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Review Article

Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016

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Key Words
Obesity · Genetics · Leptin-melanocortin pathway · Bariatric surgery · Whole-exome sequencing

Abstract
Obesity results from a synergistic relationship between genes and the environment. The phenotypic expression of genetic factors involved in obesity is variable, allowing to distinguish several clinical pictures of obesity. Monogenic obesity is described as rare and severe early-onset obesity with abnormal feeding behavior and endocrine disorders. This is mainly due to autosomal recessive mutations in genes of the leptin-melanocortin pathway which plays a key role in the hypothalamic control of food intake. Melanocortin 4 receptor(MC4R)-linked obesity is characterized by the variable severity of obesity and no notable additional phenotypes. Mutations in the *MC4R* gene are involved in 2–3% of obese children and adults; the majority of these are heterozygous. Syndromic obesity is associated with mental retardation, dysmorphic features, and organ-specific developmental abnormalities. Additional genes participating in the development of hypothalamus and central nervous system have been regularly identified. But to date, not all involved genes have been identified so far. New diagnostic tools, such as whole-exome sequencing, will probably help to identify other genes. Managing these patients is challenging. Indeed, specific treatments are available only for specific types of monogenic obesity, such as leptin deficiency. Data on bariatric surgery are limited and controversial. New molecules acting on the leptin-melanocortin pathway are currently being developed.

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Introduction

Obesity, defined as an excess of fat mass with an impact on physical health, is a complex and multifactorial disease. It is a public health concern, and the World Health Organization estimates that 1.9 billion adults are overweight (BMI > 25 kg/m^2), among which 600 million are obese (BMI > 30 kg/m^2). Also, in children, the worldwide prevalence of overweight and obesity increased from 4.2% in 1990 to 6.7% in 2010 but has stabilized in recent years [1]. Obesity results from the interaction of genetic factors with numerous environmental factors (such as overeating and/or reduction of physical activity). The comprehension of the molecular mechanisms of obesity progressed enormously in the last years thanks to the development of faster and more precise genetic screening tools applied in cohort studies or in examinations with focus on subjects and their families. In particular, whole-exome sequencing showed its power to identify new syndromes associated with obesity or new forms of obesity due to a single naturally occurring dysfunctional gene (i.e. monogenic obesity).

