

# Chapter 2

## Monogenic Forms of Obesity

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### Introduction

Obesity, defined as an excess fat mass, is a complex and multifactorial disease resulting from the interaction of numerous environmental and genetic factors. It is characterized by a wide phenotypic heterogeneity. Numerous epidemiological and intervention studies carried out in different cohorts (twins brought up together or separately, adopted children, nuclear families, among others) have recognized the role of individual genetic and biological susceptibilities in response to the current weight-gain promoting environment [1]. There are also individual differences in progression of weight (i.e. different trajectories) and risk of associated comorbidities. It is now well accepted that the development of obesity stems from the interaction of multiple environmental factors (such as overeating and/or reduction in physical activity) with genetic factors. The severity of obesity will be thus determined by the impact of environment on the genetic background of each individual.

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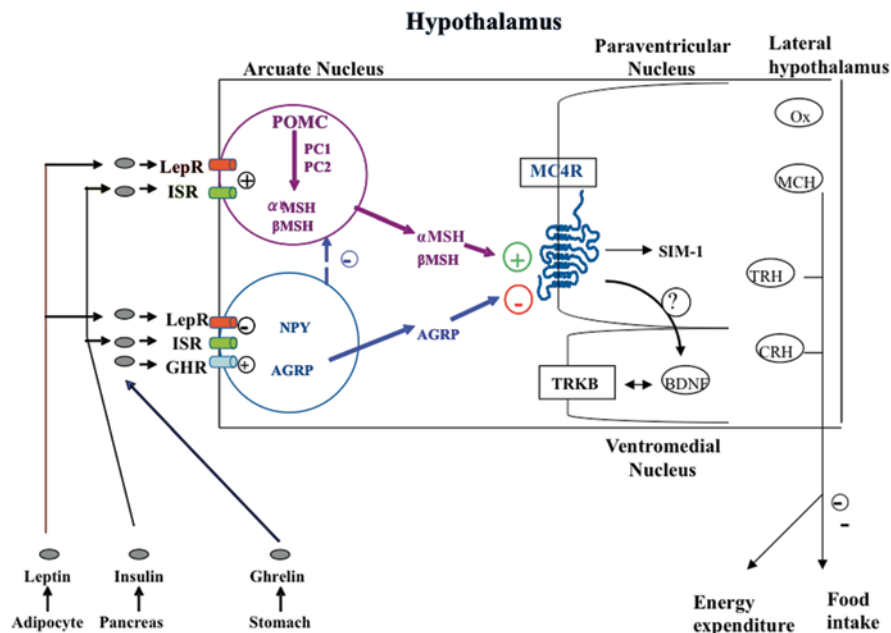
Several clinical presentations are described in obesity depending on the involved genes:

- a. Monogenic obesity described as rare and severe early-onset obesity associated with endocrine disorders. There are mainly due to mutations in genes of the leptin/melanocortin axis involved in food intake regulation (genes of leptin (*LEP*) and its receptor (*LEPR*), proopiomelanocortin (*POMC*), proconvertase 1 (*PC1*), etc).
- b. Syndromic obesity corresponding to obesity associated with others genetic syndromes. Patients are clinically severely obese and additionally distinguished by mental retardation, dysmorphic features and organ-specific developmental abnormalities. Prader-Willi and Bardet-Biedl syndromes are the 2 most frequent. But more than 100 syndromes are now associated to obesity.
- c. Melanocortin 4 receptor (*MC4R*) linked obesity characterized by a variable severity of obesity and the absence of specific phenotype. They are responsible for 2–3 % of obesity in adults and children.
- d. Polygenic obesity, which is the more common clinical situation (>95 % of cases). Here each susceptibility gene, taken individually, would only have a slight effect on weight. The cumulative contribution of these genes would become significant only in an ‘obesogenic lifestyle’ (such as overfeeding, sedentariness, stress).

The comprehension of the obesity molecular mechanisms progressed enormously these last years thanks to the development of faster, precise and effective genetic screening tools. In particular, the whole-exome sequencing showed its power to identify new monogenic obesities due to mutations in the leptin/melanocortin pathway or in other genes. Rare genetic obesities are, in fact, important to clinically detect because it allows to progress in understanding obesity physiopathology and on the other hand there is a specific management of these forms of obesity depending on specific and multidisciplinary teams.

