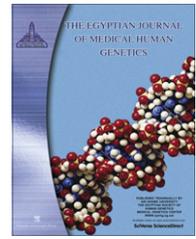




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## The Egyptian Journal of Medical Human Genetics

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### REVIEW

# Genetics of obesity

Rabah M. Shawky <sup>a,b,\*</sup>, Doaa I. Sadik <sup>b</sup>

<sup>a</sup> *Pediatrics Department, Faculty of Medicine, Ain Shams University, Egypt*

<sup>b</sup> *Medical Genetics Centre, Ain Shams University, Cairo, Egypt*

Received 15 May 2011; accepted 30 August 2011

Available online 9 December 2011

#### KEYWORDS

Obesity;  
Body weight regulation;  
Obesity syndromes

**Abstract** There is now widespread recognition that the continuing increase in the prevalence of obesity seen in many countries is likely to have major adverse effects on public health. The National Center for Health Statistics reports that 61% of adults in the United States are overweight and 26% are obese. Also The National Health and Nutrition Examination Survey IV, 1999–2002, documents that 16% of children are overweight and 31% are at risk of becoming overweight or are already overweight, representing nearly a 300% increase since the 1960s. The genetic influences are likely to be particularly powerful in people with severe and early-onset obesity, the group is most likely to suffer adverse clinical consequences. In this review we will discuss the Genetics of body weight regulation including genes encoding factors regulating food/energy intake, genes encoding factors implicated in energy expenditure, and genes encoding factors implicated in adipogenesis as well as syndromic forms of obesity.

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\* Corresponding author at: Medical Genetics Center, Ain Shams University, Cairo, Egypt. Tel.: +20 2 26859398.  
E-mail addresses: shawkyrabah@yahoo.com (R.M. Shawky), doaadoaaibrahim@yahoo.com (D.I. Sadik).

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Peer review under responsibility of Ain Shams University.

doi:10.1016/j.ejmhg.2011.08.005



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## 1. Introduction

There is now widespread recognition that the continuing increase in the prevalence of obesity seen in many countries is likely to have major adverse effects on public health [1,2]. Obesity in children is defined as a body mass index (BMI) at or above the 95th percentile for children of the same age and sex based on the Centers for Disease Control and Prevention (CDC) growth charts for children in the United States [3]. With over 1 billion people now overweight or obese [4], the World Health Organization has proclaimed this to be a global epidemic. Particularly alarming is the explosion of childhood obesity. The National Health and Nutrition Examination Survey (NHANES) IV, 1999–2002, documents that 16% of children are overweight and 31% are at risk for becoming overweight or are already overweight, representing a nearly 300% increase since the 1960s and a 45% increase since the last complete NHANES survey for 1988–1994 [5].

In the search for the environmental drivers of this epidemiological phenomenon, there is some danger that we may overlook the critical importance of inherited factors in the determination of interindividual differences in fat mass. The

identification of such factors is of great clinical, as well as theoretical importance for a number of reasons. Firstly, genetic influences are likely to be particularly powerful in people with severe and early-onset obesity, the group is most likely to suffer adverse clinical consequences [6] (Fig. 1). Secondly, the use of genetics to identify critical molecular components

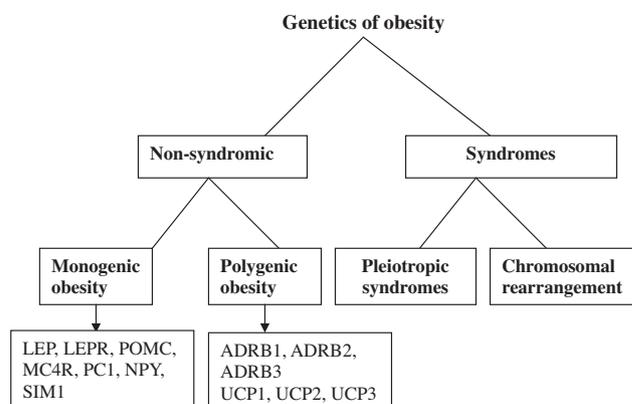


Figure 1 Genetics of obesity.

of the human control system for energy homeostasis may help to target safe and specific drug development. Finally, it is known that diet and exercise programs, while frequently effective in inducing weight loss, rarely maintain this. It is very likely that the genetic makeup of an individual may influence his/her response to particular measures. Ultimately, it should be possible to identify genetic subgroups of subjects who might be particularly responsive or resistant to specific environmental modulations [7].