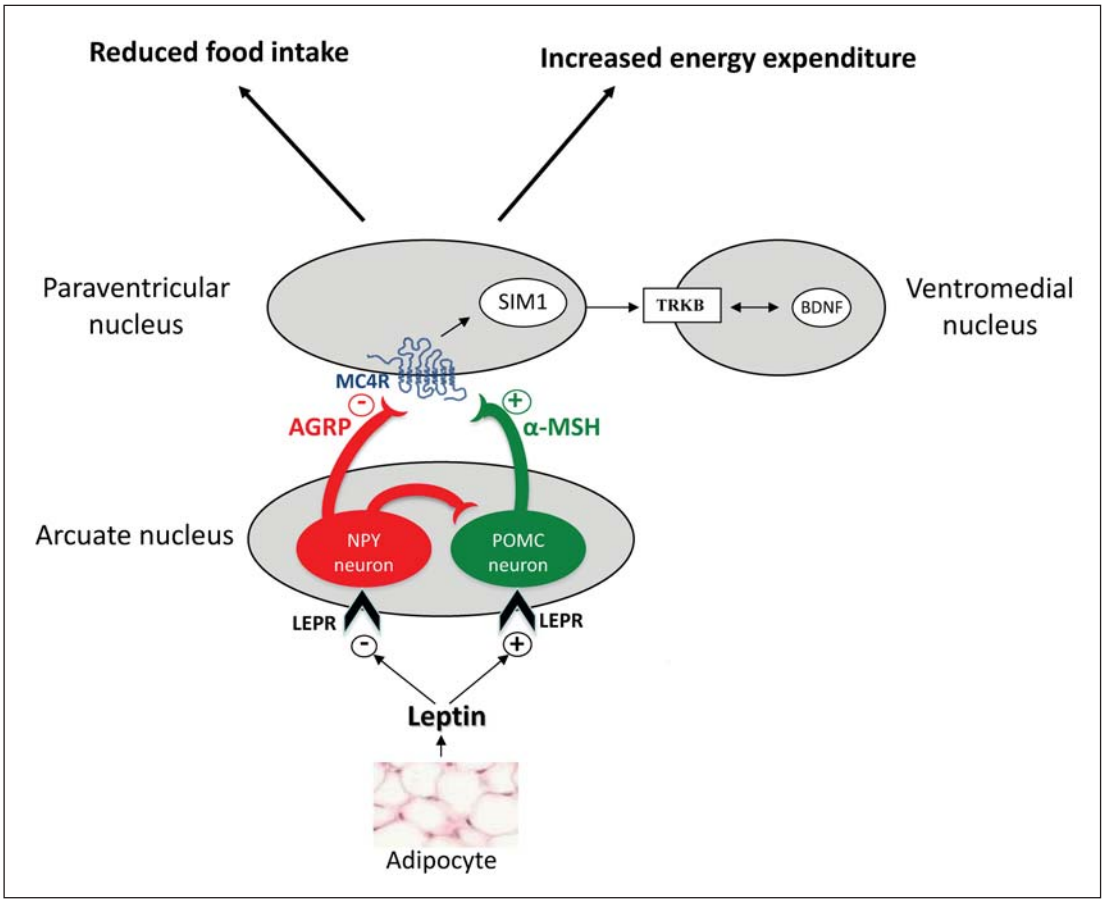

Fig. 1. The leptin/melanocortin pathway. POMC neurons in the arcuate nucleus are activated by leptin and produce the α-melanocyte stimulating hormone (α-MSH), which then activates the MC4R receptor in the paraventricular nucleus resulting in a satiety signal. A separate group of neurons expressing NPY and AGRP produce molecules that act as potent inhibitors of MC4R signaling. The downstream roles of SIM1, BDNF, and TKRB are currently being explored. AGRP = agouti-related protein; BDNF = brain-derived neurotropic factor; LEPR = leptin receptor; NPY = neuropeptide Y; POMC = proopiomelanocortin; SIM1 = single-minded 1; TRKB = tyrosine kinase receptor.

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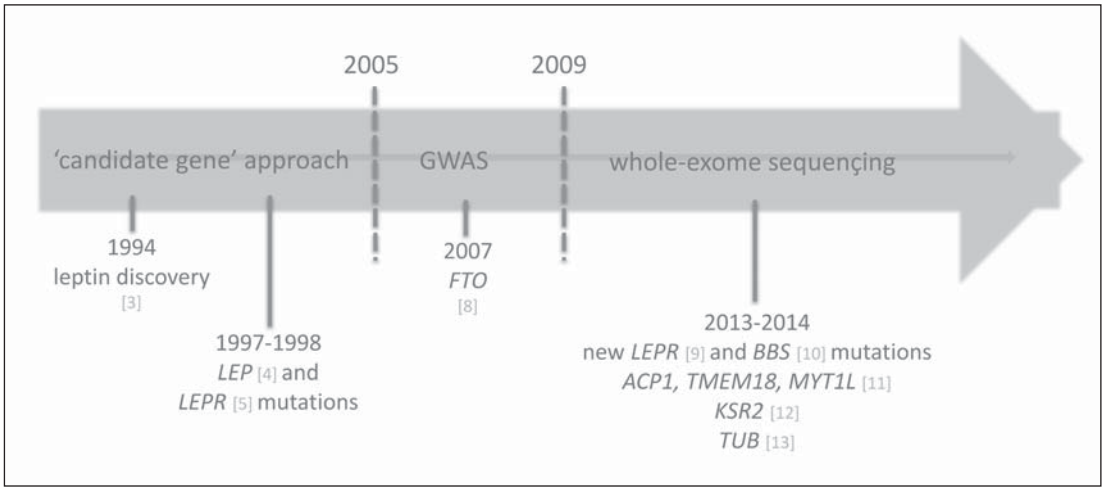

Fig. 2. Historical steps leading to the discovery of genetic mutations in obesity. ACP1 = acid phosphatase 1, soluble; BBS = Bardet-Biedl syndrome; FTO = fat mass and obesity; GWAS = genome wide scan association study; KSR2 = kinase suppressor of Ras 2; LEP = leptin; LEPR = leptin receptor; MYT1L = myelin transcription factor 1-like; TMEM18 = transmembrane protein 18; TUB = tubby bipartite transcription factor.

Several clinical presentations are described in obesity depending on the genes involved:

- Monogenic obesity is described as rare and severe early-onset obesity associated with endocrine disorders. The impact of genetics is high and only little dependent on environmental factors. This form of obesity is mainly due to mutations in genes of the leptin/melanocortin axis (fig. 1) involved in food intake regulation (genes of leptin (*LEP*) and leptin receptor (*LEPR*), proopiomelanocortin (*POMC*), proconvertase 1 (*PC1*)) or in specific genes linked to these pathways. New mutations were identified in the past few years.
- Syndromic obesity corresponds to severe obesity associated with additional phenotypes (mental retardation, dysmorphic features, and organ-specific developmental abnormalities). Prader-Willi (PWS) and Bardet-Biedl (BBS) syndromes are the 2 syndromes most frequently linked to obesity, but more than 100 syndromes are now associated with obesity.
- Oligogenic obesity, such as melanocortin 4 receptor(MC4R)-linked obesity, is characterized by a variable severity of obesity, partly dependent on environmental factors and the absence of a specific phenotype. This type of obesity is responsible for 2–3% of obesity in adults and children.

These rare forms of obesity distinguish themselves from the polygenic obesity, which is the most common clinical presentation. Here, each susceptibility gene considered individually would only have a slight effect on weight. The cumulative contribution of these genes would be amplified by an 'obesogenic' lifestyle (such as overfeeding, sedentary living, stress, etc.) [2]. This presentation of obesity will not be elaborated further in this review.

Rare genetic forms of obesity are important to be detected clinically because it allows to progress in understanding the physiopathology of obesity. On the other hand there is a specific management of these forms of obesity provided by specialized and multidisciplinary teams. Thus, this article aims to give an updated summary of genetic forms of obesity and their available therapeutic options, including bariatric surgery, for clinical care specialists occupied in the obesity field.

