OBESITY, A GENE REVIEW

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Abstract: Obesity has become during the past decades a worldwide pandemic, affecting individuals of all ages, races, sexes and coming from different social and natural environments. The genetic factor has been identified as playing a major role in the etiopathogenesis of obesity. More and more genes are discovered to be involved in the onset of this disorder and at the same time more and more genetic syndromes and rare diseases show obesity among their major clinical features. This review describes the main genes associated with obesity in humans and indicates the main genetic syndromes with obesity that mutations or abnormal variants of these genes may cause.

Key words: obesity, genes, genetic syndromes, rare disease.

1. Introduction

Among all the metabolic disorders, obesity is the most common. The World Health Organization (W.H.O.) stated in 2005 the existence of over 1.6 billion overweight adults worldwide among which 400 million were obese. In the same year, the number of overweight and obese children was 20 million reaching an alarming 42 million in 2010. [1, 36]

The Geneva European Congress on Obesity in May 2008 concluded that obesity is caused by a genetic polymorphism, starting from the thrifty genome (represented by DNA hypothalamic variants, by the FTO and PCSK1 genes and by genetic mutations affecting the leptin-melanocortin pathway) and leading to the thrifty phenotype. [31]

The genetic causes of human obesity are diverse and may produce different types of obesity. At present, there are 38 genetic markers found to be correlated with a high body mass index (BMI) and possibly leading to monogenic obesity syndromes, while over 60 regions have been identified throughout the whole human genome which seem to have a role in the adipose tissue distribution and mass, in the energetic balance of the organism and in the regulation of satiety hormones (leptin and insulin) and causing polygenic or common obesity. At the same time, a number of over 30 complex pleiotropic genetic syndromes with obesity as a main clinical feature are described. Twins and family studies state that obesity is a heritable disorder, today being a well-known fact that the family history of obesity is a high risk predictor for the early onset of this disease in children.

This review aims to underline the advances in understanding the genetic causes of obesity highlighting the main genes involved in the pathological process of this condition, describing their main functions, mutations and polymorphisms.

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The more we know about obesity and about the genetic monogenic and polygenic syndromes associated with it, the better we will be able to treat or in the future to prevent this disease and its severe complications.

2. Human genes involved in the ethiopathogenesis of obesity

A number of genes have been identified of being linked to the onset of obesity or to an increase in the susceptibility to this disorder: FTO (fat mass and obesity associated gene), LEP (leptin), LEP-R (leptin receptor), MC4R (melanocortin receptor 4), PRL (prolactin), NPC1 (Niemann-Pick Disease type C1), MAF (V-maf musculoaponeurotic fibrosarcoma oncogene homolog), IL-6 (interleukin 6), POMC (proopiomelanocortin), INSIG2 (insulin induced gene 2), ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1), visfatin (PBEF1, pre-B cell colony-enhancing factor 1), AdipoQ (adiponectin), AdipoR1 (adiponectin receptor 1), TRKB (BDNF – brain-derived neurotrophic factor receptor), RETN (rezistin), TUB (tubby homolog), TNF-α (tumor necrosis factor α), CETP (cholesteryl ester transfer protein), TMEM18 (transmembrane protein 18), NEGR1 (neuronal growth regulator 1), GNPDA2 (glucosamine-6-phosphate deaminase 2), KCTD15 (potassium channel tetramerisation domain containing 15), BNDF (brain-derived neurotrophic factor), ETV5 (ETS variant 5), SEC16B (protein SEC16 homolog B = LZTR2 = Leucine Zipper Transcription Regulator 2), SH2B1 (SH2B adapting protein 1), MTC2H (mitochondrial carrier homolog 2), etc. [30]

Alterations in these genes’ expression due to mutations or abnormal variants (polymorphisms) are known of being the cause of several monogenic obesity syndromes and also of being involved in the common, polygenic obesity.

