

# The genetics of obesity: the role of the melanocortin 4 receptor

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Keywords: genetics; obesity; melanocortin 4 receptor

## Abstract

Obesity, which is described clinically by a body mass index (BMI) of  $> 30 \text{ kg/m}^2$  is increasing at an alarming rate, and is recognised as a chronic disease by the World Health Organization (WHO). This epidemic decreases life expectancy, and its prevalence is increasing within the global paediatric and adult populations in most African countries, South Africa included. Research has revealed the importance of the genetic component of obesity, with much emphasis to date having been placed on monogenic disease. Polymorphisms within the gene encoding for the melanocortin-4 receptor (MC4R), a hypothalamic receptor with the primary function of regulating food intake, are a significant cause of severe human obesity. Studies have shown a correlation between the degree of MC4R dysfunction and the severity and age of onset of obesity. The accepted mode of inheritance for MC4R mutations is co-dominance with modulation of penetrance and expressivity, which would explain why homozygous carriers are more obese than heterozygotes. MC4R mutation frequency is also dependent on the ethnicity of the population. The use of genetic markers for diagnostic strategies and as predictors of therapeutic outcome will be of importance in the future management of obesity.

Peer reviewed. (Submitted: 2009-07-21, Accepted: 2009-10-01)

JEMDSA 2010;15(1):45-47

## Introduction

Obesity (body mass index [BMI]  $> 30 \text{ kg/m}^2$ ) has been recognised as a chronic disease by the World Health Organization (WHO). It is characterised by alterations in metabolic function, which result in an increase in total body fat mass as well as an accumulation of visceral adipose tissue.<sup>1</sup> In the modern era, excess energy is available to fuel obesity because of a general decrease in energy expenditure and an overall increase in calorie intake.

The rise of obesity is exponential and has been described as an epidemic within an epidemic.<sup>2</sup> Between 1986 and 2000 the prevalence of obesity (BMI  $\geq 30 \text{ kg/m}^2$ ) doubled, morbid obesity (BMI  $\geq 40 \text{ kg/m}^2$ ) quadrupled and super obesity (BMI  $\geq 50 \text{ kg/m}^2$ ) increased five-fold in adults in the USA.<sup>2</sup> Even more alarming is the fact that a similar increase is being observed in the paediatric population.<sup>2</sup> The morbidly obese population is characterised by an average decrease in life expectancy of nine years in females and twelve years in males.<sup>2</sup> The prevalence of obesity is increasing in most African countries, particularly in individuals living in urban areas.

Although obesity is strictly dependent on an excess of energy intake over energy expenditure, a large body of research has illustrated the importance of the genetic susceptibility of certain individuals in the generation of this imbalance. Thus, obesity can be described as a multi-factorial disease, meaning that both genetic and environmental factors contribute to its development, as well as to the expression of its co-morbidities.<sup>3</sup> The focus of this review is to address obesity from

a basic science perspective, with specific reference to monogenic abnormalities that appear to be associated with the disease.

## Obesity in South Africa

Obesity is seen in both developed and developing countries and South Africa is one of several developing countries in which obesity is becoming increasingly prevalent.<sup>4</sup> It is not unusual to see individuals who are underweight and obese in the same household. Another striking feature is the correlation, in the same individual, between low birth weight and the appearance of features of the metabolic syndrome later in life.<sup>4</sup> According to the guidelines of the International Diabetes Federation (IDF), these include the following: abdominal obesity (based on race-specified values for waist circumference), a fasting plasma glucose of  $\geq 5.6 \text{ mmol/L}$  or previously diagnosed type 2 diabetes, elevated blood pressure (systolic  $\geq 130 \text{ mmHg}$  or diastolic  $\geq 85 \text{ mmHg}$  or treatment of previously diagnosed hypertension), dyslipidaemia (plasma triglycerides  $> 1.7 \text{ mmol/L}$ ; HDL cholesterol: men  $< 1.03 \text{ mmol/L}$ ; women  $< 1.29 \text{ mmol/L}$  or treatment for any of these two lipid abnormalities).

In South Africa, the prevalence of combined overweight (BMI 25–30  $\text{kg/m}^2$ ) and obesity (BMI  $> 30 \text{ kg/m}^2$ ) has reached alarming levels in the economically active adult population (18 to 65 years). In a random sample of 13 089 South African individuals, mean BMI figures were 22.9  $\text{kg/m}^2$  and 27.1  $\text{kg/m}^2$  for men and women respectively.<sup>5</sup> A total of 29.2% of the men and 56.6% of the women were overweight or obese (BMI  $\geq 25 \text{ kg/m}^2$ ). Abdominal obesity was

**Table I: Percentage of South African adults with a BMI > 25 kg/m<sup>2</sup>**

Ethnic group	Female	Male	Ref
Black	57.2	27.1	5
	74.6	49.3	6
Mixed race	52.4	31.2	5
	66.0	45.7	6
Asian	48.0	32.7	5
	37.0	35.5	6
White	50.8	56.1	5
	42.2	56.4	6