## **Monogenic Obesity Due to Mutations in the Leptin/Melanocortin Pathway**

As described in rodents, monogenic obesities are mainly due to mutations in the genes encoding proteins involved in the leptin/melanocortin pathway that plays a pivotal role in the hypothalamic control of food intake (Fig. 2.1). The hypothalamic leptin/melanocortin pathway is activated following the systemic release of the adipokine LEP and its subsequent interaction with its receptor LEPR located on the surface of neurons of the arcuate nucleus. The downstream signals that regulate satiety and energy homeostasis are then propagated via POMC, cocaine-and-amphetamine-related transcript (CART) and the melanocortin system [2]. While POMC/CART neurons synthesize the anorectic peptide  $\alpha$ -melanocyte stimulating hormone



**Fig. 2.1** The leptin/melanocortin pathway. Neuronal populations propagate the signaling of various molecules (leptin, insulin, ghrelin) to control food intake and satiety. POMC-neurons in the arcuate nucleus are activated by leptin and insulin and produce the  $\alpha$ -MSH, which then activates the MC4R receptor in the paraventricular nucleus resulting in a satiety signal. The downstream roles of SIM1, BDNF and TRKB are currently being explored. A separate group of neurons expressing NPY and AGRP produce molecules that act as potent inhibitors of MC4R signaling. Several mutations of those genes involved in the leptin/melanocortin pathway are responsible for severe early-onset obesity. *AGRP* agouti-related protein, *BDNF* brain-derived neurotrophic factor, *CRH* corticotrophin-releasing hormone, *GHR* ghrelin receptor, *ISR* insulin receptor, *LepR* leptin receptor, *MC4R* melanocortin-4 receptor, *MCH* melanin-concentrating hormone,  $\alpha$ -MSH  $\alpha$ -melanocyte stimulating hormone,  $\beta$ -MSH  $\beta$ -melanocyte stimulating hormone, *NPY* neuropeptide Y, *Ox* orexins, *PC1* and *2* proconvertase 1 and 2, *POMC* proopiomelanocortin, *SIM1* single-minded 1, *TRH* thyrotrophin-releasing hormone, *TRKB* tyrosine kinase receptor

( $\alpha$ -MSH), a separate group of neurons express the orexigenic neuropeptide Y (NPY) and the agouti-related protein (AGRP), which acts as a potent inhibitor of melanocortin 3 (MC3R) and MC4R receptors. The nature of the POMC derived peptides depends on the type of endoproteolytic enzyme present in the specific brain region. In the anterior pituitary, the presence of the PC1 enzyme produces ACTH (adrenocorticotrophic hormone) and  $\beta$ -lipotrophin peptides, while the combined presence of PC1 and PC2 in the hypothalamus controls the production of  $\alpha$ -,  $\beta$ -,  $\gamma$ -MSH and  $\beta$ -endorphins. Mutations in human genes coding for *LEP* [3–5], *LEPR* [6, 7], *POMC* [8] and *PC1* [9] lead to severe obesity occurring soon after birth, with generally complete penetrance and autosomal recessive transmission (Table 2.1).

**Table 2.1** Rare monogenic forms of human obesity

Gene	Mutation type	Obesity	Associated phenotypes
Leptin (LEP)	Homozygous mutation	Severe, from the first days of life	Gonadotropic and thyrotropic insufficiency
Leptin receptor (LEPR)	Homozygous mutation	Severe, from the first days of life	Gonadotropic, thyrotropic and somatotropic insufficiency
Proopiomelanocortin (POMC)	Homozygous or compound heterozygous mutation	Severe, from the first months of life	ACTH insufficiency Mild hypothyroidism and ginger hairs if the mutation leads to the absence of POMC production
Proprotein convertase subtilisin/kexin type 1 (PCSK1)	Homozygous or compound heterozygous mutation	Severe obesity occurring in childhood	Adrenal, gonadotropic, somatotropic and thyrotropic insufficiency Postprandial hypoglycemic malaises Central diabetes insipidus
Single-minded 1 (SIM1)	Translocation between chr 1p22.1 and 6q16.2 in the SIM 1 gene	Severe obesity occurring in childhood	Inconstantly, neurobehavioral abnormalities (including emotional lability or autism-like behavior)
Neurotrophic tyrosine kinase receptor type 2 (NTRK2)	De novo heterozygous mutation	Severe obesity from the first months of life	Developmental delay Behavioral disturbance Blunted response to pain
Dedicator of cytokinesis 5 (DOCK5)	Variable number tandem repeats (VNTRs)	Childhood and adult severe obesity	–
Kinase suppressor of Ras2 (KSR2)	Heterozygous frameshift, nonsense or missense variants	Severe obesity	Hyperphagia in childhood Low heart rate Reduced basal metabolic rate Severe insulin resistance
Tubby-like protein (TUB)	Homozygous frameshift mutation	Early-onset obesity	Night blindness, decreased visual acuity and electrophysiological features of a rod cone dystrophy

