11.2, Fragile X, Smith-Magenis, and BBS, eating behaviours similar to PWS have been described in children, showing preoccupation with food and active food seeking behaviour. Patients with variants in the leptin/melanocortin pathway also display hyperphagia albeit with various degree of severity. These eating disorders have a major impact on the quality of life of these patients and their family and represent a heavy burden on the family shoulders from an early age of the children but also in adulthood.

It is important to mention that the evolution of eating behaviour varies over time, depending not only on the genetic origin, but also on the environment in which the person lives. In addition, psychotropic treatments prescribed for specific behavioural or psychiatric disorders can trigger or increase eating disorders and weight gain, in particular neuroleptics or anti-epileptics.

Taking care medically of these eating disorders at an early stage can help improving patient condition at later age as seen in PWS (https://www.has-sante.fr/jcms/p_3291625/fr/syndrome-prader-willi). Thus it is recommended to physician or caregivers to early detect these behaviours. Practical tools for

evaluation are provided in the *PNDS* (https://www.has-sante.fr/jcms/p_3280217/fr/generique-obesites-de-causes-rares).

Endocrine abnormalities

Endocrine abnormalities vary according to the syndromes and genes involved (Tables 1 and 2). PWS is again illustrative in this respect with global hypothalamic insufficiency including central and/or peripheral gonadotropic deficiency, somatotrophic deficiency, thyrotrophic deficiency, and, more rarely, corticotrophic deficiency [6, 16-20]

Other syndromes are also associated with endocrine deficits that need to be systematically investigated to propose appropriate hormonal substitution:

- thyroid hormone deficiency in Alström syndrome (central or peripheral), BBS, or pseudohypoparathyroidism (hormone resistance)
- corticotrophic insufficiency described in Alström syndrome
- sexual hormone deficiency, sometimes present in Alström syndrome (central or peripheral), BBS (central or peripheral), pseudohypoparathyroidism (hormone resistance disorder), or in some patients with Fragile X syndrome
- growth alteration, frequently observed in syndromic obesity and sometimes associated with growth hormone (GH) deficiency

Patients with autosomal recessive variants in the melanocortin pathway genes also frequently exhibit endocrine deficits (Table 2). Due to the crucial role of leptin in activating the hypothalamic-gonadal axis, patients carrying variants in the *LEP* or *LEPR* gene exhibit hypogonadotropic hypogonadism. They can display delayed pubertal development, which suggests a recovery of the hormonal function with time in some individuals. For example, long-term follow-up of a *LEPR* deficient woman diagnosed at the age of 13 showed normal pregnancies at 20 years of age [21]. Given the wide importance of leptin in human physiology, somatotrophic and thyrotrophic insufficiencies have also been described in several patients with *LEPR* deficiency. A systematic review found that among 88 patients

carrying *LEPR* variants, 100% had early-onset obesity (< 5 years of age), 96% had hyperphagia, and 34% had one or more pituitary hormone deficiencies [10].

POMC is the precursor of alpha and beta-melanocyte-stimulating hormone (i.e. α MSH, β MSH) and adrenocorticotrophic hormone (ACTH). As such, subjects with obesity due to complete *POMC* deficiency (homozygous or compound heterozygous variants) have an ACTH deficiency and mild central hypothyroidism [22, 23]. They sometimes display alterations in the somatotrophic and gonadotropic axes [24]. Red hair is also a reported phenotype. Modifications in hair colour, adrenal function, and body weight are consistent with the lack of *POMC*-derived ligands for the melanocortin receptors MC1R (α MSH), MC2R (ACTH), and MC4R (α MSH). In our cohort of French subjects with early-onset severe obesity genetically screened in the last 20 years, we found 12 subjects with a heterozygous variant of *POMC*. Among them, two showed hypogonadotropic hypogonadism and growth hormone (GH) deficiency [11].

Proconvertase 1 (*PC1*), encoded by the *PCSK1* gene, is an enzyme involved in the processing of *POMC*, proglucagon, and insulin. Patients carrying homozygous or compound heterozygote variants in the *PCSK1* gene (leading to PC1 deficiency) exhibit early-onset severe obesity, postprandial hypoglycaemia, hypogonadotropic hypogonadism, central hypothyroidism, and adrenal insufficiency [25, 26]. Some patients may also show persistent polydipsia and polyuria due to central diabetes insipidus [27]. A number of heterozygous variants have also been described for the *PCSK1* gene. Overall, endocrine deficits are frequent in patient with genetic obesity and need investigation and follow-up during medical management.

Other associated signs

Other signs that are varyingly associated with obesity include:

- neuropsychological abnormalities and/or neurodevelopmental disorder: intellectual disability of varying intensity and/or adaptive developmental disorders present in numerous syndromes, such as in PWS, autism spectrum disorder in SH2B1, MYT1L deficiency or Smith Magenis syndrome, cognitive disorders with difficulties in emotional regulation (BBS or certain variants located on genes of the

melanocortin pathway), and behavioural disorders and psychiatric co-morbidities (e.g., PWS, Smith-Magenis syndrome, etc.).