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Table 1. Rare monogenic forms of human obesity

Gene	Mutation type	Prevalence	Obesity	Associated phenotypes
Leptin	Homozygous mutation	Diagnosed in fewer than 100 patients worldwide	Severe, from the first days of life	Gonadotropic and thyrotropic insufficiency Alteration in immune function
LEPR	Homozygous mutation	2–3% of patients with severe early-onset obesity	Severe, from the first days of life	Gonadotropic, thyrotropic and somatotropic insufficiency Alteration in immune function
POMC	Homozygous or compound heterozygous	Diagnosed in fewer than 10 patients worldwide	Severe, from the first months of life	ACTH insufficiency Mild hypothyroidism and ginger hair if the mutation leads to the absence of POMC production
PCSK1	Homozygous or compound heterozygous	Diagnosed in fewer than 20 patients worldwide	Severe obesity occurring in childhood	Adrenal, gonadotropic, somatotropic and thyrotropic insufficiency Postprandial hypoglycemic malaises Severe malabsorptive neonatal diarrhea Central diabetes insipidus
SIM1	Translocation between chr 1p22.1 and 6q16.2 in the *SIM1* gene	Diagnosed in fewer than 50 patients worldwide	Severe obesity occurring in childhood	Inconstantly, neurobehavioral abnormalities (including emotional lability or autism-like behavior)
NTRK2	De novo heterozygous mutation	Diagnosed in fewer than 10 patients worldwide	Severe obesity from the first months of life	Developmental delay Behavioral disturbance Blunted response to pain

Evaluation of Strategies in Genetic Explorations of Obese Cases

Different molecular strategies were used to determine the genetic factors involved in obesity (fig. 2). The 'candidate gene' approach was one of the first and allowed, in association with the precise clinical analysis of subjects presenting with early-onset extreme obesity (prior to 6 years of age), to define rare monogenic forms of obesity (table 1). The highlighted genetic anomalies affect key factors related to the leptin-melanocortin pathway, which are known to be pivotal in energy balance regulation (fig. 1) [4–7].

Since 2005, the genome-wide association study (GWAS) has made it possible to identify 119 independent loci associated with BMI and common obesity status in large populations [8]. Among these, the most replicated gene was the *FTO* (fat mass and obesity) gene in obese children and adults [9]. Interestingly, the GWAS showed that almost all genes involved in monogenic and oligogenic forms of obesity (*LEPR*, *POMC*, *MC4R*, *PC1*) display common variants associated with BMI and polygenic obesity as well [8].

Recently, faster, more precise and effective genetic screening tools, such as whole-exome sequencing, have been developed. Whole-exome sequencing allowed identifying mutations responsible for rare genetic diseases in a small number of affected subjects. In genetic obesity, it notably revealed 2 novel homozygous *LEPR* mutations [10] and 5 novel mutations in BBS genes [11]. In case of BBS, this approach confirmed the importance of genes involved in the functioning of the primary cilium. It highlighted that dysfunction in primary cilia can be responsible for various metabolic defects and particularly plays a role in energy homeostasis dysregulation leading to severe obesity. This method was also helpful to identify new variants and mutations in patients with syndromic obesity [12–17]. For example, it demonstrated a

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paternal deletion, encompassing the *ACP1* (acid phosphatase 1), *TMEM18* (transmembrane protein 18), and *MYT1L* (myelin transcription factor 1-like) genes, in 5 unrelated patients presenting with severe early-onset obesity, intellectual deficiency, and severe behavioral difficulties [12]. It also enabled to identify multiple rare variants in the *KSR2* (kinase supressor of Ras 2) gene in 45 unrelated individuals presenting with a low heart rate, reduced basal metabolic rate, and severe insulin resistance in addition to severe obesity [13]. A homozygous frameshift mutation in the *TUB* (tubby-like protein) gene was also identified using whole-exome sequencing in a proband who presented with obesity, night blindness, decreased visual acuity, and electrophysiological features of a rod-cone dystrophy [14] (table 2). Exome sequencing also revealed a mutation of the *CPE* (carboxypeptidase E) gene in a morbidly obese woman with intellectual disability, type 2 diabetes mellitus, and hypogonadotropic hypogonadism [15], and it showed a mutation of the *RAI1* (retinoic acid-induced 1) gene in a child with morbid early-onset obesity, hypoventilation, and autonomic and behavioral disturbances [16].

Clinical Phenotypes

The most frequent forms of syndromic obesity are PWS and BBS (table 2).

The PWS (1 in 20,000–25,000 births) is characterized by severe neonatal hypotonia, eating disorders evolving in several phases (from anorexia with sucking disorders in the first months of life to hyperphagia with major food impulsiveness at about 4–8 years of age) [18], body composition abnormalities [19], endocrine anomalies (growth hormone (GH) deficiency, hypogonadism), variable intellectual deficiency, behavioral difficulties, and dysmorphy [20]. This syndrome is due to the physical or functional absence of the paternal chromosomal segment 15q11-q13. At least 5 genes, located in the PWS chromosomal region and expressed in the hypothalamus, have been identified, but their functions have not yet been understood completely: *MRKN3* (makorin 3), *MAGEL2* (MAGE-like 2), *NDN* (necdin), *NPAP1* (nuclear pore associated protein 1), *SNURF-SNRPN* (*SNRPN* upstream reading frame – small nuclear ribonucleoprotein polypeptide N) [21, 22]. The exact mechanisms by which these genes contribute to the development of early-onset obesity are still to be defined. Several other unknown genes are probably mutated, and this could explain the variability of PWS phenotype.