Twin studies suggest a heritability of fat mass of between 40% and 70% with a concordance of 0.7–0.9 between monozygotic twins compared with 0.35–0.45 between dizygotic twins [8,9]. Correlation of monozygotic twins reared apart is virtually a direct estimate of the heritability (although monozygotic twins do share the intrauterine environment, which may contribute to lasting differences in body mass in later life). Estimates vary from 40% to 70%, depending on the age of the separation of twins and the length of follow-up [10].

## 2. Genetics of body weight regulation

Body weight regulation and stability depends upon an axis with three interrelated components: food intake, energy expenditure and adipogenesis, although there are still many unknown features concerning fuel homeostasis and energy balance. There are 358 studies on obese humans reporting positive associations with 113 candidate genes, among them, 18 genes are supported by at least five positive studies [6].

### 2.1. Genes encoding factors regulating food/energy intake

It was generally accepted that hypothalamic and brain stem centres are involved in the regulation of food intake and energy balance but information on the relevant regulatory factors and their genes was scarce until the last decade [1]. Insulin remained the only candidate for the key role in body weight regulation for a long time.

#### 2.1.1. Mutations in genes encoding leptin and its receptors (*LEP*, *LEPR*)

This cytokine-like peptide mainly expressed by adipocytes is believed to be a key regulator of fat metabolism and energy intake. Leptin is the product of human homologue of mouse 'obese' gene, whose homozygous mutation caused hereditary obesity in mice (monogenic). Certain areas of the hypothalamus are rich in specific receptors binding regulatory peptides and triggering central regulatory mechanisms. Studies in humans have failed to find leptin or any other mutant gene to be the unique 'obesity gene'. Conversely, multifactorial patterns involving the actions of numerous polymorphic gene products now look more likely, (proopiomelanocortin (POMC), MC4R and proprotein convertase 1 (PC1) deficiency [11]). Congenital human leptin deficiency has been identified in subjects showing severe early-onset obesity (8 years and 86 kg, or 2 years and 29 kg) with intense hyperphagia and undetectable levels of serum leptin due to a frame-shift mutation in the *ob* gene (deletion G133) in a homozygosis, which resulted in a truncated protein not secreted [12]. Children with leptin deficiency had also profound abnormalities in T-cell number and function consistent with the high rates of infection and childhood mortality from infections. Leptin therapy in these

subjects has a major effect on appetite with normalisation of hyperphagia and reductions in body weight. Leptin receptor-deficient subjects were also found, with the phenotype being similar to those with leptin deficiency. The birth weight was normal, but a rapid weight gain was seen in the first months of life, with severe hyperphagia and aggressive behaviour when food was denied [11,12]. Basal temperature and resting metabolic rate were normal and they were normoglycemic with mildly elevated plasma insulin. They also had mild growth retardation and impaired basal and stimulated growth hormone secretion [12].

#### 2.1.2. Mutations in proopiomelanocortin (*POMC*) gene

Homozygous and heterozygous subjects for mutations in POMC have been found. In neonatal life these subjects showed adrenocorticotrophic hormone (ACTH) deficiency (the POMC gene encoded ACTH and other peptides), the children have red hair and pale skin due to the lack of melanocyte-stimulating hormone (MSH) action at the melanocortin-1 receptors in skin and hair follicles [12]. The POMC deficiency is associated with hyperphagia and early-onset obesity due to the lack of activation of the melanocortin-4 receptor.

#### 2.1.3. Mutations in melanocortin 4 receptor (*MC4R*) gene

Since 1998 many groups have reported at least 70 mutations in MC4R that were associated with early onset obesity [13,14]. Other clinical features of MC4R mutation carriers are hyperphagia, accelerated linear growth in children and marked increase in bone mineral density. Proband with homozygous MC4R mutations show more severe obesity than their heterozygous relatives; thus, the mode of inheritance is codominant [12]. Severe obesity and early age of onset, may be markers of MC4R mutations. It has been also shown that pathogenic MC4R mutations are more prevalent in northern European populations than in the Mediterranean or even Asian populations [13]. MC4R mutations have been extensively reported in French, English, German, American, Italian and Spanish populations [2,7–10]. It has been estimated that 1–6% of extremely obese individuals harbour functionally relevant MC4R mutations [7]. Functional analyses of MC4R mutations (missense, nonsense and frameshift mutations) allow us to classify them on the basis of their effects on receptor signalling. Mutations that caused intracellular retention of the receptor in vitro were associated with earlier age of onset and greater severity of obesity than other mutations [12]. Functional studies showed that many of the missense mutations also lead to a loss-of-function of the MC4R [2].

