Acta Biomed 2019; Vol. 90, Supplement 10: 87-89 DOI: 10.23750/abm.v90i10-S.8766

Review

Mendelian non-syndromic obesity

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Summary. Obesity is highly heritable and arises from the interplay of many genes and environmental factors. It can be defined as the result of prolonged imbalance between calorie intake and energy utilization. About 5% of cases of non-syndromic obesity are monogenic (Mendelian obesity). The amount of adipose tissue in the body is mainly regulated by leptin, a hormone produced by adipocytes, and Mendelian obesity is mainly caused by mutations that disrupt the leptin/melanocortin pathway. In this article, we summarize the genes involved in genetic obesity and the test we use for genetic analysis. (www.actabiomedica.it)

Key words: Mendelian obesity, leptin/melanocortin pathway, adipogenesis

Obesity is a chronic disease defined by the World Health Organization as a "condition characterized by excessive body weight due to adipose tissue accumulation, which has a negative influence on health status". Obesity is the most common nutritional disorder in the western world, and its prevalence is constantly increasing in developing countries. In 2014, about 39% of the world adult population was overweight and about 13% obese (1). Obesity is associated with several metabolic co-morbidities and higher mortality risk due to onset of type 2 diabetes, hypertension, cardiopathies and some cancers (1).

In 2000, the WHO set classification criteria for obesity on the basis of body mass index (BMI). The normal range of BMI is 18.5-24.9, whereas for different types of obesity it is 25-29.9 (type I), 30-39.9 (type II) and >40 (type III) (2).

Most of the genes known to be associated with monogenic obesity belong to the leptin/melanocortin pathway and are expressed in the hypothalamus. They encode proteins involved in the food intake/energy expenditure balance. The adipocyte differentiation pathway, which involves several growth and transcription factors (3,4), is also related to obesity.

Leptin is secreted by adipose tissue and binds to the leptin receptor in the hypothalamus, where it controls food intake through the melanocortin pathway. In the hypothalamus, leptin activates neurons expressing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript protein (CARTPT), and inhibits neurons expressing neuropeptide Y (NPY) and Agouti related neuropeptide (AGRP). POMC is cleaved into melanocortins α-, β- and γ-MSH which bind to their receptors: MC3R and MC4R (3).

Adipogenesis is the differentiation of adipocytes from mesenchymal stem cells. Differentiation into the adipocyte lineage is induced by chronic excessive energy intake and elevated glucose uptake. Many factors involved in this process have been identified, but

Table 1. Genes associated with various forms of Mendelian non-syndromic obesity

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
UCP3	602044	Severe obesity, T2D	601665	AR, AD	Uncoupling of oxidative phosphorylation, energy dissipation, modulation of tissue respiratory control, thermogenesis, energy balance
CARTPT	602606	Obesity	601665	AR, AD	Inhibition of feeding
CEP19	615586	Morbid obesity and spermatogenic failure	615703	AR	Required for ciliation
DYRK1B	604556	Abdominal obesity-metabolic syndrome 3	615812	AD	Enhancement of adipogenesis
KSR2	610737	Severe early-onset obesity	/	AD, AR	Regulation of cell energy homeostasis through AMPK activation
LEP	164160	Morbid obesity	614962	AR	Major role in regulation of energy homeostasis
LEPR	601007	Morbid obesity	614963	AR	
MC4R	155541	Obesity	618406	AD, AR	
NR0B2	604630	Early-onset mild obesity	601665	AD, AR	Transcriptional regulator of HNF4A, involved in onset of MODY
PCSK1	162150	Obesity	600955	AR	Processing of POMC, insulin
POMC	176830	Obesity, adrenal insufficiency, red hair	609734	AR	Energy homeostasis
PPARG	601487	Severe obesity	601665	AD, AR	Regulator of adipocyte differentiation
PPP1R3A	600917	NIDDM, obesity	125853	AD	Regulation of glycogen metabolism
SH2B1	608937	Hyperphagia, early onset obesity, insulin resistance and short stature	/	AD	Adaptor protein involved in insulin, BDNF and leptin signaling pathways
SIM1	603128	Severe obesity, neurobehavioral disorder	/	AD	Transcription factors essential for formation of the hypothalamic paraventricular nucleus
TUB	601197	Retinal dystrophy and obesity	616188	AR	Involved in hypothalamic regulation of body weight
NTRK2	600456	Obesity, hyperphagia, developmental delay	613886	AD	Mediation of neuronal plasticity in hypothalamus
ADCY3	600291	Obesity, T2D	/	AR	Control of adipose tissue development, function and insulin secretion in beta cells
BDNF	113505	Hyperphagia, severe obesity, cognitive impairment, hyperactivity	/	AD	Regulation of food intake, body weight

AD=autosomal dominant; AR=autosomal recessive; T2D=type II diabetes; MODY=diabetes of the young; NIDDM=non-insulin dependent diabetes mellitus.

PPARγ is the only factor which is necessary and sufficient for adipocyte differentiation, establishing it as the master regulator of adipogenesis (3).

The most common form of Mendelian non syndromic obesity is associated with mutations in *MC4R*, with a prevalence in the general population of 1-5:10000. Patients with mutations in this gene can also present with hyperinsulinemia and increased linear growth (5).

Other relatively frequent forms of obesity are associated with mutations in the leptin and the leptin receptor gene: *LEP* and *LEPR* (prevalence of both forms <1:1000000). Patients with mutations in these genes show hyperphagia and severe early-onset obesity, and may also have immune function alterations and hypogonadotropic hypogonadism (5). Obesity due to mutations in *POMC* has a prevalence <1:1000000. Besides obesity, patients with *POMC* mutations show hypocortisolism, hair and skin hypopigmentation, neonatal hypoglycemia, seizures, cholestasis and voracious appetite (5). Obesity linked to *PCSK1* mutations has a prevalence in the general population of <1:1000000. Mutation carriers display severe early-onset obesity, hyperphagia, hypoglycemia, hypogonadotropic hypogonadism, hypocortisolism, elevated plasma levels of proinsulin and low plasma concentrations of insulin (5).

Diagnosis is based on clinical findings and lipid panel measurements. Genetic testing is useful for confirming diagnosis and for differential diagnosis, recurrence risk calculation and prenatal diagnosis in families with a known mutation.

Mendelian non syndromic obesity can have autosomal dominant or autosomal recessive inheritance (Table 1). Pathogenic variants may be missense, nonsense, splicing or small indels. MAGI uses a multigene NGS panel to detect nucleotide variations in coding exons and flanking introns of the genes listed in Table 1.

Worldwide, 34 accredited medical genetic laboratories in the EU and 37 in the US, listed in the Orphanet (5) and GTR (6) databases, respectively, offer genetic tests for Mendelian non syndromic obesity. The guidelines for clinical use of genetic testing are available in Genetics Home Reference (7).

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with Mendelian obesity. When this suspects is present we perform the analysis of all the genes present in this short article.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of ≥99% (coverage depth ≥10x).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 5 April 2019
Accepted: 5 September 2019
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