

# [Obesity caused by mutations in melanocortin 4 receptors essay](https://assignbuster.com/obesity-caused-by-mutations-in-melanocortin-4-receptors-essay/)

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AbstractPresent paper observes key regulators of energy balance in the body, including the association between obesity and melanocortin 4 receptors. The results of recent studies are discussed, diagnosis and therapy observations are included in the paper. Obesity Caused By Mutations In Melanocortin 4 ReceptorsIntroductionObesity is a disease, which is often treated as a cause for mortality and morbidity. Approximately 50% of adults are affected by it as well as the significant part of the pediatric population in the USA. Thus, obesity can be regarded as one of those health problems all over the world in general and in the US in particular. There are lots of interrelated factors that cause obesity directly or indirectly.

Although there are distinct viewpoints on direct causes of obesity, this problem has gained much attention from the society and produced policy and health responses. In the USA, the authorities are focusing primarily upon controlling obesity among children, which significantly influences public health. Social programs are aimed at reformatting meal program at schools, limiting food marketing addressed to children and limiting consumption of sweetened beverages. In Europe social programs are targeted at reducing the amount of advertising addressed to children and to reformatting agriculture policy preventing production of food that may cause overweight, which leads to obesity in state population.

Obesity is treated as severe among 10 per cent of children ill for obesity. In approximately 5% of children influences by obesity it is connected to alteration in the gene for melanocortin 4 receptor, and these are autosomal dominant transformations. DefinitionBefore speaking about mutations of melanocortin 4 receptor, which cause obesity, it is necessary to define what melanocortin 4 receptor is. This receptor, a 332–amino-acid, couples to the heterotrimeric protein, transforming the signal, which leads to an activation of adenylate cyclase.

This receptor is responsible for regulation of food ingestion, collecting a specific signal, produced by -MSH and a signal produced by AGRP, agouti-related protein.            These legands are produced in different populations of neurons that are present in the arcuate nucleus part of the hypothalamus and are directly regulated by leptin, a hormone, secreted by adipocytes. It is responsible for controlling food ingestion and regulation of homeostasis of long-term energy. Latest research results suggest that melanocortin 4 receptor espresses an activity, to which agouti-related protein serves as an antagonist. According to recent data:“ Heterozygous mutations in the MC4R gene have been implicated in a significant proportion of cases of severe childhood-onset obesity.

These multiple studies have led to the discovery of a total of 91 mutation carriers, most of them heterozygous, in 3057 children and adolescents, representing 2. 98% of childhood-onset obesity.” (Crowley et al)The defects in functionality of the mutated receptors for patients involve full decrease of activity, referred to intracellular retention of the affected protein, reduced agonist-induced activity of receptors or reduced activity of constitutive character, performed by the receptor. Studies in this field demonstrate that the largest amount of mutations related to obesity are fully or partially intracellularly retained.            A series of studies have been conducted to evaluate the role of variants of melanocortin 4 receptor, played in adult obesity. For instance, according to the studies in France, 4% of obese patients in this country express patogenicmutations in melanocortin 4 receptor (209 adults with body mass index above 35kg/m2). Almost the same results were received after observing obese patients in Northern California – 3.

5% or 166 adults with body mass index above 40 kg/m2. (Nisoli)            Such changes are linked to obesity in probands families are not distinguished by nonobese controls. On the contrary, some other studies obtained distinct results, demonstrating lower occurrence of mutations of pathogenic nature in obese patients in various countries. The experiential happening may be baffled due to differences in onset of the disease for adults in different countries, and the consequences of these studies led the experts to the following supposition:“ MC4R mutations cause a specific form of early-onset highly penetrant obesity and that other genes or different gene-environment interactions are implicated in later-onset severe obesity”. (Govaerts et al)            It is always necessary to early diagnose obesity, which is related to mutations in the gene for melanocortin 4 receptor, because this illness cannot be resolved without active treatment.

One of the reasons causing obesity is child’s inability to feel a sense of fullness, so parents should be attentive to understand and recognize the behavior of their child to reach the limits in child’s food intake. Besides, diagnosis of obesity, caused by mutations in the gene for melanocortin 4 receptor, may produce the sense of shame or guilt, related to the weight problems of a child, in both children and their parents. The only way to diagnosis of obesity caused by mutations in the gene for melanocortin 4 receptor is genetic testing. It provides a definite result, and may also help in defining the carriers of those gene mutations that produce obesity, which is necessary to prevent from developing obesity in case such carriers appear. There are several monogenic causes that are identified for obesity.