#### 2.1.4. Mutations in proprotein convertase 1 (*PC1*) gene

Subject carriers of PC1 mutations mainly have severe early-onset obesity, impaired prohormone processing and hypocortisolaemia. Another clinical feature is small intestine dysfunction, which may result from an erroneous maturation of propeptides within the PC1-secreting cells along the gut [12].

#### 2.1.5. Mutations in neuropeptide Y (*NPY*) gene

NPY is released from the arcuate hypothalamic nucleus in fasting or in hypoglycaemia situations, its secretion being inhibited after food intake. The Leu7Pro polymorphism in the NPY gene appears to be implicated in lipid metabolism regulation. Some works reported that carriers of the Pro7 allele had higher NPY levels and also body fatness [15].

### 2.1.6. Mutations in ghrelin receptor gene

For the ghrelin receptor gene, two SNPs were reported: Ala204Glu and Phe279Leu, which selectively impair the constitutive activity of the receptor in humans leading to short stature and obesity that apparently develop during puberty [16].

### 2.1.7. Mutations in genes related to food preferences

The identification of relevant genes related to food preferences has just started. A novel family of 40–80 human and rodent G protein-coupled receptors expressed in taste receptor cells of tongue and palate epithelia has been identified. Taste 2 receptors (T2Rs) have been shown to function as bitter taste receptor and T1Rs as putative receptor for sweet taste. There is no information on polymorphism in the T1R family genes while some SNPs in T2R have been reported [17,18]. Rapid progress has been made in this field to elucidate the genetic mechanism controlling formation of food preferences.

## 2.2. Genes encoding factors implicated in energy expenditure

The adaptive thermogenesis in humans is closely related to the active mobilization of lipids from fat tissues and demands special interest in relation to obesity. Central neural pathways responsible for the food intake and energy expenditure regulation are tightly interconnected. The peripheral transmission of central commands to the fat stores is mediated by the sympathetic nervous system. The b-adrenoceptor gene families (ADRB2, ADRB3, ADRB1) are intensively studied candidate genes in the obesity field for their participation in energy expenditure regulation.

### 2.2.1. Mutations in b2-adrenoceptor gene

The b2-adrenergic receptor gene (ADRB2) encodes a major lipolytic receptor protein in human fat cells. Two common polymorphisms of the ADRB2 gene, characterised by an amino acid replacement of arginine by glycine in codon 16 (Arg16Gly) and glutamine by glutamic acid in codon 27 (Gln27Glu), have been explored in several diseases such as hypertension and obesity [19–23]. A relationship between the Arg16Gly polymorphism and an altered function of the ADRB2 has been reported leading to decreased agonist sensitivity. Meanwhile, the Gln27Glu variant was also found to be linked to obesity in some populations. In men, the 27Glu allele has been associated with increased BMI and subcutaneous fat and with elevated leptin and triglyceride levels, while in women, the 27Glu variant was reported to be linked to increased BMI, body fat mass and waist to hip ratio [23]. However, other studies in Caucasians (Danish men, Austrian women and German subjects) found no association between the Gln27Glu variant of the ADRB2 gene and obesity [24].

### 2.2.2. Mutations in b3-adrenoceptor gene

The b3-adrenergic receptor (ADRB3) protein plays a role in adipocyte metabolism. It mediates the rate of lipolysis in response to catecholamines and their agonists which have potential anti-diabetes and anti-obesity properties [25,26]. A common polymorphism in this gene, characterised by an amino acid replacement of tryptophan by arginine at position 64 (Trp64Arg), has been identified and may be linked to lower

lipolytic activity and account for lipid accumulation in the adipose tissue [27]. This polymorphism has been associated with abdominal/visceral fat obesity in several populations such as Caucasians and Japanese subjects. Similarly, several studies carried out among Mexican American, Japanese and Caucasian women have shown that carriers of the Arg allele had a higher BMI and lower reduction in visceral fat after weight loss [27]. Some authors, however, failed to reproduce the finding on b-adrenoceptors gene variants and further confirmation is required.