BBS is a highly heterogeneous disease. It is characterized by severe early-onset obesity, retinal dystrophy, malformed extremities (syndactyly, polydactyly), kidney diseases, hypogonadism, dysmorphy, and eventually mental disabilities. At least 19 different genes are implicated in the BBS, but all are involved in primary cilium function [23]. Consequently, BBS is now defined as a ciliopathy (primary cilium dysfunction) [24]. The specific mechanisms leading to obesity in BBS are still to be elucidated. Several hypotheses were suggested. In the first place, the hypothesis of a central origin of obesity due to hypothalamic dysfunction and leptin resistance associated with hyperphagia was developed. BBS proteins are, in particular, required for LEPR localization in the hypothalamus [23]. Other hypotheses of a peripheral origin from adipose tissue and adipocyte proliferation or other endocrine tissues (pancreas, stomach, intestine) were also proposed [25].

Additional rare syndromic forms of obesity are presented in table 2.

Mutations in human genes encoding for leptin [4], LEPR [5], POMC [6], and PC1 [7] lead to severe obesity occurring soon after birth (table 1). Patients carrying mutations show a rapid and very early important increase in weight, as illustrated by the weight curve of *LEPR*-deficient subjects [26]. Feeding behavior is mainly characterized by major hyperphagia and ravenous hunger [27]. But, surprisingly, a leptin-deficient Austrian girl has been detected with more moderate obesity (BMI 31.5 kg/m^2) and extremely low daily calorie intake in

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Table 2. Main syndromic forms of obesity

Syndrome	Clinical features in addition to obesity	Prevalence	Genetic
Prader-Willi	Neonatal hypotonia, mental retardation, hyperphagia, facial dysmorphy, hypogonadotrophic hypogonadism, short stature	1/25,000 births	Lack of the paternal segment 15q11-q13 (microdeletion, maternal disomy, imprinting defect or reciprocal translocation)
Bardet-Biedl	Mental retardation, retinal dystrophy or pigmentary retinopathy, dysmorphic extremities, hypogonadism, kidney anomalies	1/125,000 to 1/175,000 births	BBS1 (11q13); BBS2 (16q12.2); BBS3 (*ARL6*, 3q11); BBS4 (15q24.1); BBS5 (2q31.1); BBS6 (*MKKS*, 20p12); BBS7 (4q27); BBS8 (*TTC8*, 14q31); BBS9 (*PTHB1*, 7p14); BBS10 (*C12ORF58*, 12q21.2); BBS 11 (*TRIM32*, 9q33.1); BBS12 (*FLJ35630*, 4q27); BBS13 (*MKS1*, 17q23); BBS14 (*CEP290*, 12q21.3); BBS15 (*WDPCP*, 2p15); BBS16 (*SDCCAG8*, 1q43); BBS17 (*LZTFL1*, 3p21); BBS18 (*BBIP1*, 10q25); BBS19 (*IFT27*, 22q12)
Cohen	Retinal dystrophy, prominent central incisors, dysmorphic extremities, microcephaly, cyclic neutropenia	Diagnosed in fewer than 1,000 patients worldwide	Autosomal recessive *COH1* gene (chr 8q22-q23)
Alström	Retinal dystrophy, neurosensory deafness, diabetes, dilated cardiomyopathy	Diagnosed in about 950 patients worldwide	Autosomal recessive *ALMS1* gene (chr 2p13-p14).
X fragile	Mental retardation, hyperkinetic behavior, macroorchidism, large ears, prominent jaw	1/2,500 births	X-linked *FMR1* gene (Xq27.3)
Borjeson-Forssman-Lehmann	Mental retardation, hypotonia, hypogonadism, facial dysmorphy with large ears, epilepsy	Approximately 50 reported patients	X-linked *PHF6* gene (Xq26-q27)
Albright hereditary osteodystrophy	Short stature, skeletal defects, facial dysmorphy, endocrine anomalies	1/1,000,000 births	Autosomal dominant *GNAS1* gene (20q13.2)
16p11.2 deletion syndrome	Developmental delay, intellectual disability, autism spectrum disorders, impaired communication, socialization skills	Approximately 3/10,000 births	Autosomal dominant Microdeletion of 16p11.2
Kinase suppressor of Ras2 (KSR2) variants	Hyperphagia in childhood, low heart rate, reduced basal metabolic rate, severe insulin resistance	Approximately 65 reported patients	Rare *KSR2* variants (12q24.22-q24.23)
TUB mutation	Night blindness, decreased visual acuity and electrophysiological features of a rod-cone dystrophy	Identified in 3 affected sibs from a consanguineous Caucasian family	Homozygous *TUB* mutation (11p15.4)
ACP1, *TMEM18*, *MYT1L* deletion	Hyperphagia, intellectual deficiency, severe behavioral difficulties	Approximately 13 reported patients	Paternal deletion encompassing the *ACP1*, *TMEM18*, *MYT1L* genes (2p25)

everyday life despite a rapid increased consumption of calories in a test meal [28]. This observation might illustrate the determinant effect of the patient's (familial) environment and/or the possibility that voluntary caloric restriction may sometimes counteract the consequence of a lacking leptin signal. However, despite this particular case, severe early-onset obesity with major hyperphagia is recognized as the main clinical presentation of leptin or LEPR deficiency [27].