- sleep disorders and disturbances in the regulation of the major hypothalamic functions: neurovegetative system with symptoms related to dysautonomia (heart rhythm , orthostatic hypotension, and digestive and sweating disorders), increase in the pain threshold, and alterations in the regulation of body temperature

- malformations of the extremities, kidneys, heart, and brain and or functional consequences on organs: ophthalmological (nystagmus, pigmentary retinopathy, severe myopia, aniridia, etc.), auditory, or cerebral (epilepsy)

For a detailed description of most common syndromic obesities, the reader is invited to refer to Table 1 and the corresponding *PNDS* for each syndrome (https://www.has-sante.fr/jcms/c_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds).

The abnormalities associated with obesity in subjects carrying variants of the melanocortin pathway are presented in Table 2.

4. The diagnostic process

Clinical assessment

Drawing or examining patients' growth chart is a cornerstone of patient evaluation, showing a very early onset of obesity (BMI > IOTF30 before the age of six years) characterized by the earliness or absence of rebound of adiposity, and a rapid progression of body weight and BMI.

The clinical interview should seek information pertaining to present or past eating disorders, consanguinity, family history, hypotonia or sucking problems, with difficulties in feeding during the neonatal period suggesting PWS, behavioural problems (impulsivity, aggressiveness in the school environment, and intolerance to frustration), and delayed psychomotor development or learning difficulties. The stages of puberty examining whether puberty was delayed or advanced must also be recorded.

Psychomotor developmental delay accompanying early obesity and eating disorders is suggestive of syndromic obesity whereas neurodevelopmental disorder can themselves be a risk factor for obesity. Therefore, collecting all clinical information from birth to adulthood, allows the clinician to orient the diagnosis towards syndromic obesity, with parents' help, even in adults. Clinical examination includes the search for dysmorphic features (facial shape, orientation of the palpebral slits, nose, philtrum, ears, head circumference), abnormalities of the extremities, skin, or nails and neurological or ophthalmological abnormalities (strabismus, myopia, and retinitis pigmentosa) since they are frequent features found associated with genetic obesity.

Paraclinical assessment

When suspecting rare genetic obesity, it is recommended to perform an evaluation of endocrine features (pituitary axes, serum leptin level, and phosphocalcium balance), metabolic characteristics, and morphological exploration (X-rays of the hands, feet and forearms in search of bone anomalies, brain MRI in the case of intellectual deficiency and/or pituitary MRI in the case of hypopituitarism, and an ophthalmological check-up with an electroretinogram when suspicion of visual problem). The morphological assessment is completed by a cardiac and abdominal ultrasound to screen for associated malformations.

Genetics

Genetic diagnosis should be discussed with specialists (clinical geneticists) in conjunction with a reference centre for rare diseases and based on the type of abnormality associated with obesity. The genetic diagnosis is also a cornerstone of patient care. In many cases, providing a genetic diagnosis is a relief of guilt for the patients and their family and helps to provide the most appropriate medical care and social management according to the disabilities associated with the disease. As such, based on the genetic diagnosis, the patients and their family can be oriented to patient associations, an essential support for disease acceptance and day-to-day life. Additional genetic counselling for relatives can also be envisaged with the family.

When obesity is associated with a neurodevelopmental disorder, genetic analysis should at least include methylation analysis of chromosome 15 (for PWS), analysis of the *FMRI* gene (for Fragile X syndrome), and chromosomal microarray analysis (ACPA or CGH-array). If abnormal 15q11-q13 methylation is identified, further genetic analysis is required to identify the underlying genetic mechanism (deletion, disomy, or centre of imprinting abnormality) explaining PWS. When clinical features are suggestive of BBS (in particular, retinal dystrophy), a ciliopathy should be sought. More specific investigations for other single-gene defects (*MYTIL*, *RAII*) should be discussed on a case-by-case basis, depending on the clinical phenotype. Exome or even whole genome testing is also now available in certain specialised centres as a second-line genetic tests if the results of the first-line investigations are negative.

In cases of severe early-onset obesity associated with endocrine abnormalities without neurodevelopmental disorder, suggesting non-syndromic monogenic obesity, initial sequencing of the main candidate genes (*LEP*, *LEPR*, *POMC* and *PCSK1*) is necessary to confirm the diagnosis. This allows the detection of homozygous, heterozygous, or composite heterozygous genetic variants. In cases of severe early onset obesity without associated endocrine anomalies, *MC4R* variants may be screened by direct sequencing of the *MC4R* gene (one exon). Next-generation sequencing (NGS), which allows the simultaneous analysis of a large panel of genes, and exome sequencing are being developed to analyse, in addition to these "classic" genes, newly identified genes playing a role in the regulation of the melanocortin pathway.

A web tool (*ObsGen*) developed by our team, guides French clinicians in the diagnostic process when faced to a suspicion of rare genetic obesity (<http://obsген.nutriomics.org>).