### 2.2.3. Mutations in b1-adrenoceptor gene

ADRB1 is considered a potential candidate gene for obesity because of its role in catecholamine-induced energy homeostasis. Stimulation of ADRB1, a member of G-protein-coupled receptors, mediates energy expenditure and lipolysis in adipose tissue [28,29].

### 2.2.4. Mutations in uncoupling proteins (UCPs) gene

Uncoupling proteins (UCPs) are involved in the modulation of heat-generating uncoupled respiration at the mitochondrial level. They represent a family of carrier proteins localised in the inner layer of mitochondrial membranes [26]. There are different members: UCP1, mostly expressed in brown adipose tissue, and has a role in thermogenesis, UCP2 is ubiquitously present in any tissue and UCP3 is mainly expressed in skeletal muscle and brown adipose tissue. UCP1, UCP2 mediate mitochondrial proton leak releasing energy stores as heat and thereby affecting energy metabolism efficiency [26]. The actual functions for UCP3 proteins are still under investigation. It has been proposed that uncoupling proteins act as regulators of energy metabolism. They are fatty acid transmembrane transporters in the mitochondria facilitating proton exchange [26]. UCP2 and UCP3 are considered as candidate genes for obesity, given their function in the regulation of fuel metabolism. Several UCP2 gene variants have been described: a G/A mutation in the promoter region 2866G/A, a valine for alanine substitution at amino acid 55 in exon 4 (Ala55Val) and a 45 base pair insertion/deletion in the untranslated region of exon 8 [26,30]. From the literature, it seems that allele G in the promoter region of UCP2 increases obesity risk while it affords relative protection for type 2 diabetes [26]. Meanwhile the Ala55Val polymorphism has shown to be associated with increased exercise efficiency [31,32].

## 2.3. Genes encoding factors implicated in adipogenesis

The last group of genes acting in connection with the peripheral regulation of energy expenditure comprises the transcription factors leading to adipogenesis and adipocytes differentiation. The key factor is peroxisome proliferator-activated receptor  $\gamma$ , particularly the adipose specific isoform PPARG2. In a meta-analysis examining the Pro12Ala polymorphism in 19 136 subjects, a positive association with BMI was found [26]. In this study, the frequency of the Ala allele, similar to other Caucasian populations, was higher in obese subjects (allelic frequency 0.13) than in controls (0.08), suggesting that this polymorphism was associated with obesity [33]. There is also information on the functional role of PPARG gene variants. Some mutant proteins appear to have reduced activity [26].

### 3. Syndromic forms of obesity

#### 3.1. Monogenic human obesity: pleiotropic syndromes

There are about 30 Mendelian disorders with obesity as a clinical feature, often in association with mental retardation, dysmorphic features and organ specific developmental abnormalities (i.e., pleiotropic syndromes) [12,34]. Positional genetic strategies have led to the recent identification of several different causative mutations underlying such syndromes; however, in most cases the defective gene product is an intracellular protein that is expressed throughout the body and its function is unknown. These syndromes include:

##### 3.1.1. Bardet-Biedl syndrome (BBS)

The origin of obesity is more complex in Bardet-Biedl syndrome (prevalence of BBS, 1/100 000). It is an autosomal recessive syndrome characterised by central obesity (75%), polydactyly, learning disabilities, rod-cone dystrophy, hypogonadism and renal abnormalities. It is a genetically heterogeneous disorder that is known to map to at least eight loci, seven of which have now been identified at the molecular level (mutations in BBS1–BBS11 genes) [12,34,35].

##### 3.1.2. Albright's hereditary osteodystrophy syndrome

Albright's hereditary osteodystrophy is an autosomal dominant disorder due to mutations in GNAS1, which encodes for a-subunit of the stimulatory G protein (Gs  $\alpha$ ). Maternal transmission of GNAS1 mutations leads to Albright's hereditary osteodystrophy (obesity, short stature, round facies, ectopic tissue ossification) plus resistance to several hormones, such as parathyroid hormone which activate Gs in their target tissues, while paternal transmission leads only to pseudohypoparathyroidism [12,34].