2.1. FTO

The FTO gene on chromosome 16 is a nuclear protein belonging to the AlkB related non-haem iron and 2-oxoglutarate-dependent oxygenase superfamily. Studies have shown that the FTO gene is strongly correlated with obesity risk, BMI and type 2 diabetes, at the same time playing a role in the cardiovascular and nervous systems. It is estimated that about 70% of the obese individuals reveal mutations within the FTO gene. [2, 32-35]

Several polymorphisms showing a high risk for obesity and type 2 diabetes have been identified in the FTO gene. The rs9939609 SNP (small nuclear polymorphism) within intron 1 of the FTO gene has a high correlation with obesity in a number of European populations, being associated with abnormal BMI and obesity in children up to 7 years old, obesity that increases towards adulthood. [2] The rs7202116 SNP is also linked to obesity and BMI, while the rs8050136, rs17817449 and the rs1421085 SNPs have been reported in association studies of type 2 diabetes. [10, 14]

2.2. PRL

The PRL gene, with its cytogenetic location 6p22.3 and coding for the pituitary prolactin hormone, which mainly has its role on the mammary gland in lactation, is associated with obesity more particularly in adults. [32, 33]

Genome wide associated studies (GWAS) also found among the common genetic variants contributing to the increase in the susceptibility for obesity a SNP, rs4712652, in the very vicinity of the PRL gene. [20, 23]
2.3. NPC1

Mutations in the Niemann Pick disease type C1 gene (18q11.2), an intracellular cholesterol transporter found in the endosome/lysosome limiting membrane, lead to Niemann Pick type C disease, an autosomal recessive disorder. [32, 33]

Studies indicate that the NPC1 gene expression levels in the white adipose tissues’ adipocytes are high in obese persons and decrease with the body mass index. About 10% of the obese children and 14% of the obese adults are caused by mutations in the NPC1 gene. [4]

2.4. IL-6

Interleukin-6 is a cytokine with the cytogenetic location 7p21 produced equally in a number of tissues, including the adipocytes and with a variety of functions. It plays a role in inflammation, triggers the acute phase response, is implicated in lymphocyte and monocyte maturation, functions as a myokine, induces the protein C synthesis within the liver, etc. [3, 32, 33]

High levels of IL-6 are correlated with insulin resistance, a specific IL-6 gene promoter polymorphism, -174 G/C, having been reported to play a role in obesity related diabetes and insulin resistance. [2, 9, 13]

2.5. TNF-α

The tumor necrosis factor, TNF-α, is a proinflammatory cytokine belonging to the tumor necrosis factor superfamily and is produced by several types of cells, but mostly by the macrophages and monocytes. [25, 32]

The gene, found on chromosome 6 (6p21.3), has various functions in coagulation, endothelial disfunction and lipid metabolism. It also activates the NFkB proinflammatory pathway, producing insulin resistance, an increase in the circulating TNF-α levels being identified in obese individuals. [3, 32, 33]

During the past years, the TNF-α gene and its receptors have become interesting treatment targets for obesity, insulin resistance and type 2 diabetes.

2.6. AdipoQ

The 3q27.3 AdipoQ gene encodes, exclusively within the adipocyte, for the protein adiponectin, an adipokine with multiple and important actions and functions. It plays a role in the lipid and glucid metabolisms, is an insulin sensitizing factor, functions in the skeletal muscles and liver by stimulating AMP kinase activation, negatively mediates TNF-α gene expression, takes part in processes such as angiogenesis and cell growth, etc. [3, 32, 33]

Low levels of adiponectin are correlated with insulin resistance, type 2 diabetes and coronary artery disease, while high levels of this hormone are associated with a decrease in the risk of cardiovascular disease. Studies point out that adiponectin possesses important anti-diabetic, anti-atherogenic and anti-inflammatory characteristics. [32]

Certain SNPs in the AdipoQ gene have been described to being associated with an increased risk of developing obesity, metabolic syndrome and type 2 diabetes. The -11,377C > G, -11,391G > A, +45T > G, and +276G > T polymorphisms cause an increased risk for severe obesity, while SNP276 is correlated with obesity, metabolic syndrome and type 2 diabetes in the elder population. [6, 18, 28, 29]

2.7. AdipoR1

Adiponectin has 2 cloned receptors – the adiponectin receptors 1 (AdipoR1, on
chromosome 1q32.1) and 2 (AdipoR2, chromosome 12p13.31). Mutations in these genes will cause abnormal functions of adiponectin [32, 34]. However, although some studies suggest that these receptors, especially AdipoR1, are somehow connected to obesity, the mechanisms are not yet fully understood [2].