5. Rare obesity management

Comprehensive assessment and care

Comprehensive, specialised, multidisciplinary, and coordinated care should be implemented as early as possible, from early childhood. In adulthood, an unorganised transition after paediatric care is a

major cause of obesity aggravation. It is therefore important to organise this transition phase between paediatrician and adult physician teams [28, 29];

For organizing patients' evaluation and care management, patients should initially be referred to one reference centre for rare diseases and/or complex obesity, which assembles specialised multidisciplinary team enabled to help with the coordination of care between attending physicians and other specialists, as well as with the medico-social actors [30-32].

The objective of the care management, beyond the initial physical evaluation, is to detect and treat comorbidities accompanying each syndrome and obesity from mild to severe forms.

Nutritional management combined measures to improve the regulation of the eating behaviour and increase the physical activities.

An early aetiological diagnosis allows the family to be better informed and prepared to deal with the consequences of eating disorders and weight gain, and to establish a bond of trust between the caregivers, the patients and their family. Nutritional support includes the restrained access to food and stabilised eating behaviour by establishing a structured setting for meals with rituals. Eating disorders are very often part of wider behavioural difficulties (intolerance to frustration, relationship difficulties, etc.) and it is recommended to have an overall management of these behavioural difficulties with specialized professionals. For more details useful in clinical practice, the reader is invited to consult Table 3.

The prescription of physical activity (PA) is another essential pillar of the management, emphasising the notions of physical leisure and, psychological well-being. Patients' relatives and friends must be aware of the importance of PA at early stage and throughout the life. Various types of PA programs have been evaluated, and those carried out at the patient home or close environment appear to be of particular interest. For example, in a French study by Bellicha et al., women with PWS participated in a four-month PA program carried out at their home or care facility [33]. Two individual PA sessions per week, supervised by a PA instructor were offered. The experience of PA instructors with patients with disabilities and training to PWS specificities appeared to be essential to the success of the

program. These reported the need to adapt PA session content based on patients' condition, mood, or motivation. They also explained that one-to-one interaction with the patient allowed them to build confidence, and reinforce self-esteem and motivation. Practical advice on assessment and specific management are given in Table 4.

Physical rehabilitation can also be required in order to improve the patient's quality of life and to limit/compensate for the functional impact of the deficiencies. For example, most patients with obesity and neurodevelopmental disorder will require adapted rehabilitation (motor physiotherapy, speech therapy, psychomotricity, ergotherapy, etc.) at an early stage, involving the family. An admission to an expert centre, specialised in such multidisciplinary management and rehabilitative care can be sometimes recommended.

Neuropsychiatric management should also be proposed in case of genetic obesity with assessment performed by a professional specialised in neurodevelopmental disorders. It includes a detailed medical history from birth, and a diagnostic evaluation of intellectual proficiency, attention and executive functions, and degree of autonomy. This multidimensional assessment is key to highlight the acquired abilities and difficulties in daily life and the person's strengths and weaknesses in each domain, following a developmental progression of acquired abilities. The aim is to improve the educational and professional orientation of individuals and to personalize the medico-psychological care to provide. If behavioural disorders are present, patients must be referred to psychiatrists competent in the care of patients with neurodevelopmental disorders at least for an evaluation, to enable support for the local care structures and to discuss the benefit-risk balance of psychotropic medication

Therapeutic patient-education programs that include caregivers could also have a beneficial impact and are being developed.

Finally, strong links between the healthcare and social actors (daily life environment) are critical to better support the care pathways and life projects in these complex situations.

Medications

Early diagnosis of rare genetic forms of obesity is crucial because it allows for specific and adapted drug management, particularly in the case of neurodevelopmental disorders, and for indication of specific treatment targeting the leptin/melanocortin pathway, such as recombinant leptin in cases of leptin deficiency and more recently, pharmacological agonists of the MC4R receptor, such as setmelanotide, review in [34 , 35]. Obesity linked to bi-allelic variants upstream of MC4R in the leptin/melanocortin pathway are indications recognised by the American and European agencies for this treatment (IMCIVREE®). Its notable effect is weight loss of over 10% of the initial weight in most cases (average loss of 25.6% for *POMC* variants and 12.5% for *LEPR* variants), with a reduction in hunger scores of 27.1% and 43.7%, respectively [36]. In the future, patients with genetic variants in the melanocortin pathway might be candidate to these treatments if clinical trial results are conclusive.

Bariatric surgery

Evidence on the effects of bariatric surgery in syndromic obesity have been reported for a limited number of cases with variable follow-up times. The largest serie was based on the analysis of 60 American patients with PWS with a mean age of 19.7 years and a preoperative BMI of 51.6 kg/m². The beneficial effects were lower in PWS patients compared to those with common obesity, with a mean weight loss of 2.4% five years after gastric bypass surgery. Moreover, the rate of complications, including death, pulmonary embolism, infection of the intestinal wall, and gastric perforation was higher in PWS operated patients [37]. We consider surgery to be usually contraindicated in cases of syndromic obesity with eating and neuropsychological disorders, apart from exceptional cases that should be discussed with an expert team. The benefit-risk balance is indeed largely unfavourable given: 1) the modest effects on weight (weight regain observed in most published studies), 2) the inherent risk of multi-organ damage linked to the syndrome (digestive, osteopenia, anaemia, and thromboembolic risk), 3) the psychological vulnerability, and that 4) postoperative complications can be masked due to absence of fever, reduction in the pain threshold, and difficulties in feeling discomfort and expressing complaints.