In addition to severe early-onset obesity, hypogonadotropic hypogonadism completes the phenotype of patients carrying mutations in the *LEP* or *LEPR* gene. No pubertal development was observed in some individuals with *LEP* or *LEPR* mutations, while in others there was evidence of spontaneous pubertal development suggesting a recovery of hormonal functions with time. For example, the follow-up of LEPR-deficient sisters revealed a normal spontaneous pregnancy [29]. Insufficient somatotropic secretion and thyrotropic insufficiency are also described in some patients with a *LEPR* mutation [5, 26]. *LEPR* mutations in severely obese subjects are not so rare with an estimated prevalence of 2–3% and need to be searched for in case of extreme obesity associated with endocrine abnormalities [23, 26, 30]. Recently, a congenital leptin deficiency due to biologically inactive leptin,was discovered in a young boy presenting with a clear clinical phenotype including extreme early-onset obesity and hyperphagia but high circulating leptin levels [31]. We recently reported on obese patients carrying homozygous *LEPR* mutations with slightly increased circulating leptin [26]. In summary, these observations demonstrate that circulating levels of leptin appearing normal in relation to BMI and fat mass do not rule out *LEP* or *LEPR* mutations.

Obese children with complete POMC deficiency have ACTH deficiency, mild central hypothyroidism [6] and sometimes alterations in the somatotropic and gonadotropic axes or inconstantly ginger hair [32]. The modifications in hair color, adrenal function, and body weight are consistent with the lack of *POMC*-derived ligands for the melanocortin receptors MC1R, MC2R, and MC4R, respectively.

Patients carrying a rare mutation in the proprotein convertase subtilisin/kexin type 1 (*PCSK1*) gene have, in addition to severe obesity, postprandial hypoglycemic malaises, hypogonadotropic hypogonadism, central hypothyroidism and adrenal insufficiency [7]. The mutation in *PCSK1* leads to a PC1 deficiency, an enzyme also involved in the maturation of insulin. Severe and rebel diarrhea, secondary to a lack in mature GLP-1 (glucagon-like peptide-1), is also described in case of *PC1* deficiency [33, 34] as well as persistent polydipsia and polyuria due to a central diabetes insipidus [35].

Other rare forms of obesity, due to mutations in several genes involved in the development of the hypothalamus and central nervous system, have been described in humans, allowing the identification of new pathways. Deletions of the *SIM1* (single-minded homolog 1) gene have been identified in subjects with early-onset obesity associated with hyperphagia, food impulsivity and variable Prader-Willi-like features (neonatal hypotonia, dysmorphy, developmental delay, early-onset obesity, short stature, hypopituitarism) [36, 37]. *SIM1* encodes a transcriptional factor involved in the development of the hypothalamic paraventricular nucleus, which plays a role in the melanocortin signaling pathway [38]. Sequencing of the coding region of *SIM1* identified also rare heterozygous variants in patients who presented with severe obesity, hyperphagia, and variable neurobehavorial phenotype (impaired concentration, memory deficit, emotional lability or autistic spectrum behavior) [39]. Likewise, a de novo heterozygous mutation in the *NTRK2* (neurotrophic tyrosine kinase receptor type 2) gene was described in an 8-year-old boy with severe early-onset obesity, mental retardation, developmental delay, and anomalies of higher neurological functions such as the impairment of early memory, learning, and nociception [40]. This gene encodes the brain-derived neurotropic factor (BDNF), and its associated tyrosine kinase receptor (TRKB) is involved in feeding regulation via a role downstream of MC4R signaling [41]. Other

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mutations in *NTRK2* were found in patients with early-onset obesity and developmental delay, but their functional consequences and their implication in obesity are yet to be determined.

Obesity related to *MC4R* mutations can be positioned between the exceptional forms of monogenic obesity and the polygenic common obesity and represents approximately 2–3% of childhood and adult obesity [42]. It is mostly characterized by an autosomal dominant mode of transmission with incomplete age-related penetrance and a lack of additional obvious phenotypes. The severity of the phenotype is variable (moderate to severe obesity), depending on the role of the environment and other potentially modulating genetic factors [43]. Subjects carrying *MC4R* mutations are usually heterozygous [44]. Homozygous or compound heterozygous carriers of *MC4R* mutations are very rare, and their phenotype is thus more severe [45–47]. In addition to obesity, children carrying *MC4R* mutations have a marked hyperphagia that decreases with age [48]. Meanwhile, the association between binge eating disorder and *MC4R* mutations [49] has not been confirmed [43, 44]. Hundreds of mutations have been identified with many functional alterations.

Genetic Diagnosis

If a rare genetic form of obesity is suspected, genetic diagnosis must be discussed and confided to specialists in reference centers (fig. 3).

In case of obesity associated with intellectual deficiency and/or behavioral difficulties, the genetic tests should include at least high-resolution karyotype, investigation of DNA methylation on chromosome 15, fragile X search, and study by comparative genomic hybridization (CGH) array. Specific research for other monogenic anomalies (*SIM1*, *MAGEL2*, *NTRK2*) must be discussed depending on the clinical phenotype.

In the event of obesity associated with retinal dystrophy, a ciliopathy should be searched, in particular BBS.

In case of severe early-onset obesity associated with endocrine anomalies suggesting a monogenic obesity, direct sequencing of the candidate gene (*LEP*, *LEPR*, *POMC*, *PCSK1*) is necessary to confirm the diagnosis. It will detect homozygous or compound heterozygous mutations responsible for interruption of the leptin-melanocortin axis. Family members need to be tested by segregation analysis to evaluate the risk of recurrence.

In case of early-onset, severe, and isolated obesity, *MC4R* mutations are detected by direct sequencing of the *MC4R* gene (1 exon). The diagnosis can be performed in several centers in France and in Europe.

Current Medical Treatment in Genetic Obesity

It is important to diagnose genetic forms of obesity because specific management, provided by specialized and multidisciplinary teams, is needed as soon as possible (starting in early childhood).