##### 3.1.3. Borjeson, Forssman and Lehmann syndrome

Borjeson, Forssman and Lehmann is described as a syndrome characterized by obesity, moderate to severe mental retardation, epilepsy, hypogonadism, and with marked gynaecomastia. Mutations in a novel, widely expressed zinc-finger gene plant homeodomain (PHD)-like finger (PHF6) have been identified in affected families [36], although the functional properties of this protein remain unclear.

##### 3.1.4. Cohen syndrome

Cohen syndrome is an autosomal recessive disorder characterized by obesity, mental retardation, microcephaly, prominent upper central incisors and progressive retinochoroidal dystrophy that is over-represented in the Finnish population, although cases have been reported worldwide [37]. The genetic locus for Cohen syndrome was mapped to chromosome 8q, and a novel gene, COH1, in this locus was shown to carry mutations in many patients from different ethnic groups [38].

##### 3.1.5. Alström syndrome

Alström syndrome is another autosomal recessive disorder that is characterized by childhood obesity associated with hyperinsulinaemia, chronic hyperglycaemia and neurosensory deficits [39]. Subsets of affected individuals present with additional features such as dilated cardiomyopathy, hepatic

dysfunction, hypothyroidism, male hypogonadism, short stature and mild to moderate developmental delay [40]. Mutations in a single gene, ALMS1, have been found to be responsible for all cases of Alström syndrome so far characterized [41]. The ALMS1 protein has no signal sequences or transmembrane regions, suggesting an intracellular localization.

##### 3.1.6. Fragile X syndrome

Fragile X syndrome is characterized by moderate to severe mental retardation, macroorchidism, large ears, macrocephaly, prominent jaw (mandibular prognathism), high-pitched jocular speech and mild obesity. In 1991, the molecular cloning of the fragile X locus revealed unstable expansions of a CGG trinucleotide repeat located in the FMR1 (fragile X mental retardation) gene [42]. The CGG repeat is polymorphic in normal population, with alleles of 6 to about 50 CGGs. Large expansions of the repeat (from 230 to >1000 CGGs) are seen in affected patients, with moderate expansions (from 60 to about 200 CGGs) that are unmethylated are found in normal transmitting males and in the majority of clinically normal carrier females. Although the exact function of FMR protein is not known, it may play a role in the regulation of transport, stability or translation of some messenger RNAs [43].

##### 3.1.7. Ulnar-mammary syndrome

This syndrome characterized by ulnar defects, delayed puberty, and hypoplastic nipples, is due to defect in the gene TBX3 located in 12q24.1 [44]

##### 3.1.8. Simpson-Golabi-Behmel, type 2 (SGBS)

It is an X-linked overgrowth syndrome with associated visceral and skeletal abnormalities. Alterations in the glypican-3 gene (GPC3), which is located on Xq26, have been implicated in the aetiology of relatively milder cases of this disorder. Not all individuals with SGBS have demonstrated disruptions of the GPC3 locus, which raises the possibility that other loci on the X chromosome could be responsible for some cases of this syndrome [45].

##### 3.1.9. Wilson-Turner syndrome

This syndrome characterized by X-linked mental retardation (XLMR), obesity, gynaecomastia, speech difficulties, emotional lability, tapering fingers, and small feet. [46].

##### 3.1.10. Mehmo syndrome

MEHMO (Mental retardation, Epileptic seizures, Hypogonadism, Microcephaly and Obesity) is an X-linked disorder characterised by mental retardation, epileptic seizures, hypogonadism, microcephaly and obesity. It was recently assigned to the locus Xp21.1-p22.13 [47].

#### 3.2. Obesity syndromes due to chromosomal rearrangements

##### 3.2.1. Prader-Willi syndrome

The most frequent syndrome is the Prader-Willi syndrome with a prevalence of about one in 25 000 births and a population prevalence of one in 50 000 [48], and is characterised by obesity, hyperphagia, hypotonia, mental retardation, short stature and hypogonadotropic hypogonadism. It is usually caused by lack of the paternal segment 15q11.2-q12, either through deletion

of the paternal critical segment (75%) or through loss of the entire paternal chromosome 15 with the presence of two maternal homologues in 22% of patients (uniparental maternal disomy). One suggested mediator of the obesity phenotype is ghrelin, the stomach-secreted peptide that increases appetite by interacting with POMC/CART (cocaine- and amphetamine-regulated transcript) and NPY hypothalamic neurons whose levels are high in Prader-Willi syndrome patients.