Only a few cases of surgery have been described for leptin/ melanocortin pathway deficiencies, with inconsistent results and duration of follow-up. A recent Franco-German study analysed the weight

evolution of eight patients with homozygous or heterozygous composite variants of *POMC* (n = 2), *LEPR* (n = 5), and *MC4R* (n = 1), a median age of 19 years, and a mean BMI of 51.9 kg/m² who underwent band, sleeve, or bypass surgery (n = 5), sometimes with multiple procedures [38]. Although the surgery was accompanied by initial weight loss, weight regain was observed in all cases, in the mid to long term.

A Dutch group published the results of bariatric surgery in their cohort of 1,014 patients, including 30 (3%) with a diagnosis of monogenic obesity caused by heterozygous pathogenic variants, notably in the *POMC* and *PCSK1* genes. Weight loss after gastric bypass was not significantly different from that of non-mutated patients [39] but with a follow-up duration of only two years. In a recent review, Vos et al. concluded that there is no strong argument for proposing bariatric surgery as a treatment for severe obesity for either syndromic or monogenic obesity [40]. However, if surgery is nevertheless performed, there should be a specialised multidisciplinary assessment beforehand.

The effect of bariatric surgery on short-term weight loss for patients with heterozygous *MC4R* variants has been reported to be identical to that of control groups without variants [41]. However, the presence of a heterozygous gain-of-function variant was associated with a higher risk of binge eating disorder preoperatively and more re-interventions and postoperative complications [42]. In the Dutch cohort, 11 heterozygous *MC4R* carriers who underwent gastric bypass had equivalent weight loss to non-variant carriers. By contrast, weight loss was significantly lower for those who underwent sleeve-gastrectomy (n = 3) during the two years of follow-up [39], suggesting a preferred indication for bypass surgery in these particular cases.

Thus, melanocortin pathway variants, in the absence of psychiatric disorders, major eating disorder, and neurodevelopmental disorder, are not an absolute contraindication to bariatric surgery. However, the disappointing results of bariatric surgery on weight loss, likely linked to the primary energy balance disorder, contrasting with the emergence of new effective pharmacologic treatments in certain genetic situations, call for caution before deciding on surgery and should be discussed in the national framework.

Conclusion

Rare genetic forms of obesity have various aetiologies but share the phenotype of severe, early-onset obesity associated with abnormalities of hypothalamic function, including eating disorders and endocrine abnormalities. All genetic forms and intermediate phenotypes of combined heterozygous genetic variants are not as rare when targeting a population with severe obesity and eating disorders. The role of a reference centre is to help clinicians in the diagnosis, assessment and management. For this purpose, the French *PNDS Generic Obesity of Rare Causes* is available to health professionals on the HAS website. Genetic diagnosis is clinically oriented, for which the *Obsgen* website represents a practical tool.

Care must be early and comprehensive, with particular attention for transition periods, with close collaboration between the reference centre and the multidisciplinary specialists involved (psychiatrist, neurologist, pneumologist, etc.). Even if the genetic abnormality plays a major role in the development of obesity, it is necessary to work on the environment and encourage extended support. Coordination between the caregivers and social actors is essential to improve the care pathways and daily life of patients, which are very strongly intertwined. Actors involved in these pathways must be in place to help the families of these patients, who require coordinated care that needs to be promoted and further developed. Such medical and psycho-social care, which supports the therapeutic strategy, can now also count on therapeutic hopes, which mainly target the leptin/melanocortin pathways.

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Figure legends

Figure 1. The hypothalamic leptin/melanocortin pathway and regulation of the energy balance.

Leptin (encoded by *LEP*), via its receptor (*LEPR*), acts at the hypothalamic arcuate nucleus, where it activates anorectic neurons that express the *POMC* gene. It has inhibitory effects on neurons expressing the orexigenic peptides, neuropeptide Y (*NPY*) and Agouti related-protein (*AGRP*) (not shown here). The *POMC* protein is cleaved by the enzymes prohormone convertase 1/3 and 2 (encoded by *PCSK1* and *PCSK2*, respectively), expressed within the arcuate nucleus. The cleavage of *POMC* results in the production of melanocortins (α -, β -, and γ -melanocyte stimulating hormone [MSH]). Melanocortins, in particular α -MSH, act via G protein-coupled receptors (notably encoded by *MC3R* and *MC4R*). Other genes, such as *SH2B1* and *MRAP2*, encode regulators of *LEPR* and *MC4R* proteins, respectively. *SIMI*, *ADCY3*, *NTRK2*, and *BDNF* are genes involved in the development of neuronal populations in the hypothalamic region. Ghrelin, secreted mainly by the stomach, stimulates orexigenic neurons via its receptor (GHS-R). Mutations known in humans are indicated by a red cross.