No specific treatment is described for syndromic obesity except for its general management (diet and physical activity, psychomotricity, adapted physical activities, hormone substitution, etc.). In PWS, GH therapy with doses typically used for childhood growth (starting before 1 year of age) can improve growth, body composition, muscle thickness, physical strength and agility, motor performance, fat utilization, and lipid metabolism in children and adults with PWS [50, 51]. Moreover, current active research on several molecules (beloranib, oxytocin, topiramate, ghrelin) is very promising for future treatment

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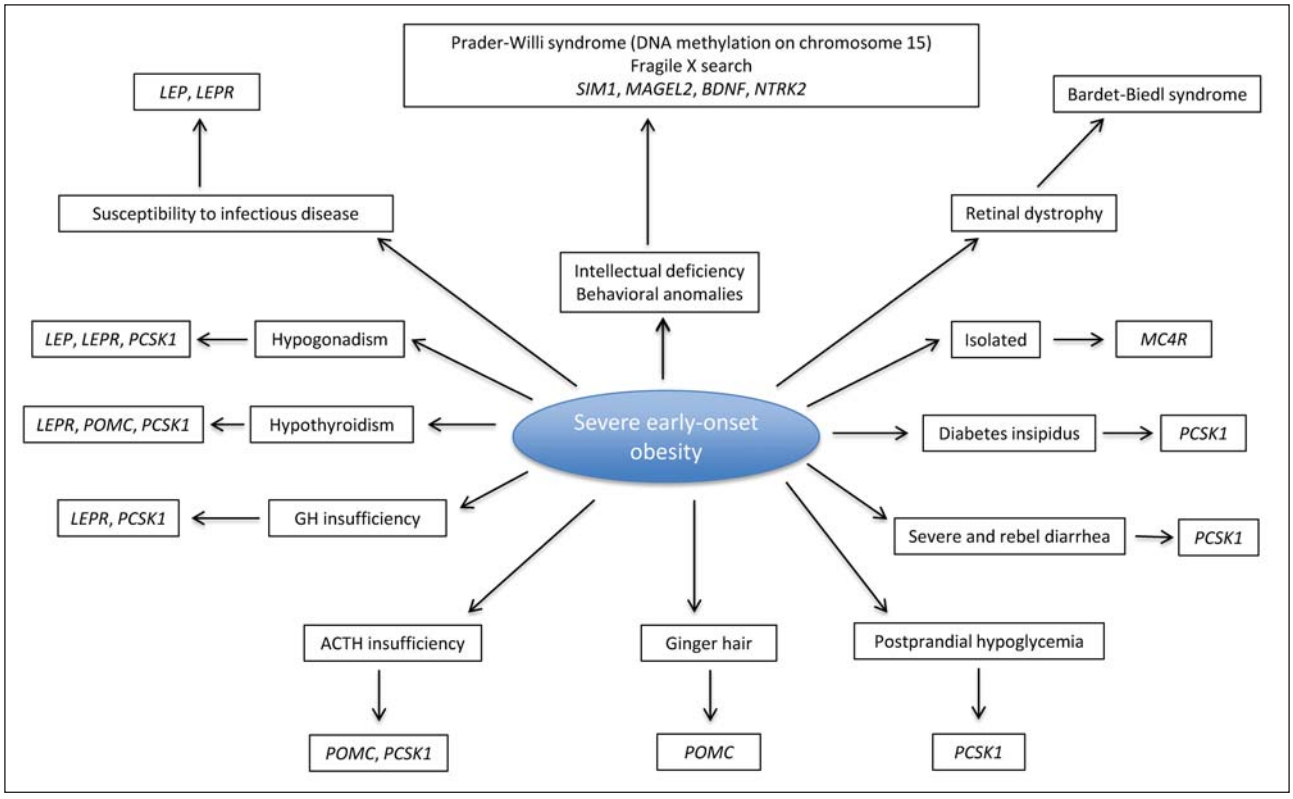

Fig. 3. Genetic diagnosis prioritization for severe early-onset obesity [4–7, 20, 22, 26, 36, 75]. BDNF = brain-derived neurotropic factor; LEP = leptin; LEPR = leptin receptor; MAGEL2 = MAGE-like 2; MC4R = melanocortin 4 receptor; NTRK2 = neurotrophic tyrosine kinase receptor 2; PCSK1 = proprotein convertase subtilisin/kexin type 1; POMC = proopiomelanocortin; SIM1 = single-minded 1.

of PWS. Individuals with PWS have a significant reduction in the number of oxytocin-producing neurons in the hypothalamic paraventricular nucleus; and a number of the PWS features, such as hyperphagia, obesity and behavioral anomalies, may be due to consequent hypothalamic hyposecretion of oxytocin. Preliminary studies in mice and humans have investigated the capacity of exogenous oxytocin to improve physical, behavioral, and cognitive aspects of PWS, but further research is necessary to better understand the exact effects of oxytocin on syndrome-specific behaviors in patients with PWS [52, 53].

In case of monogenic obesity, subcutaneous injection of leptin in children and adults with *LEP* mutations resulted in weight loss, mainly of fat mass, with a major effect on reducing food intake [31, 54]. Leptin treatment also induces aspects of puberty, even in adults [27]. Because of a non-functional LEPR, leptin treatment is useless in LEPR-deficient subjects. Their medical management is challenging, just as that of POMC- and PC1-deficient patients. Drugs that could safely bypass normal leptin delivery systems are being developed but are currently not available for humans [55].