2.8. TUB

The tubby homolog gene, found on chromosome 11p15, encodes for one of the members of the Tubby family transcription factors. The TUB gene is highly expressed in the hypothalamus, its main functions being in signal transduction and transcription regulation [32, 33].

Mutations in this gene will cause obesity and insulin resistance in mice. Three SNPs have also been discovered in human to being linked to obesity – rs1528133, rs2272382 and rs2272383 [2, 26].

2.9. Visfatin/PBEF1

Visfatin is a recently discovered adipokine on chromosome 7q22.3, corresponding actually to the PBEF1 gene [2]. Visfatin is mainly expressed in human in the visceral adipose tissue and is involved in insulin expression by activating the insulin receptor, being at the same time correlated with inflammation – visfatin is considered to be a proinflammatory cytokine [2, 32] a link between inflammation and obesity – and apoptosis [8].

Studies suggest that visfatin is associated with obesity, insulin resistance, type 2 diabetes, metabolic syndrome and cardiovascular disease, its possible use as a predictor of this conditions being taken under consideration [7].

Two SNPs have been identified to being linked to obesity and its comorbidities: the G-948T SNP, involved in obesity and type 2 diabetes, and rs4730153 with effects on the glucose and lipid metabolisms [2, 17].

2.10. ENPP1

Another obesity-associated gene is the ectonucleotide pyrophosphatase/phosphodiesterase 1 gene, a member of the ENPP genes family, found on chromosome 6q23.2 [2]. The function of the protein expressed by this gene is to hydrolyze different types of bonds, including nucleotides’ phosphodiester and pyrophosphate bonds, possibly regulating insulin sensitivity. Mutations in this gene cause insulin resistance, infantile arterial calcification and the ossification of the posterior longitudinal ligament of the spine. [32, 33]

Until now there is only one SNP of the ENPP1 gene, K121Q, found to play a role in the BMI and obesity, and in other metabolic disorders as well [2, 27].

2.11. MAF

The V-maf musculoaponeurotic fibrosarcoma oncogene homolog (chromosome 16q23.2) regulates the insulin and glucagon expression. MAF gene, a member of the MAF gene family, is a transcription factor modulating cell differentiation and gene transcription in humans [32].

About 6% of the cases of childhood obesity and 16% of all the obese adults have revealed the involvement of the MAF gene. A SNP of the gene, rs1424233, is correlated with weight gain in tested individuals [14, 16].

2.12. NEGR1, INSIG2, CETP and other genes

NEGR1 gene, mapped to chromosome 1p31.1, is apparently implicated in cell
adhesion [32] Variants of this gene are associated with obesity [19].

The INSIG2 gene is located on chromosome 2q14.2 and is thought of being correlated with extreme cases of obesity [15].

The CETP gene on chromosome 16q13 codes for the cholesteryl ester transfer protein, which has the role of transporting cholesteryl esters between lipoproteins. [32] The Tag1B gene polymorphism plays a role in obesity, being a HDL-cholesterol modulating factor [22].

Certain SNPs near the TMEM18, GNPD12, KCTD15, BDNF, ETV5, SEC16B, SH2B1, and MTCH2 genes show an important implication in the regulation of body mass.

3. Genes causing monogenic syndromes

A number of genes have been identified as triggers of complex monogenic syndromes in which obesity is the central but not necessarily the only clinical feature. The most common obesity single gene disorders are produced by mutations in the LEP, LEP-R, MC4R, POMC, PCSK1 genes.

3.1. Leptin

Leptin (chromosome 7q32.1) was the first adipokine to have been discovered in 1990 and is almost exclusively expressed by the white adipose tissue adipocytes [3, 32]. The most important function of the LEP gene is in modulating the body mass by transmitting the satiety signal to the hypothalamus in order to stop or decrease the food intake. Leptin plays major roles within the human organism, such as its roles in immunity, reproduction, angiogenesis, inflammation, hematopoiesis etc. [3, 32].

Leptin levels are high in obese individuals and are proportionally correlated with BMI. Mutations in this gene lead to severe obesity, type 2 diabetes, morbid obesity associated with hypogonadism, the diminishing of the normal expression of LEP gene causing obesity-related monogenic disorders such as the congenital leptin deficiency or partial leptin deficiency (in heterozygote carriers) [3, 24, 32].