Figure 2. Continuum of clinical situations in genetic obesity (Figure from the collective work carried out within the framework of the PNDS).

From left to right, rare genetic chromosomal and monogenic situations to the most common polygenic forms of obesity. In common polygenic obesity, multiple frequent variants (polymorphisms [SNPs]) contribute to the development of obesity, in interaction with environmental factors. Taken individually, they each have a small effect on weight gain, but their combination (called a polygenic score) can confer a high risk of developing obesity. A. Rare obesity with complete penetrance and a definite genetic background. B. Rare obesity with intermediate penetrance, with a less well-proven genetic background.

Table 1. The main syndromic obesities

Syndrome	Prevalence	Features associated with obesity	Mode of transmission Gene Genomic region
Alström	1-9/1 000 000	Retinal dystrophy, sensorineural deafness, dilated cardiomyopathy, renal, pulmonary, and hepatic damage	Autosomal recessive <i>ALMS1</i> 2p13
Bardet-Biedl	1/13 500 to 1/175 000	Intellectual disability, retinal dystrophy or retinitis pigmentosa, polydactyly, hypogonadism, and renal anomalies	Autosomal recessive or multi-allelic transmission > 20 genes Most common <i>BBS1</i> (11q13) and <i>BBS10</i> (12q21)
CHOPS	< 1/1 000 000	Intellectual disability, coarse facial features, cardiac anomalies, pulmonary anomalies, short stature, and skeletal dysplasia	Autosomal dominant <i>AFF4</i> 5q31
16p11.2 deletion	N.A.	Developmental delay, intellectual disability, autism spectrum disorders, macrocephaly, and epilepsy	Autosomal dominant 16p11.2 deletion
Microdeletion including <i>SH2B1</i>	< 1/1 000 000		16p11.2 (28.7-28.9 Mb)
<i>MYT1L</i>	N.A.	Intellectual disability and behavioural disorders	Autosomal dominant <i>MYT1L</i> 2p25
MO1 syndrome (Morbid obesity 1)	<1 / 1 000 000	Intellectual disability metabolic syndrome insulin resistance, spermatogenesis defect	Autosomal recessive <i>CEP19</i> 3q29
Pseudo-hypoparathyroidism type Ia with Albright* osteodystrophy	1/10 000 à 1/30 000	Facial dysmorphism, brachymetacarpia and brachymetatarsia, variable developmental delay, hormonal resistance representation (hypocalcaemia, hypothyroidism, and pubertal delay)	Autosomal dominant <i>GNAS1</i> 20q13
Prader-Willi *	N.A.	Neonatal hypotonia, intellectual disability, facial dysmorphism, stunting, hypogonadism, and hyperphagia	Anomaly in the 15q11-q13 region of paternal origin subject to imprinting
Schaaf-Yang	< 1/1 000 000	Prader-Willi-like (obesity, eating difficulties), hypotonia, intellectual disability, and autism spectrum disorders	Variants in the gene of paternal origin (imprinted region) <i>MAGEL2</i> 15q11
WAGR* Syndrome	N.A.	Wilms' tumour, aniridia, genitourinary malformations (hypospadias, cryptorchidism), and intellectual disability	Autosomal dominant <i>WT1</i> , <i>PAX6</i> , <i>BDNF</i> Deletion of 11p13-p14
X fragile*	1/5 000 (boys) 1/8 000 (girls)	Intellectual disability, hyperactivity, facial dysmorphism, and post-pubertal macro-orchidism	X-linked dominant <i>FMR1</i> Xq27

AFF4: AF4/FMR2 family member 4, ALMS1: Alström syndrome 1, BBS: Bardet-Biedl syndrome, CEP19: centrosomal protein 19, CHOPS: cognitive impairment, coarse face, heart defects, obesity,

pulmonary involvement, short stature, skeletal dysplasia, CREBBP: FMR1: fragile X mental retardation 1, GNAS1: guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1, MAGEL2:MAGE family member L2, SH2B1: SH2B adaptor protein 1,WAGR: Wilms tumor, aniridia, genitourinary malformations, mental retardation, WT1: WT1 transcription factor

*PNDS (National Diagnostic and Care Protocol) available ; N.A.: not applicable (reported cases, very rare)

Table 2. The main monogenic forms of obesity involving the leptin-melanocortin pathway