For MC4R-deficient obese patients, to date, no specific management has been suggested, except well-balanced diet and physical activity. Patients with *MC4R* mutations were able to lose weight in a 1-year lifestyle intervention based on exercise, behavior, and nutrition therapy, but the maintenance of weight loss failed in contrast to patients without mutations [56]. Novel pharmacological MC4R agonists have been tested in vitro and can restore normal activity in mutated receptors. Preclinical trials are now being performed [57]. Thus, treatment

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Table 3. Surgical treatments in genetic forms of obesity

Type of genetic obesity	Number of cases	Mean age, years	Mean follow-up, years	Bariatric procedure	Results	Postoperative complications	References
PWS	24	10.7	5	sleeve gastrectomy	BMI loss of 10.7%; 95% of comorbidities in remission or improved	no complication	Alqahtani et al, 2015 [60]
	3	18.7	2.7	2 sleeve gastrectomy 1 gastric bypass	excessive weight loss of 63.2%	no major complication	Fong et al, 2012 [61]
	3	15.6	2	mini-gastric bypass	excess weight loss of 79%; resolution of hypertension; improved sleep apnea	no surgical complication	Musella et al, 2014 [63]
	60	19.7	5	gastric bypass gastric banding	average weight loss of 2.4%	variety of postoperative issues: death, pulmonary embolus, wound infection, gastric perforation	Scheimann et al, 2008 [64]
Syndromic obesity	16 PWS 6 BBS 1 Alström syndrome	11.7	4	sleeve gastrectomy	excess BMI loss of 60.2%; resolution of more than 90% of comorbidities	no significant complication	Alqahtani et al, 2014 [62]
BBS	1	16	3.5	gastric bypass	BMI loss of 33.3%; significant improvement in hypertension and mobility	no complication	Daskalakis et al, 2010 [65]
	1	33	1	sleeve gastrectomy	weight loss of 23.9%	no significant complication	Mujahid et al, 2014 [66]
	1	35	2.2	gastric banding	weight loss of 9%; no effect on type 2 diabetes	no complication	Mujahid et al, 2014 [66]
LEPR mutations	1	16	8	vertical gastroplasty	weight loss of 20%	no complication	Le Beyec et al, 2013 [67]
	1	18	0.8	vertical gastroplasty	weight loss of 44%	no complication	Huvenne et al, 2015 [26]
	1	26	1.5	gastric bypass	weight loss of 10%	no complication	Le Beyec et al, 2013 [67]
	1	36	5	gastric bypass	weight loss of 7%	no complication	Huvenne et al, 2015 [26]

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Table 3 (continued)

Type of genetic obesity	Number of cases	Mean age, years	Mean follow-up, years	Bariatric procedure	Results	Postoperative complications	References
Heterozygous *MC4R* mutations	4	45.5	1	gastric bypass	excess weight loss of 60%	1 aspiration pneumonia	Aslan et al, 2011 [68]
	9	36.2	1	3 gastric banding 6 gastric bypass	weight loss of 25.9%	no significant complication	Valette et al, 2012 [69]
	1	22	4.8	gastric bypass	excess weight loss of 76%	no complication	Elkhenini et al, 2014 [70]
	4	18.6	1	3 gastric banding 1 sleeve gastrectomy	excess weight loss of 48.6%	no complication	Censani et al, 2014 [71]
Homozygous *MC4R* mutations	1	17	1	gastric banding	weight gain of 7%	no complication	Aslan et al, 2011 [72]

with a highly-selective novel MC4R agonist in obese animal models resulted in decreased food intake, increased total energy expenditure, weight loss, and weight-independent improvement of insulin sensitivity after 8 weeks of treatment. No side effects, particularly those affecting blood pressure or heart rate, were observed in these studies [58].

Surgical Treatments in Genetic Obesity

The question of the potential efficiency of bariatric surgery arises in patients with genetic obesity. Indeed, today, bariatric surgery (laparoscopic gastric bypass, gastric banding, or sleeve gastrectomy) is the only long-term efficient treatment for severe obesity [59]. Currently, data on such treatments in patients with genetic obesity are limited and still controversial (table 3).

In PWS, the indication of bariatric surgery is highly discussed due to early-onset morbid obesity. In 24 recently described patient cases (mean age 10.7 years), bariatric surgery was reported to be beneficial. After laparoscopic sleeve gastrectomy, BMI loss was 14.7% (n = 22 patients) and 10.7% (n = 7 patients) on the first and fifth annual visit, respectively. 95% of comorbidities (obstructive sleep apnea, dyslipidemia, hypertension, and diabetes mellitus) were in remission or improved. No postoperative complications occurred [60]. In another study, two 15- or 23-year-old patients and one18-year-old patient underwent laparoscopic sleeve gastrectomy and laparoscopic gastric bypass surgery, respectively. After a median follow-up of 33 months, mean weight loss and percentage of excessive weight loss at 2 years were 32.5 kg and 63.2%, respectively. No major complication was observed [61]. In another study, 23 syndromic patients with an average age of 11.7 years (16 with PWS, 6 with BBS, and 1 with Alström syndrome) underwent laparoscopic sleeve gastrectomy. These patients who completed 4 years of follow-up experienced an average excess BMI loss of 60.2%, with resolution of more than 90% of comorbidities and no significant complications [62]. Three additional young male PWS patients (mean age 15.6 years) were treated by mini-gastric bypass

