

## THE EFFECTS OF MUTATIONS IN MELANOCORTIN-4 RECEPTORS AND LIGAND MELANOCYTE-STIMULATING HORMONE THAT CAUSE INHERITED OBESITY IN HUMANS

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Obesity is not always the effect of improper dietetics and a maltreatment of physicality. Obesity can be a genetic mutation that is carried on from an obese proband, or person of first generation gene mutation. There are mutations that lead to changes in codons, resulting in signals that increase appetite and reduce the metabolism. This is a result of a frameshift mutation in the gene sequence that affects the Melanocortin-4 receptor of the cells, and the pre-pro-opiomelanocortin generating the melanocyte-stimulating hormone that bind the receptor. This physiological process is a key instrument in weight regulation and homeostasis. These mutations arise from a proband with a dominant form of obesity that is passed on to offspring.

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### Introduction

Today, More than 38% of U.S. adults, and approximately 17% of children are obese. Obesity is a vast and growing issue in our country, and many resources are being exhausted in research and effort to prevent it. Many believe that lethargy and substandard dieting is the root of obesity, but new breakthroughs in research show that obesity can be heritable. This newfound information could lead us to treatments that could prevent inherited obesity in humans in the future.

The Melanocortin-4 receptor (MC4-R) is a G protein-coupled, seven-transmembrane receptor that is found in every nucleus that binds alpha-melanocyte stimulating hormone (alpha-MSH). It is highly expressed in the hypothalamus, a

key brain region that is involved in weight regulation and bodily homeostasis (2). Two dominant forms of obesity were described by frameshift mutations in the human MC4-R. The first being a 4 base pair insertion at nucleotide 732 of the coding sequence leading to a nonfunctional shortened receptor lacking the sixth and seventh transmembrane domains. The mutation arose from severe obesity in the proband's family over three generations. The second form is a 4 base pair deletion at codon 211 resulting in a shortened protein form of the fifth transmembrane domain (3). The affect of these mutations is that the sixth and seventh transmembranes are not coded for, resulting in a faulty MC4-R.

Apart from these findings, there are several lines of evidence suggesting a connection between this receptor and weight regulation. First the inactivation of both copies of the MC4-R resulted in maturity onset obesity syndrome associated with increased linear weight growth. Secondly, The MC4-R deficiency phenotype repeats several characteristic features of obesity during development and growth. The antagonist for melanocortin receptors, the agouti protein, causes this. Neurons associated with the agouti protein exert continuous inhibition of feeding behavior, but this inhibitory signal is chronically disrupted. Expression of human agouti-related protein (AGRP) causes obesity; AGRP is a neuropeptide involved in the normal control of body weight (2). And lastly, Alpha-MSH, the natural ligand of MC4-R, may mediate physiological signals that tell the brain it is satiated (3). Thus, the impairment in production, processing, and responsiveness of MC4-R to alpha-MSH may lead to obesity. Alpha-MSH is derived of proopiomelanocortin (POMC). In humans, rare recessive mutations in the POMC gene lead to early onset extreme obesity. These mutations impair the alpha-MSH signaling (2).

Direct sequencing of PCR (polymerize chain reaction) products covering the entire POMC coding regions revealed two different mutations in exon 3. A Guanine to Thymine transversion in one parent allele at nucleotide 7013 results in a premature termination at codon 79. Truncation (shortening) of the POMC protein predicts the complete absence of alpha-HSM, encoded downstream. In the other parent allele, a one base pair deletion of nucleotide 7133 causes a frameshift predicted to disrupt the structure of the receptor-binding sequence of alpha-MSH and introduces a premature termination. Heterozygosity of these two mutations was confirmed in individuals. Increased body weight is consistent with the lack of POMC-derived ligands (alpha-HSM) for the MC4-R (1).

Sequencing of PCR products showing a deviant SSCP (Single-strand Conformation Polymorphism, a method for detection of

mutations in the genomic DNA) pattern, was identified in several heterozygous carriers of mutations and polymorphisms in MC4-R. A deletion of 4 base pairs results in a frameshift that introduces five deviated amino acids leading to a stop codon in the region encoding the fifth transmembrane domain, leading to a truncated protein. This mutation is likely to result in a non-functional receptor, because the seven transmembrane receptor has not been entirely coded for. This deletion results in dominantly inherited morbid obesity in humans (2).

#### Recent Progress

Increasing knowledge in the field has led us to a better understanding of how this mechanism functions. Because of the relatively low occurrence of MC4-R pathogenic phenomenon and POMC gene, and a high number of sequence variations, this has compromised the devising of a controlled intervention. The yield of MC4-R clinical testing and treatment of obesity is presently undefined (3). Hopefully, MC4-R testing can lead to the development of new therapy geared toward treating obesity. Also, the testing of MSH-analogues from POMC could be used as a therapeutic tool to control eating disturbances. Both of these advancements could be used to design an effective protocol to adjust lifestyles that these mutations cause. These types of obesity management techniques targeting MC4-R, and POMC mutated individuals could potentially be a better option than current pharmaceutical or surgical approaches.

#### Discussion

Within the nucleus of the hypothalamic neurons the prohormone POMC is posttranslationally cleaved to produce the alpha-MSH. Alpha-MSH is a peptide that exhibits appetite decreasing, and metabolism boosting effects upon activation of the MC4-R. MC4-R is expressed on the surface of target neurons, and is responsible for weight regulation signaling. Mutations to MC4-R and mutations in POMC that generate alpha-

HSM, have both been proven to elicit obesity. Results have confirmed that mutations in MC4-R are the most frequent genetic cause of common obesity described to date. The heterogeneous character of obesity linked to MC4-R mutations clearly implies that a functional routine assessment of MC4-R mutations will eventually be required to evaluate the risk of obesity in MC4-R mutated individuals.

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