Gene	Phenotype associated with obesity	Mode of transmission Genomic region
Adenylate cyclase 3 (<i>ADCY3</i>)	Olfaction disorders ± mild intellectual disability	Autosomal recessive 2p23
Brain Derived Neurotrophic Factor (<i>BDNF</i>)	Intellectual disability, hyperactivity, and hyperphagia	Autosomal dominant Deletion in 11p14
Leptin (<i>LEP</i>)	Gonadotropic and thyrotropic deficiencies and immune deficiency (variable)	Autosomal recessive 7q32
Leptin receptor (<i>LEPR</i>)	Gonadotropic, thyrotropic, and somatotropic deficiencies	Autosomal recessive 1p31
Melanocortin 4 receptor (<i>MC4R</i>)	Recessive: severe and early onset obesity	Autosomal recessive 18q21
Melanocortin Receptor Accessory Protein 2 (<i>MRAP2</i>)	High blood pressure, high blood sugar	Autosomal dominant 6q14
Neurotrophic tyrosine kinase receptor type 2 (<i>NTRK2</i>)	Developmental delay and behavioural problems	Autosomal dominant 9p21
Proprotein convertase subtilisin/kexin type 1 (<i>PCSK1</i>)	Corticotropic, gonadotropic, thyroid insufficiency, postprandial hypoglycaemic episode, central diabetes insipidus, and neonatal diarrhoea	Autosomal recessive 5q15
Proopiomelanocortin (<i>POMC</i>)	Corticotropic insufficiency, thyroid insufficiency ± red hair, and gonadal or somatotropic insufficiency	Autosomal recessive 2p23
SIM1 bHLH transcription factor1 (<i>SIM1</i>)	Behavioural disorders, autism spectrum disorders, and hyperphagia	Autosomal dominant 6q16

For a description of all genetic forms of obesity, please refer to Appendix 2 of the NDPD Obesity of Rare Causes and the link https://docs.google.com/spreadsheets/d/1vQUcZna_vjpgVLLtylDKc1zIVRNvoSPOVITsixUdTWg/edit#gid=0

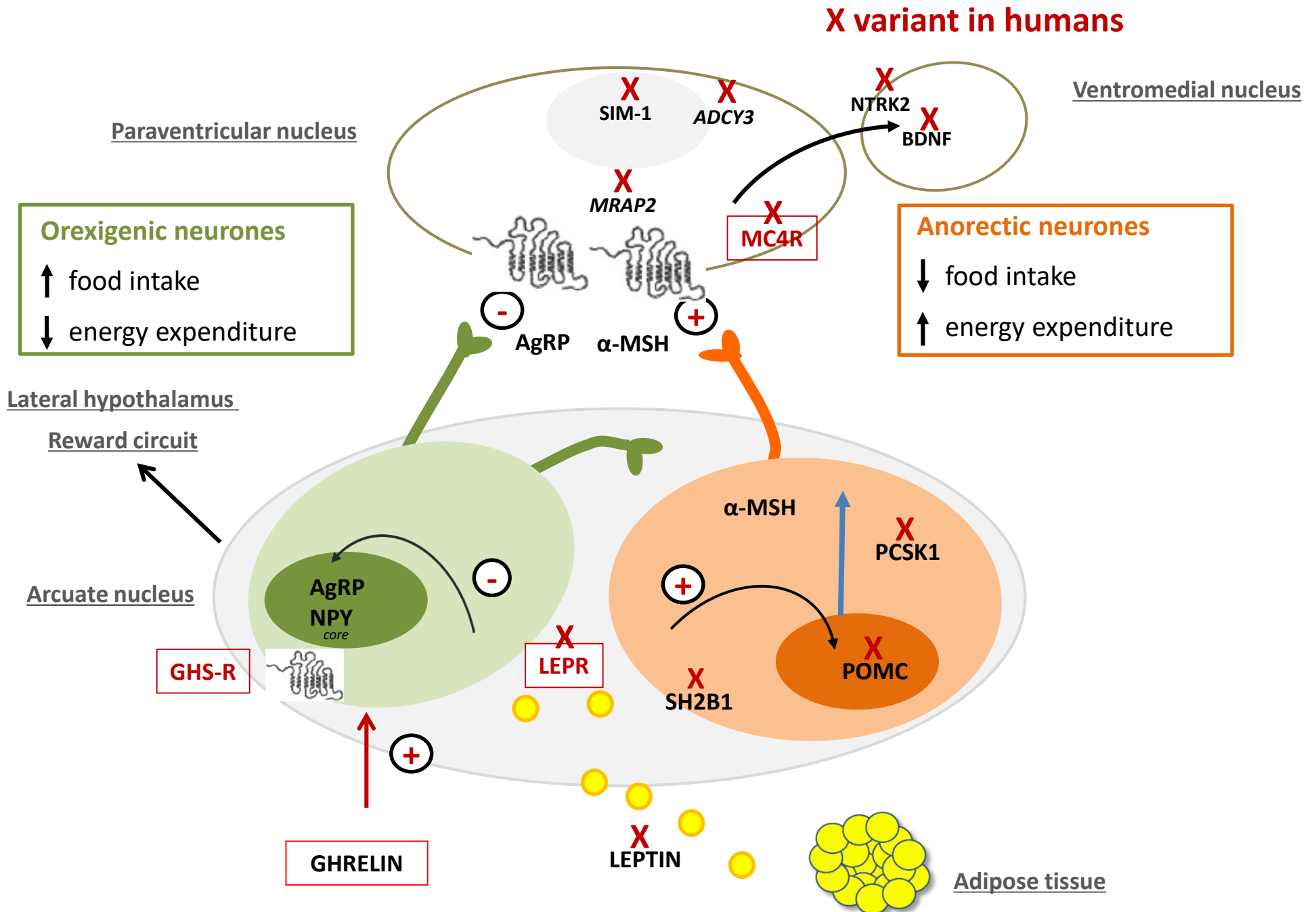
Table 3. Objectives and practical advice for the management of eating disorders according to age