### 3.2.2. *Sim-1*

A girl has been reported with hyperphagia and early-onset obesity and a balanced translocation between 1p22.1 and 6q16.2, which would be predicted to disrupt the SIM-1 gene on 6q. The *Drosophila* single-minded (*sim*) gene is a regulator of neurogenesis, and in mouse *Sim-1* is expressed in the developing central nervous system, and is essential for formation of the supraoptic and paraventricular (PVN) nuclei which express the melanocortin-4 receptor. Mice heterozygous for loss-of-function mutations in *Sim-1* are obese [48,49]. In humans, deletion or disruption of the SIM1 region results in either 'Prader-Willi-like' phenotype or an early-onset obesity linked to hyperphagia. A number of patients with obesity, hypotonia and developmental delay in association with interstitial chromosome 6q deletions have been described [50], although whether this syndrome can be attributed to SIM-1 is unclear.

### 3.2.3. *WAGR*

The WAGR syndrome (Wilms tumour, anorexia, ambiguous genitalia and mental retardation) is one of the best-studied contiguous gene syndromes associated with chromosomal deletions at 11p13, the location of the WT1 gene. [51]. Some patients with WAGR syndrome and obesity have been reported with the deletions of chromosome 11p14-p12 [52].

In conclusion, obesity is a complex phenotype, and the assessment of obese patients should be directed at identifying genetic conditions so that appropriate genetic counselling and in some cases treatment can be instituted. An increasing number of genes linked to human obesity are being identified. This knowledge will increase our understanding of the causes of obesity and the ways in which children respond to their environments and become obese.