In each particular case the mutated gene participates in a complex pathway transferring signals, thus influencing eating behavior and control over it. As refers to this pathway, linking of ?-melanocyte (or ?-MSH) hormone to mutated gene plays a central role. Here is how Clapham et al describe how mutations-affected proteins, producing obesity, should function under normal conditions:“ Affected Protein                                        Normal Physiological FunctionLeptin                                                  Protein hormone produced by adipocytes; serves as one                                                             of  inputs into signaling pathway believed to be                                                             involved in control of eating behaviorLeptin receptor in hypothalamus         Binding of leptin to leptin receptor stimulates synthesis                                                             of pro-opiomelanocortin. Pro-opiomelano-cortin (POMC)          Precursor protein for several peptide hormones,                                                              including ?-melanocyte stimulating hormone (?-MSH)Prohormone convertase-1                    Catalyzes post-translational cleavage of POMC into ?-                                                             MSHMelanocortin 4 receptor (MC4R)        ?-MSH receptor expressed in the hypothalamus;                                                             binding of ?-MSH to MC4R activates anorexigenic                                                             signals” Melanocortin 4 receptor is produced in the hypothalamus. Stimulating this receptor by the linking to ?-MSH activates the anorexigenic signals, which are supposed to cut food intake with the help of several further steps. During the studies of cell cultures a lot of melanocortin 4 receptor mutations causing obesity appeared to make the receptor protein dysfunctional. Hence, mutations of melanocortin 4 receptor reduce the anorexigenic signals activation, which should follow ?-MSH binding, so the patients with mutations in melanocortin 4 receptor, producing obesity, may not feel the satiety. Early obesity is first recognized in children under 10 years of age.

It is usually characterized by body mass index significantly higher than appropriate for this age and by hyperphagia. In contradistinction from other known obesity causes of monogenic character, affected melanocortin 4 receptor sometimes produces non-syndromic obesity. Those symptoms that are related to melanocortin 4 receptor are as follows:“ binge eating behavior, severe hyperinsulinemia, an increase in bone minerals, a higher linear growth velocity, and an earlier than normal onset of puberty.” (Mackenzie)Obesity, caused by mutations in melanocortin 4 receptor is usually inherited genetically in a autosomal dominant way. It has been noticed that the patients with mutation in two or less melanocortin 4 receptor copies of gene can express the phenotype of obesity, but those individuals that display mutations in homozygotes, or both copies of melanocortin 4 receptor gene, always show more evident obesity type:“ In heterozygotes, expression of the obesity phenotype appears to be due to haploinsufficiency, i.

e., insufficient amounts of intact MC4R protein are expressed from the remaining normal gene copy. Penetrance of the mutation varies within and between families, i. e., not all heterozygous individuals carrying an obesityassociated MC4R mutation are obese.

Within families, female carriers of obesity-linked MC4R mutations are often more severely affected than males with the same mutation.” (Hainerova et al)Diagnosis and treatmentWhile identifying melanocortin 4 receptor obesity it is always necessary to remember that its symptoms are also common for other obesity types, and sometimes they appear after a long period of time. Thus, a differential diagnosis of melanocortin 4 receptor obesity is impossible. On the contrary, genetic tests allow identifying melanocortin 4 receptor-related obesity at early stages and at any age. Traditionally, obesity was treated with the help of dietary approaches, in a combination with physical activity. But it has become evident that dietary treatment is most often not affective, and at present more and more patients are treated by bariatric surgeries.

Of course, this procedure is effective due to fast loss of weigh, but it has definite complications. ConclusionAt present several types of drugs aimed at treating obesity, caused by mutations in melanocortin 4 receptor, are being clinically developed and tested now. The therapeutic basis for this treatment is supported by the finding that a lot of patients suffering from obesity caused by mutations in melanocortin 4 receptor are heterozygous. According to the results of researches in cell culture, the normal functionality of melanocortin 4 receptor proteins is not influenced by mutated proteins that are present in the same cell. Thus, stimulating proteins that have not been affected by the mutations may appear to be effective in compensating the loss of functionality on the receptor. ReferencesCrowley V. E., Yeo G.

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