Objectives	Infants Children < 3 years	School-age children	Adolescents > 15 years and adults
To maintain habits and establishing a dietary plan	<ul style="list-style-type: none"> - Regular breaks during bottle-feeding - Respect the frequency of feeding - Adaptation of the volume according to the speed of weight gain - In exceptional cases, increase the dilution of the milk - Check the quantities offered during diversification - Avoid inter-meal feedings 	<ul style="list-style-type: none"> - Establish written breakdown of meals with a plan (timetable, structure) and, if necessary, elements of ritualisation of meals (plate and glass dedicated to the child, tray to determine the volume of the meal) - Limit impulsivity: avoid visual stimuli (do not put bread or food within reach, limit the quantities cooked, etc.), offer cutlery (mimicry), control the speed of water intake 	<ul style="list-style-type: none"> - Establishment of an individualised dietary plan in writing that is non-negotiable - Ritualisation of food intake by respecting schedules, quantities, and contents = The principle of food safety: "no doubt, no hope". Use of documents (easy to read and understand) in case of intellectual disability
Control/restrict access to food	<ul style="list-style-type: none"> - Favour the visual aspect (presentation and volume of vegetables and dedicated dishes for the child) - Offer a variety of flavours (herbs, spices, etc.) 	<ul style="list-style-type: none"> - Learn to read labels/choosing products, limiting purchases - Favour the visual aspect (presentation and volume of vegetables and choice of crockery) - Offer a variety of flavours (herbs, spices, etc.) - Lock the kitchen, no food available at home 	<ul style="list-style-type: none"> - Close the kitchen or storerooms - Identify possible sources of access to food - Means of compliance explained to shopkeepers, care facilities, and hospitals - Be vigilant on independent journeys - Avoid food stimuli (shops, professional internships, buffets) - Avoid pocket-money
Controlling behaviour		<ul style="list-style-type: none"> - Anticipate: rehearse the organisation of the following day with the child and "negotiate" any dietary changes (equivalence system) - Overall management of behavioural problems (psychiatrist/psychologist) - Daily adapted physical activity 	<ul style="list-style-type: none"> - Build trust to reduce anxiety - Under no circumstances should food be used as a punishment or reward. - Plan occupational activities throughout the day not related to food - Avoid cooking classes, especially if unsupervised, and restaurant work, - Daily adapted physical activity
Promote the coordination of actors for a coherent approach to care	<ul style="list-style-type: none"> - Individualised childcare plan at the nursery - Written food allocation for parents and childcare facilities - Telephone contact 	<ul style="list-style-type: none"> - Individualised childcare plan for school, hospitalization, and social structures - Contact with referents - Written food allocation for parents and care facilities 	<ul style="list-style-type: none"> - Contact with referents in care facilities - Written food allocation for parents and care facilities

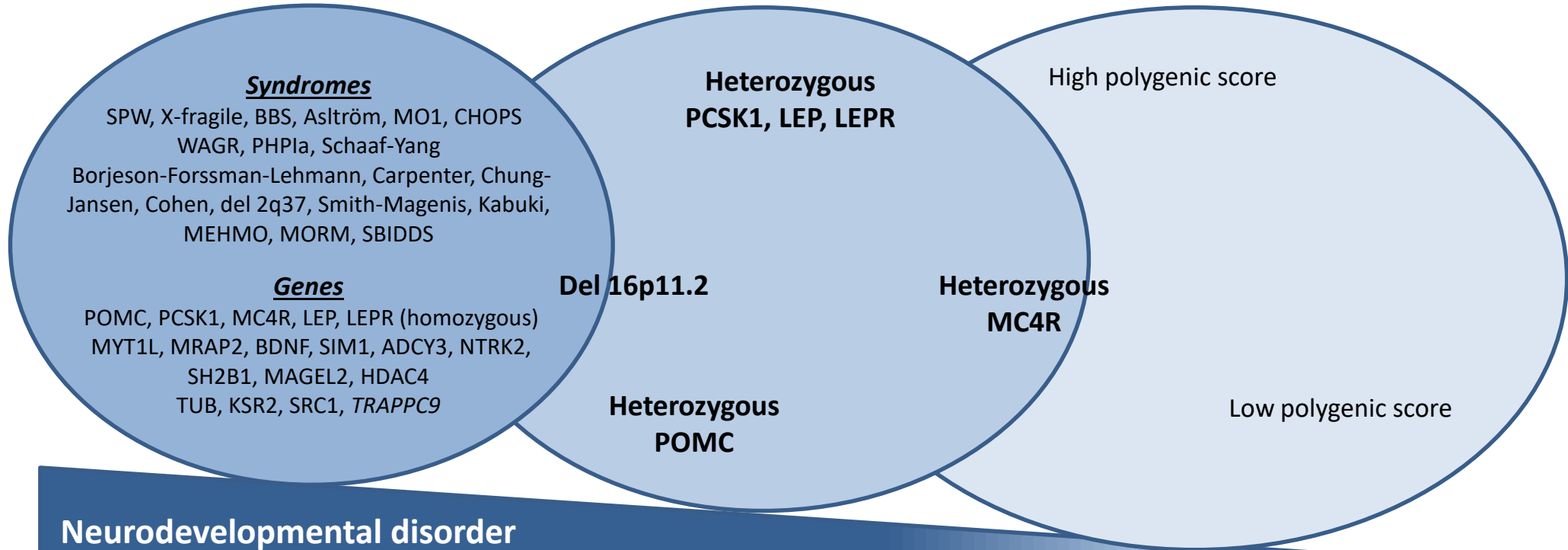
Table 4. Practical advice on the assessment and specific management of physical activity in genetic obesity

