

New interesting data on obesity genetics

Obesity is the most widespread metabolic disorder, with a growing prevalence and severe associated comorbidities such as diabetes mellitus, arterial hypertension, cardiovascular diseases, obstructive sleep apnea, and cholelithiasis. Obesity and its consequences have a major impact on present and future public health.¹ The distribution of adipose tissue is the result of an interaction between genetic and environmental factors. Discovery of the contribution of genetics was important as it revealed the frequent genetic influence on early onset severe obesity. Also, genetic studies may help in identifying groups of individuals that are resistant to modification of environmental factors and new methods of treatment.

Basic information on the genetic background of obesity has been provided by family, twin, and adoption studies: family studies suggest that the heritability rate may vary from 25%-40%, and in twins it may be 50%-80%.²

Mendelian disorders There are numerous Mendelian transmitted disorders in which obesity represents a major component, whose genetic background has been recently discovered, such as: Prader-Willi syndrome, Bardet-Biedl syndrome, Albright osteodystrophy, and others. In most cases, the product of the implicated gene is an intracellular protein that is expressed throughout the organism, but whose function is unknown.³

Monogenic syndromes Approximately 20 different genes and at least three different mechanisms have been implicated regarding monogenic causes of obesity; however, they account for fewer than 5% of all causes of severe obesity.⁴ Mutations observed in several genes induce morbid obesity that appears in childhood, and are correlated with distinct biochemical, clinical, and neuro-endocrine features.

Congenital leptin deficiency was the first monogenic disorder described. The main role of leptin is transmission of satiety to the hypothalamus in order to reduce food intake and fat storage. Unlike in animal models, in which leptin deficiency has often been found, in humans, resistance to leptin action associated with high plasma leptin levels is more frequent. In the rare cases of leptin deficiency in humans, leptin administration reduced food intake and caused significant weight loss. A few cases of leptin receptor deficiency have been discovered. Although these individuals have normal weight at birth, they experience rapid weight growth in the first months of life, associated with hyperphagia and aggressive behavior.^{5,6}

Proopiomelanocortin (POMC) and α -MSH act on the MC4 gene receptor and reduce food intake. Genetic defects in POMC production and mutations to the MC4 gene have been described as monogenic causes of obesity in humans. Recent data suggest that about 5% of obese children have melanocortin or POMC mutations.^{7,8}

Polygenic syndromes Individual variations in adipose tissue are mainly determined by multiple genetic factors. Investigations have identified several possible loci, but the 2p21 chromosome has most frequently been associated with obesity. A recent study found evidence for a link between obesity and stature in previously reported loci on 11q23, 12q12, 15q25, and 18q23, as well as 15q26 and 19q13, which have not been previously linked to stature. For body mass index, evidence has been found for two loci: one on 7q35 and another on 11q22.⁹

New technologies have discovered multiple genes with potential implications in the pathogenesis of obesity, the most studied being those from chromosomes 2p, 10p, 5p, 11q, and 20q, and most recently, Apcs on Chr 1, Ppargc 1a on Chr 5, Ucp 1 on Chr 8, Angpt16 on Chr 9, and Lpin1 on Chr 12.¹⁰

The results suggest that the genetic basis of human obesity is extremely heterogeneous, with contributions from numerous genes acting by different, as yet undiscovered, molecular mechanisms.⁴

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References:

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