The congenital leptin deficiency is an autosomal recessive disorder caused by the frameshift Δ133G mutation and is the first single gene disorder associated with obesity. The clinical features of this disease are the early onset of obesity, hypogonadotropic hypogonadism, hyperinsulemia and anomalies in the hypothalamo-pituitary-thyroidal axis, hyperphagias, etc. The disorder is treatable through leptin administration [2, 3, 11].

3.2. LEP-R

The leptin receptor gene has its locus on chromosome 1p31.3 and is a member of the gp130 cytokine receptors family. The roles of the leptin receptor gene are in the lipid metabolism and in gene transcription regulation. Possible connections of LEP-R with the reproduction process have been described [32, 33].

Mutations within the leptin receptor gene are linked to obesity and abnormal pituitary function. The decrease of the LEP-R gene synthesis leads to the leptin receptor deficiency autosomal recessive mendelian disorder [2, 11]. The patients suffering from this disease have a normal birthweight but then develop postnatal hyperphagia, severe obesity, hypogonadotropic hypogonadism, hypothyroidism, increased growth hormone (GH) expression and low levels of insulin-like growth factor 1 (IGF-1) and insulin growth factor binding protein 3 (IGFBP3) [11, 21].
3.3. POMC

The pro-opiomelanocortin gene (2p23.3) expresses a polypeptide hormone precursor. The precursor can be cleaved in 10 different peptides (lipotropins, adrenocorticotrophin, melanotropins, endorphins) with distinct functions depending on the tissue where the gene is secreted. A number of eight cleavage sites can be found on the polypeptide precursor, the protein synthesis being produced mainly in the corticotroph cells of the anterior pituitary gland [32].

Mutations in the POMC gene cause obesity, red hair and adrenal disfunction and at the same time generate monogenic obesity syndromes in human [2]. The POMC deficiency is an autosomal recessive disorder numbering adrenocorticotropic hormone deficiency, hyperphagia and early onset obesity as main signs and symptoms [11, 21].

3.4. MC4R

The MC4R gene, found on the 18q21.32 chromosome, belongs to the melanocortin receptor gene family (5 receptors) and seems to be strongly correlated with the regulation of the energy balance of the organism [32].

Mutations in the MC4R gene lead to an autosomal dominant single gene disorder called MC4R deficiency, the most common obesity-related mendelian disease in humans. Its clinical features include hyperphagia, early onset hyperinsulinemia and obesity [2, 12].

3.5. PCSK1

The PCSK1 gene (5q15 chromosome) is part of the subtilisin-like proprotein convertase family and plays a role in the hypothalamic processing of POMC and of other neuropeptides [24, 32].

Mutations in the PCSK1 gene cause the autosomal recessive protein deficiency characterized by severe childhood obesity, hypoglicemia, hypoadrenalism and neuroendocrine affection [2].

4. Genes causing polygenic obesity syndromes

Most of the obesity cases are caused by more than one gene (over 90% of all obese individuals). Genome-wide studies indicate chromosomes 2p, 3q, 5p, 6p, 7q, 10p, 20q as sites for candidate genes for polygenic obesity [5]. The 2p21 chromosome location is one of the strongest sites associated with obesity, as it contains the POMC gene [2]. A number of over 70 genes having some correlation with obesity have been found, but their involvement in the ethiopathogenesis of this disorder is not yet fully understood [5].

5. Pleiotropic obesity

Over 30 genetic syndromes have been described of including obesity among their main clinical features. These are complex disorders, each having its distinct clinical characteristics, evolution, onset of symptoms, pathogeny, inheritance, etc. Some of the main genetic syndromes with obesity are: Prader-Willi syndrome, Albright hereditary osteodistrophy, ulnar-mammary syndrome, Bardet-Biedl syndrome, Alstrom syndrome, Cohen syndrome, fragile X syndrome, Borjeson-Forssman-Lehman syndrome, MEHMO syndrome, Wilson-Turner syndrome, WAGRO syndrome, etc.

6. Conclusions

The discovery of new candidate genes, new mutations and new polymorphisms associated with obesity are an important asset in our possibility to develop new
treatment options and in the future to prevent this condition.

References