PA prescription	
Objective Contribute to increasing the patients' motivation towards PA	
Guidelines - Personalised, accounting for: age, physical fitness, impairments (functional disability, visual impairment, cognitive impairment, learning difficulties, behavioural impulsivity, social skill disorders), therapeutic goals, initial PA level, patient motivation, and possibilities offered by the environment	
Content - Tips for reducing sedentary time, increasing breaks during sedentary bouts, and increasing PA in daily life - Characteristics of recreational PA: type of PA, frequency, duration, and intensity - Individual or group-based exercise program - Medical certificate of no contraindication to the activity for the selected sport (if necessary)	
Example for a person without a neurodevelopmental disorder - Walk 20 minutes per day during transportation or daily activities - Practice 2 sessions of physical activity per week supervised by an PA instructor with varied endurance and muscle strengthening exercises - Spend < 2 h/d in front of the television or screens - At work or during daily sitting activities: stand up at least once every hour	
Recommended adaptations for genetic obesity with a neurodevelopmental disorder	
<i>Activites</i>	<ul style="list-style-type: none"> - Vary the activities and allow flexibility in the choice of exercises performed to combine the different types of recommended activities * Endurance: indoor and outdoor, brisk walking, cycling, ball games, active videos * Muscle strengthening: repeated muscle contractions using body weight, weight training equipment, or elastic bands * Reduce sedentary time: encourage patients to get up regularly, organise "active breaks" at regular intervals - Favour playful activities in the form of games to maintain adherence - Give priority to activities that are often appreciated, such as * Dancing and music (high sensitivity and receptivity to musical rhythms in many cases of ADD). * Water and non-weight bearing activities (swimming pool, balneotherapy). In addition to its soothing properties, fluid movements in water facilitate work on coordination and relieve possible musculoskeletal pain. - Team activities should be favoured whenever possible. Mutual goodwill and the collective aspect of sharing are factors that improve motivation. - Individual sessions with a 1:1 interaction with a trained PA instructor recommended, especially in case of behavioural problems. - Set up adapted exercises * Motor skills itineraries to maintain attention and motivation during the exercise period through a succession of motor activities (fast walking, ball games, racket games, cycling, go-karting, etc.). * Balance, proprioception and psychomotricity: necessary in certain syndromes, such as PWS with deficiencies of balance, spatiotemporal representation, and fine motor skills
<i>Resources</i>	<ul style="list-style-type: none"> Set up rituals and planning: reassures about known activities - Use easy to read and understand materials (i.e visual pictograms) to represent *Types of activities symbolised by a drawing: ball, motor skills itinerary, fast walking, cycling *Time: watch, weekly planner, diary *Space and place of performance: at home, in a care facility

	<p>*Supporters: parents, educators, PA instructor.</p> <ul style="list-style-type: none"> - Use a visual pleasure scale to quantify the pleasure felt after each session = a good way for the caregiver or family member to identify activities to encourage or avoid
<i>Monitoring and conditions of implementation</i>	<ul style="list-style-type: none"> - Evaluate on a regular basis, reward even minimal progress to reinforce confidence, and be encouraging - Involve family and friends who should be informed of the benefits of physical activity and, if possible, be involved in the day-to-day implementation of physical activity and be given a "practical sheet" on the daily practice of physical activity to facilitate and reinforce their commitment - Design the PA programs as much as possible jointly by the reference centre and experienced PA instructors whose objectives are complementary to a physical medicine and rehabilitative approach



Early severe obesity
Eating disorder



Neurodevelopmental disorder

Endocrine deficiencies
Other symptoms