## *Leptin Deficiency*

Mutations in the human genes coding for LEP [3–5] and LEPR [6, 7] lead to rapid and dramatic increase in weight since the first months of life, as illustrated by the weight curve of LEPR deficient subjects (Fig. 2.2). Evaluating body composition in some *LEPR* mutation carriers show a large amount of total body fat mass (>50%) but resting energy expenditure remains related to the level of body corpulence. Feeding behaviour is characterized by major hyperphagia and ravenous hunger [10]. Surprisingly, one LEP deficient Austrian girl has been recently described with more moderate obesity (BMI 31.5 kg/m<sup>2</sup>), despite an increased consumption

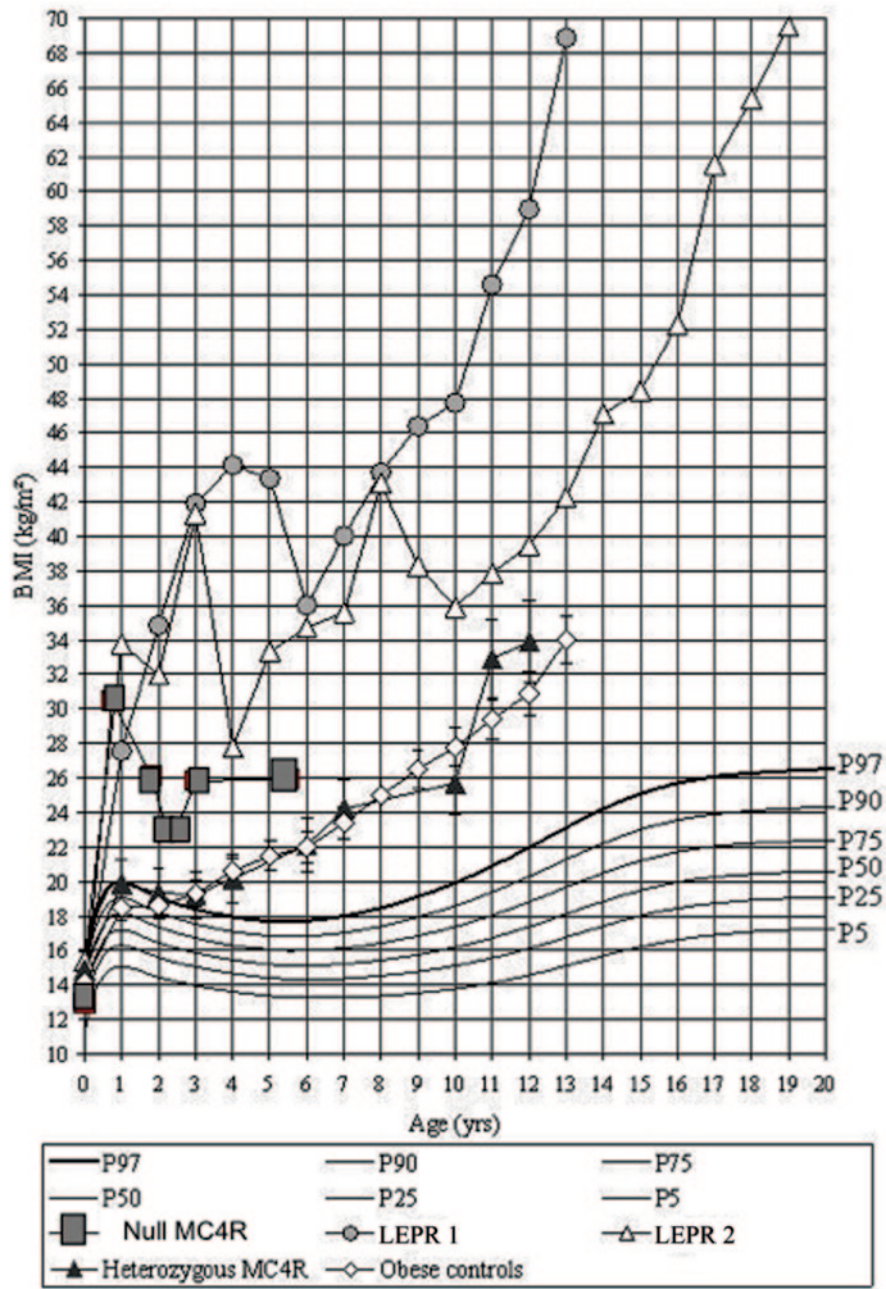


Fig. 2.2 BMI curves of 2 homozygous null *LEPR* mutants (LEPR 1 and 2), 1 homozygous null *MC4R* patient, 6 heterozygous *MC4R* carriers and 40 non mutated obese controls [47]. The reference curves are the standard French/Institut National de la Santé et de la Recherche Médicale percentile curves