### Conflict of interest

The author declares that there is no conflict of interest

### References

- [1] Kopelman PG. Obesity as a medical problem. *Nature* 2000;404:635–43.
- [2] Friedrich MJ. Epidemic of obesity expands its spread to developing countries. *JAMA* 2002;287:1382–6.
- [3] Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey, 2006. Retrieved from <<http://www.cdc.gov/nchs/nhanes.htm>> .
- [4] Froguel P, Boutin P. Genetics of pathways regulating body weight in the development of obesity in humans. *Exp Biol Med* 2001;226:991–6.
- [5] Joseph A, Skelton Colin D, Rudolph. Overweight and obesity. Kliegman: Nelson Textbook of Pediatrics, 18th ed. 2007; vol. 1(44).
- [6] Maillard G, Charles MA, Tibult N. Trends in the prevalence of obesity in children and adolescents in France between 1980 and 1991. *Int J Obes* 2000;24:1608–17.
- [7] Stephen O'Rahilly I, Sadaf Farooqi, Giles S, Yeo H, Challis Benjamin G. Minireview: human obesity—lessons from monogenic disorders. *Endocrinology* 2003;144(9):3757–64.
- [8] Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. *JAMA* 1986;256:51–4.
- [9] Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. The body-mass index of twins who have been reared apart. *N Engl J Med* 1990;322:1483–7.
- [10] Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. *Behav Genet* 1997;27:325–51.
- [11] Zurbano R, Ochoa MC, Moreno-Aliaga MJ, Marti A. Estudios sobre obesidad de origen monogénico en humanos. *Revista Espanola de Obesidad* 2004;2:269–78.
- [12] Farooqi IS. Genetic and hereditary aspects of childhood obesity. *Best Pract Res Clin Endocrinol Metab* 2005;19:359–74.
- [13] Kublaoui BM, Zinn AR. MC4R mutations—weight before screening! *J Clin Endocrinol Metab* 2006;91:1671–2.
- [14] Lubrano-Berthelier C, Dubern B, Lacorte JM, Picard F, Shapiro A, Zhang S, et al. Melanocortin 4 receptor mutations in a large cohort of severely obese adults: prevalence, functional classification, genotype-phenotype relationship, and lack of association with binge eating. *J Clin Endocrinol Metab* 2006;91:1811–8.
- [15] Van Rossum CT, Pijl H, Adan RA, Hoebee B, Seidell JC. Polymorphisms in the NPY and AGRP genes and body fatness in Dutch adults. *Int J Obes (London)* 2006;30:1522–8.
- [16] Holst B, Schwartz TW. Ghrelin receptor mutations – too little height and too much hunger. *J Clin Invest* 2006;116:637–41.
- [17] Hinrichs AL, Wang JC, Bufe B, Kwon JM, Budde J, Allen R, et al. Functional variant in a bitter-taste receptor (hTAS2R16) influences risk of alcohol dependence. *Am J Hum Genet* 2006;78:103–11.
- [18] Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science* 2003;299:1221–5.
- [19] Macho-Azcarate T, Marti A, Gonzalez A, Martinez JA, Ibanez J. Gln27Glu polymorphism in the beta2 adrenergic receptor gene and lipid metabolism during exercise in obese women. *Int J Obes Relat Metab Disord* 2002;26:1434–41.
- [20] Macho-Azcarate T, Calabuig J, Marti A, Martínez JA. A maximal effort trial in obese women carrying the beta2- adrenoceptor Gln27Glu polymorphism. *J Physiol Biochem* 2002;58:103–8.
- [21] Corbala'n MS, Marti A, Forga L, Martinez-Gonzalez MA, Martinez JA. The 27Glu polymorphism of the beta2-adrenergic receptor interacts with physical activity influencing obesity risk among female subjects. *Clin Genet* 2002;61:305–7.
- [22] Corbalan MS, Marti A, Forga L, Martinez-Gonzalez MA, Martinez JA. Beta(2)-Adrenergic receptor mutation and abdominal obesity risk: effect modification by gender and HDL-cholesterol. *Eur J Nutr* 2002;41:114–8.
- [23] Marti A, Corbalan MS, Martinez-Gonzalez MA, Martinez JA. TRP64ARG polymorphism of the beta3-adrenergic receptor gene and obesity risk: effect modification by a sedentary lifestyle. *Diabetes Obes Metab* 2002;4:428–30.
- [24] Marti A, Martinez JA. Genetics of obesity: gene3diet interaction. *Int J Vitam Nutr Res* 2006;76:184–93.
- [25] Ochoa MC, Marti A, Azcona C, Chueca M, Oyarzabal M, et al Grupo de Estudio Navarro de Obesidad Infantil (GENOI). Gene-gene interaction between PPARG2 and ADR beta 3 increases obesity risk in children. *Int J Obes Relat Metab Disord* 2004;28(Suppl. 3):S37–41.
- [26] Ochoa Mdel C, Marti A, Martinez JA. [Obesity studies in candidate genes]. *Med Clin (Barcelona)* 2004;122:542–51.
- [27] Park HS, Kim Y, Lee C. Single nucleotide variants in the beta2-adrenergic and beta3-adrenergic receptor genes explained 18.3% of adolescent obesity variation. *J Hum Genet* 2005;50:365–9.