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and showed excessive weight loss of 79% within 2 years, resolution of hypertension, and improved sleep apnea. No surgical complication was reported [63]. These observations are in contrast to a retrospective review including 60 cases of PWS patients who underwent bariatric surgery (mean age at the time of bariatric procedure 19.7 ± 6.4 years). Various bariatric procedures have been used, with poor results in PWS patients in comparison to normal obese individuals. Five years after gastric bypass surgery and after gastric banding, the reported average weight loss was only 2.4% and 3.5% compared to the preoperative weight, respectively. In addition to poor results on weight, a variety of postoperative issues was reported, including death, pulmonary embolus, postoperative wound infection, and gastric perforation [64]. In conclusion, the indication of this therapeutic option in PWS needs to be discussed extensively in reference centers. Surgery should not replace multidisciplinary medical management, i.e. early diagnosis and multidisciplinary care with GH treatment, reduced-energy diets with restricted access to food, and regular physical activity, which has proven its effectiveness and safety in patients with PWS.

In BBS, the indication of bariatric surgery is also discussed. A morbidly obese 16-year-old patient with BBS underwent laparoscopic Roux-en-Y gastric bypass surgery. The postoperative period was uneventful. The BMI decreased from 52.28 to 34.85 kg/m^2 within 42 months after surgery, with significant improvement in hypertension and mobility [65]. In another study, a 33-year-old morbidly obese woman with BBS underwent a sleeve gastrectomy without significant postoperative complications. The intervention resulted in a significant weight loss of 23.9% within 12 months [66]. In contrast, gastric banding, performed in a 35-year-old morbidly obese man with BBS, resulted in only a small weight loss of 9% without effect on type 2 diabetes [66]. Apparently, longer follow-up is required to evaluate long-term safety and efficacy of bariatric surgery in patients with BBS.

In two LEPR-deficient patients, vertical gastroplasty appears to be beneficial inducing a weight loss of 40 kg (–20% of the initial weight) in a 16-year-old patient within 8 years of regular follow-up [67] and a significant initial weight loss (–44% of weight in 9 months) in an 18-year-old patient [26]. In contrast, relative failure was observed in another 26-year-old LEPR-deficient morbidly obese woman with rapid weight regain 1 year after bypass surgery. However, this patient with low socioeconomic status was noncompliant to the recommendations provided for this type of surgery and had a very irregular medical follow-up [67]. In another 36-year-old LEPR-deficient patient, gastric bypass did not induce significant weight loss in the long term either (–7% 5 years after surgery) [26]. These reports probably illustrated the important role of familial environment regarding the efficacy of bariatric surgery in monogenic forms of obesity.

In patients with heterozygous *MC4R* mutations (mean age 32.2 years), effects of weight loss surgery are identical to those in patients without *MC4R* mutations, suggesting that heterozygous *MC4R* mutation status should not influence the decision [68–71]. In contrast, laparoscopic adjustable gastric banding in a 17-year-old teenager with homozygous *MC4R* mutation resulted in the absence of a long-term weight loss (12 months postoperatively), suggesting that the full interruption of the melanocortin pathway may not be counteracted by bariatric surgery [72]. More studies with a long-term follow-up on the effect of bariatric surgery in *MC4R*-mutated patients are required.

Thus, due to the limited number of cases, the long-term efficacy and safety of bariatric surgery in genetic forms of obesity need further evaluation. A multidisciplinary team approach should always be adopted in order to discuss a possible surgery procedure in this context. It should be kept in mind that severe eating disorders are usually an argument against bariatric surgery. The position of the French Reference Center of Prader-Willi Syndrome is cautious and does not recommend the use of surgery in case of syndromic obesity with food impulsivity.

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Perspectives

Deep brain stimulation (DBS) targeting the hypothalamus and the nucleus accumbens, two brain regions for which dysfunction appears to be directly associated with food stimuli, seems to be promising for treatment-refractory obesity. In particular, patients with PWS may represent a target group for treatment with DBS, given the overlap between the obesity secondary to hyperphagia and the dysregulation reward circuitry observed in this disorder (abnormal basal activity in the lateral hypothalamus and the nucleus accumbens). Clinical trials will have to evaluate the efficacy of DBS for genetic forms of obesity [73].

Using pharmacological chaperones for MC4R represents a possibility for the development of a targeted treatment of severe early-onset obesity caused by *MC4R* mutations. A study demonstrated that a novel human MC4R antagonist, Ipsen 17, serving as a pharmacological chaperone of human MC4R, increased the cell surface expression of *MC4R* mutants and their signaling capacity upon α-MSH stimulation [74]. Thus, using pharmacological chaperones against *MC4R* mutants provides an exciting disease-modifying opportunity for severe early-onset morbid obesity.

Conclusion

Genetic forms of obesity are important to diagnose because they need a specific management based on multidisciplinary teams which is to be set up as soon as possible. New treatments have recently emerged, particularly for PWS and mutations of the leptin/melanocortin pathway, which could change the prognosis for these rare severe forms of obesity. However, to date, causal therapy is not available for most forms of obesity.

Moreover, progress in understanding of genetic obesity mechanisms, particularly by applying whole-exome sequencing, may probably help physicians to identify new molecular anomalies in patients with severe early-onset obesity in the near future in order to better understand the pathophysiology of more common forms of obesity and to improve their care management.

Disclosure Statement

The authors have not declared any conflicts of interest.

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