of calories in a test meal [11]. The phenotype was explained by extremely low daily calorie intake. Even if one takes into account a substantial underreporting, this observation might suggest that despite LEP deficiency, it was possible to control energy intake and thus to prevent extreme obesity. In that specific case, the parents' role was determinant by providing a favourable environment with vigorous control of the patient's eating behaviour from early infancy onward. A further explanation might be related to the different genetic backgrounds of different subjects with LEP or LEPR deficiency. However, despite this particular case, severe early-onset obesity with major hyperphagia is recognized as a main clinical presentation of LEP or LEPR deficiency.

Associated to the severe early-onset obesity with major hyperphagia, hypogonadotrophic hypogonadism and thyrotrophic insufficiencies complete the phenotype. Insufficient somatotrophic secretion, leading to moderate growth delay, is also described in some patients with a *LEPR* mutation. In LEP deficient subjects, it was described a high rate of infection, particularly recurrent respiratory tract infections, associated with a deficiency in T cell number and function [6, 12, 13]. In individuals with leptin deficiency either due to *LEP* or *LEPR* mutations, no pubertal development was observed while in others there is evidence of spontaneous pubertal development suggesting a recovery of hormonal functions with time. For example, the follow-up of the initially described *LEPR* deficient sisters revealed the normalization of thyroid mild dysfunction at adult age and normal spontaneous pregnancy [14].

Measurement of circulating leptin may help in the diagnosis: it is undetectable in *LEP* mutation carriers and correlated to fat mass or unusually elevated in *LEPR* mutation carriers [3, 6, 7]. Thus, *LEPR* gene screening might be considered in subjects with severe early-onset obesity associated to endocrine dysfunctions with leptin related to corpulence level [7].

### ***Mutations of POMC and PCSK1 Genes***

Obese children with a complete POMC deficiency have ACTH deficiency, which can lead to acute adrenal insufficiency from birth. These children display also a mild central hypothyroidism that necessitates hormonal replacement [8]. Alterations in the somatotrophic and gonadotrophic axis are also described [15]. The reason of these endocrine anomalies is unknown even if the role of melanocortin peptides in influencing the hypothalamic pituitary axis has been proposed. Ginger hair due to the absence of  $\alpha$ -MSH, which activates the peripheral MC1R involved in pigmentation is classically described. However, it might be inconstant as reported in several observations suggesting that the skin and hair phenotype might vary according to the ethnic origin of *POMC* mutation carriers [15–17]. The modifications in color hair, 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 rare mutation in the *PCSK1* (proprotein convertase subtilisin/kexin type 1) gene leading to PC1 deficiency, have also endocrine anomalies in addition to severe obesity. They are mainly postprandial hypoglycemic malaises, fertility disorders due to hypogonadotrophic hypogonadism, central hypothyroidism and adrenal insufficiency secondary to lack of POMC maturation. The delayed postprandial malaises are explained by the accumulation of proinsulin through lack of PC1, which is involved in the synthesis of mature insulin from proinsulin. The absence of POMC maturation causes a dysfunction in the melanocortin pathway that explains the obese phenotype [9]. Severe persistent diarrhea, due to defect in intestinal absorption, is also described, secondary to lack in mature GLP-1 (glucagon-like peptide-1) [18]. Alteration of the processing of prohormones, progastrin and proglucagon, explains, at least in part, the intestinal phenotype and also suggests the role of PC1 in absorptive functions in the intestine. Recently, central diabetes insipidus improved by oral desmopressin was noted in one compound heterozygous proband and in 13 children with a total PC1 deficiency. These observations suggest that PCSK1 may be involved in the full functioning or central sensing of osmolality in humans [19, 20]. Growth hormone deficiency was also noted in the 13 children with complete PC1 deficiency [20].