- [28] Li S, Chen W, Srinivasan SR, Boerwinkle E, Berenson GS. Influence of lipoprotein lipase gene Ser447Stop and beta(1)-adrenergic receptor gene Arg389Gly polymorphisms and their interaction on obesity from childhood to adulthood: the Bogalusa Heart Study. *Int J Obes (London)* 2006;30(8):1183–8.
- [29] Linne Y, Dahlman I, Hoffstedt J. beta1-Adrenoceptor gene polymorphism predicts long-term changes in body weight. *Int J Obes (London)* 2005;29:458–62.
- [30] Zurbano R, Ochoa MC, Moreno-Aliaga MJ, Martinez JA, Marti A Grupo de Estudio Navarro de la obesidad infantil. [Influence of the 2866G/A polymorphism of the UCP2 gene on an obese pediatric population]. *Nutr Hosp* 2006;21:52–6.
- [31] Marti A, Corbalan MS, Forga L, Martinez-Gonzalez MA, Martinez JA. Higher obesity risk associated with the exon-8 insertion of the UCP2 gene in a Spanish case-control study. *Nutrition* 2004;20:498–501.
- [32] Alonso A, Marti A, Corbalan MS, Martinez-Gonzalez MA, Forga L, Martinez JA. Association of UCP3 gene 255C.T polymorphism and obesity in a Spanish population. *Ann Nutr Metab* 2005;49:183–8.
- [33] Marti A, Corbalan MS, Martinez-Gonzalez MA, Forga L, Martinez JA. CHO intake alters obesity risk associated with Pro12Ala polymorphism of PPARgamma Gene. *J Physiol Biochem* 2002;58:219–20.
- [34] Bell CG, Walley AJ, Froguel P. The genetics of human obesity. *Nat Rev Genet* 2005;6:221–34.
- [35] Chiang AP, Beck JS, Yen HJ, Tayeh MK, Scheetz TE, Swiderski RE, et al. Homozygosity mapping with SNP arrays identifies TRIM32, an E3 ubiquitin ligase, as a Bardet-Biedl syndrome gene (BBS11). *Proc Natl Acad Sci USA* 2006;103:6287–92.
- [36] Lower KM, Turner G, Kerr BA, et al. Mutations in PHF6 are associated with Borjeson–Forssman–Lehmann syndrome. *Nat Genet* 2002;32:661–5.
- [37] Cohen Jr MM, Hall BD, Smith DW, et al. A new syndrome with hypotonia, obesity, mental deficiency, and facial, oral, ocular, and limb anomalies. *J Pediatr* 1973;83:280–4.
- [38] Chandler KE, Kidd A, Al-Gazali L, et al. Diagnostic criteria, clinical characteristics, and natural history of Cohen syndrome. *J Med Genet* 2003;40:233–41.
- [39] Russell-Eggitt IM, Clayton PT, Coffey R, et al. Alstrom syndrome. Report of 22 cases and literature review. *Ophthalmology* 1998;105:1274–80.
- [40] Michaud JL, Heon E, Guilbert F, et al. Natural history of Alstrom syndrome in early childhood: onset with dilated cardiomyopathy. *J Pediatr* 1996;128:225–9.
- [41] Collin GB, Marshall JD, Ikeda A, et al. Mutations in ALMS1 cause obesity, type 2 diabetes and neurosensory degeneration in Alstrom syndrome. *Nat Genet* 2002;31:74–8.
- [42] Hagerman PJ, Hagerman RJ. The fragile-X premutation: a maturing perspective. *Am J Hum Genet* 2004;74:805–16.
- [43] Jin P, Warren ST. New insights into fragile X syndrome: from molecules to neurobehaviors. *Trends Biochem Sci* 2003;28:152–8.
- [44] Bamshad M, Lin RC, Law DJ, Watkins WC, Krakowiak PA, Moore ME, Franceschini P, Lala R, Holmes LB, Gebuhr TC, Bruneau BG, Schinzel A, Seidman JG, Seidman CE, Jorde LB. Mutations in human TBX3 alter limb, apocrine and genital development in ulnar-mammary syndrome. *Nat Genet* 1997;16:311–5.
- [45] Brzustowicz LMFS, Khan MB, Weksberg R. Mapping of a new SGBS locus to chromosome Xp22 in a family with a severe form of Simpson-Golabi-Behmel syndrome. *Am J Hum Genet* 1999;65:779–83.
- [46] Wilson M, Mulley J, Gedeon A, Robinson H, Turner G. New X-linked syndrome of mental retardation, gynecomastia, and obesity is linked to DXS255. *Am J Med Genet* 1991;40:406–13.
- [47] Leshinsky-Silver E, Zinger A, Bibi CN, Barash V, Sadeh M, Lev D, Sagie TL. MEHMO (mental retardation, epileptic seizures, hypogonadism, microcephaly, obesity): a new X-linked mitochondrial disorder. *Eur J Hum Genet* 2002;10:226–30.
- [48] Goldstone AP. Prader–Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab* 2004;15:12–20.
- [49] Michaud JL, Boucher F, Melnyk A, et al. Sim1 haploinsufficiency causes hyperphagia, obesity and reduction of the paraventricular nucleus of the hypothalamus. *Hum Mol Genet* 2001;10:1465–73.
- [50] Faivre L, Cormier-Daire V, Lapierre JM, et al. Deletion of the SIM1 gene [6q16.2] in a patient with a Prader–Willi-like phenotype. *J Med Genet* 2002;39:594–6.
- [51] Rose EA, Glaser T, Jones C, et al. Complete physical map of the WAGR region of 11p13 localizes a candidate Wilms' tumor gene. *Cell* 1990;60:495–508.
- [52] Gul D, Ogur G, Tunca Y, Ozcan O. Third case of WAGR syndrome with severe obesity and constitutional deletion of chromosome [11]p12p14. *Am J Med Genet* 2002;107:70–1.