## Diagnosis Genetic Testing of Monogenic Obesity

In case of clinical situation suggesting a monogenic obesity (severe early-onset obesity associated to endocrine anomalies and potentially consanguineous parents), direct sequencing of the candidate gene (*LEP*, *LEPR*, *POMC*, etc.) is necessary for diagnosis confirmation. It will detect homozygous or compound heterozygous mutation responsible for an interruption of the leptin-melanocortin axis. Family members are needed to be tested for segregation analysis and to evaluate the risk of recurrence.

A few genetics laboratories routinely perform those analyses that usually are part of research programs. For example in Europe, this genetic testing can be found at

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## Treatment

In case of LEP deficiency, children and adults benefit from subcutaneous injection of leptin, resulting in weight loss, mainly of fat mass, with a major effect on reducing food intake and on other dysfunctions including immunity, as described previously [21]. A detailed microanalysis of eating behavior of three leptin deficient adults, before and after leptin treatment, revealed reduced overall food consumption, a slower rate of eating and diminished duration of eating of every meal in the three subjects after leptin therapy. Leptin treatment also induces features of puberty even in adults [10]. This study supports a role of leptin in influencing the motivation to eat before each meal [22]. Another study shows that leptin treatment had a major effect on food intake. *Ad libitum* energy intake in a test meal was reduced, hunger ratings in the fasted state decreased and satiety following a meal increased. Leptin acts on neural circuits governing food intake to diminish perception of food reward while enhancing the response to satiety signals generated during food consumption [23]. In a separate study, hormonal and metabolic changes were evaluated before and after leptin treatment [10]. Leptin treatment was able to induce aspects of puberty even in adults, as illustrated by the effect of leptin treatment in one 27 year-old adult male with hypogonadism. In two women between 35–40 years, leptin treatment led to regular menstrual periods and hormonal peaks of progesterone evoking a pattern of ovulation. Although cortisol deficiency was not initially found in LEP deficient patients, eight months of leptin treatment modified the pulsatility of cortisol with a greater morning rise of cortisol. Leptin could have a previously unsuspected impact on human hypothalamic-pituitary-adrenal function. Metabolic parameters of leptin deficient patients improved in parallel with weight loss.

In the LEPR deficient subjects, leptin treatment is useless because of a non-functional LEPR. Factors that could possibly bypass normal leptin delivery systems are being developed but are not yet currently available. The ciliary neurotrophic factor (CNTF) was one of the candidate molecules. CNTF activates downstream signaling molecules such as STAT-3 in the hypothalamus area that regulates food intake, even when administered systemically. Treatment with CNTF in humans and animals induced substantial loss of fat mass [24]. The neurotrophic factor, Axokine, an agonist for the CNTF receptor, has been under development by the Regeneron Company, for the potential treatment of obesity and its metabolic associated complications. But the phase III clinical trials were stopped due to development of antibodies against Axokine in nearly 70% of the tested subjects after approximately 3 months of treatment. In addition, Axokine had a small positive effect [25]. It is also possible that side effects of CNTF, a molecule possibly acting in the immune function, might be expected [26].

In children with a complete POMC deficiency, a 3 months trial using MC4R agonist with low affinity was inefficient on weight or food intake [8]. POMC, PC1 or LEPR deficient families might benefit from the development of new MC4R agonists if such drugs become available, in order to restore the melanocortin signal. Likewise, deep brain stimulation trials with an electrode inserted in the anterior



third ventricle contiguous to the ventromedian hypothalamus are actually performed. In monkeys, this chronic 8-week stimulation induces a significant decrease in corpulence with reduction of 8% of body weight and 18% of fat mass, without side effects [27].

Today, bariatric surgery is the only long-term efficient treatment for severe obesity [28] using several surgical techniques (laparoscopic gastric bypass, gastric banding or sleeve gastrectomy). The question of such treatment and its potential efficiency is crucial in patients with monogenic obesity. But currently, data on bariatric surgery in these patients are limited and controversial. In one LEPR deficient patient, vertical gastropasty was beneficial and sufficient to induce and maintain a 40 kg weight loss (−20% of the initial weight) over 8 years of regular follow-up, whereas the patient remained obese [29]. In contrast, a relative failure of surgical therapy was illustrated by the rapid weight regain 1 year after bypass in another LEPR deficient morbidly obese woman. But this patient with low socioeconomic status had extreme difficulties after postsurgical counselling. She was noncompliant with the recommendations provided in this type of purely restrictive surgery and her medical follow-up was very irregular. This report illustrated the important role of environment on the benefice of bariatric surgery especially in case of monogenic obesities or underlined the poor efficiency of bariatric surgery in these patients [29].

So, due to the limited number of cases, the long-term efficacy and safety of bariatric surgery need further evaluation. A multidisciplinary team approach should always be adopted in order to establish the correct indication and realistic explanation after surgical treatment of obese patients.

## Other Monogenic Obesities

Several additional genes, implicated in the hypothalamus and central nervous system development, have been found to cause monogenic obesity in humans. A deletion of the *SIMI* (single-minded homolog 1) gene, located on the 6q chromosome, secondary to a *de novo* translocation between 1p22.1 and 6q16.2 chromosomes, was identified in one girl with severe early-onset obesity associated to hyperphagia and food impulsivity [30]. She had a rate of early weight gain comparable to the weight curve of LEP and LEPR deficient children. Izumi et al. identified also an interstitial 6q deletion including the *SIMI* gene in a subject with Prader-Willi-like features (neonatal hypotonia, dysmorphism, developmental delay, early-onset obesity, short stature, hypopituitarism) [31]. *SIMI* encodes a transcriptional factor implicated, in mouse, in the development of the hypothalamic paraventricular nucleus. It plays a role in the melanocortin signaling pathway and appears to regulate feeding rather than energy expenditure [32, 33]. The sequencing of the coding region of *SIMI*, in 2100 unrelated patients with severe early-onset obesity and in 1680 unrelated population-based controls, identified 13 different heterozygous variants in 28 severely obese patients. Variants carriers exhibited severe obesity, increased *ad libitum* food intake in a test meal, normal basal metabolic rate and inconstantly

neurobehavioral phenotype (impaired concentration, memory deficit, emotional lability or autistic spectrum behavior). Nine of the 13 variants significantly reduced the ability of *SIM1* to activate a *SIM1*-responsive reporter gene. These mutations co-segregated with obesity in extended family studies with variable penetrance. So, rare variants in *SIM1* should be considered in patients with hyperphagic early-onset obesity associated or not to Prader-Willi-like syndrome features or neurobehavioral abnormalities such as emotional lability or autism-like behavior [34–36].

Likewise, decreased expression of the brain-derived neurotrophic factor (BDNF) was found to regulate eating behavior [37]. BDNF, encoded by *NTRK2* (neurotrophic tyrosine kinase receptor type 2) gene, and its associated tyrosine kinase receptor (TRKB) are both expressed in the ventromedial hypothalamus. They have been attributed a role downstream of MC4R signaling implicated in feeding regulation [38]. A *de novo* heterozygous mutation in *NTRK2* gene was described in an 8-year-old boy with severe early-onset obesity, mental retardation, developmental delay and anomalies of higher neurological functions, like the impairment of early memory, learning and nociception [39]. Other 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 demonstrate. In vitro studies of some mutations have suggested that these mutations could impair hypothalamic-signaling processes [40].

Finally, the contribution of copy number variants (CNVs) to complex disease susceptibility, such as severe obesity, has been the subject of debates in recent years. Variable number tandem repeats (VNTRs) constitute a relatively under-examined class of genomic variants in the context of complex disease. Rare CNVs have been shown to be responsible for severe highly penetrant forms of obesity. For example, investigation of a complex region on chromosome 8p21.2 encompassing the *DOCK5* (dedicator of cytokinesis 5) gene has shown a significant association of the *DOCK5* VNTRs with childhood and adult severe obesity [41]. So, more systematic investigation of the role of VNTRs in obesity had to be performed to study their relatively unexplored contribution to this disease and their potential link with the leptin/melanocortin pathway.

The rapid development of new tools such as whole-exome sequencing will probably help to identify novel genes in severe early-onset obesity or monogenic obesity. The whole-exome sequencing is a diagnostic approach for identification of molecular defects in patients with suspected genetic disorders. It showed its power to identify mutations responsible for rare diseases, in a small number of unrelated affected individuals. Indeed, it contributed greatly to the discovery of disease-causing genes in several rare inherited human diseases. So, this tool could probably help to reveal new molecular abnormalities in patients with monogenic obesity. It was tested and validated in a study for the molecular diagnosis of 43 forms of monogenic diabetes or obesity. Forty patients (19 with a monogenic form of diabetes and 21 with a monogenic form of obesity) carrying a known causal mutation for those subtypes according to diagnostic laboratories were blindly re-analyzed. Except for one variant, all causal mutations in each patient were re-identified, associated with an almost perfect sequencing of the targets (mean of 98.6%). Moreover,

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