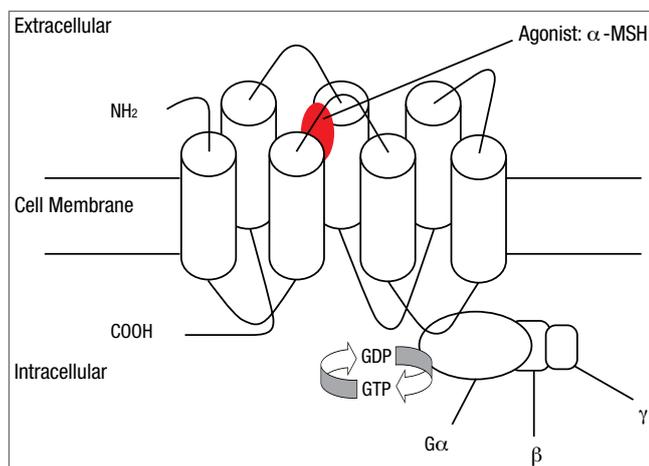
found in 9.2% of the men and 42% of the women.<sup>5</sup> Table I shows the percentage of South African adults with a BMI > 25 kg/m<sup>2</sup> according to population groups:

Urbanisation is a major contributor to the high prevalence of obesity seen in South African communities.<sup>5</sup> With regard to patterns of nutritional status and food intake, there appears to be a correlation between urbanisation and lack of concern for dietary composition and intake.<sup>5</sup> With regard to dietary intake, the adult South African population (age ≥ 15 yrs) is characterised by overnutrition, due largely to an increase in calorie intake in the form of total fat.<sup>5</sup> Abdominal obesity and overweight are therefore highly prevalent in adult South Africans, specifically in black African women and white men.<sup>5</sup> Education in general, and the challenging of certain cultural perspectives with regard to obesity, are necessary steps in the management of the South African obesity epidemic.<sup>5</sup>

### The melanocortin 4 receptor (MC4R)

The Melanocortin 4 Receptor (MC4R) is expressed in a number of locations in the central nervous system, and is concentrated in the paraventricular nucleus of the hypothalamus.<sup>7</sup> The MC4R is a member of the A super-family of G protein-coupled receptors.<sup>8</sup> It is encoded by a gene that contains a single exon and is located on chromosome 18q22.<sup>9</sup> It consists of a single 332 amino acid polypeptide chain that contains seven  $\alpha$ -helical transmembrane domains, an extracellular N-terminus, three extracellular loops, three intracellular loops and an intracellular C-terminus (Figure 1).<sup>10</sup>

**Figure 1: The structure of MC4R showing the seven  $\alpha$ -helical transmembrane domains, the three extracellular and three intracellular loops, the extracellular N-terminus, the intracellular C-terminus and the coupling of the receptor to a heterotrimeric G-protein.**



The MC4R is involved mainly in energy homeostasis, but also in sexual function, particularly erectile function.<sup>11</sup> Its primary function is to regulate food intake following the binding of  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), which provides an anorexigenic/satiety signal through the activation of the cyclic adenosine monophosphate (cAMP) second messenger system.<sup>9</sup>

### Polymorphisms in MC4R and their phenotypic classification

Individuals who carry mutations in the MC4R gene are not characterised by impairment in energy expenditure. Obesity in these individuals is due to a hyperphagic state.<sup>12</sup> The phenotype includes an increase in fat mass, linear growth and lean mass, extensive hyperinsulinaemia,<sup>13</sup> an increase in bone mineral density,<sup>14</sup> hyperphagia in early childhood and possibly binge-eating disorder.<sup>15</sup> These individuals also present with an elevated prevalence of the metabolic syndrome, which includes an increase in abdominal obesity, glucose intolerance, dyslipidaemia and hypertension.<sup>16</sup>

The extent of the differences in eating behaviour between carriers of pathogenic MC4R polymorphisms and non-carriers has not been observed in individuals with mutations in other genes that are involved in the leptin/melanocortin pathway, for example pro-opiomelanocortin (POMC) and the leptin receptor. This points to the importance of MC4R polymorphisms in affecting eating behaviour.<sup>16</sup> This was confirmed by Farooqi and colleagues, who found that the severity of the functional defect of the receptor correlated positively with food intake at a test meal.<sup>17</sup>

Male and female adult subjects harbouring pathogenic MC4R mutations have an elevated risk of obesity; the quantification of this observation in relation to BMI has revealed an increase of ~4 and ~9.5 kg/m<sup>2</sup> respectively when compared to wild-type relatives.<sup>18</sup> According to Lubrano-Berthelie and colleagues, a specific MC4R mutation carrier phenotype has not been identified and therefore the prediction of an MC4R mutation cannot be made based on phenotypic (clinical) observation alone.<sup>19</sup> However, these authors confirm that MC4R mutations are a significant cause of severe human obesity in both early and late onset forms of the disease.

### Functional impact of MC4R mutations

A correlation between the severity and onset of obesity and the degree of MC4R dysfunction has been clearly defined. Functional defects in the MC4 receptor that are responsible for obesity include decreased or absent ligand binding, decreased cell surface receptor expression (due to intracellular receptor retention), incorrect protein folding (which prevents the release of the receptor from the endoplasmic reticulum<sup>20</sup>) and a reduction in signal transduction.<sup>9</sup> Of these functional defects, those that cause intracellular receptor retention result in the most severe forms of obesity,<sup>19</sup> and are proposed to be the best predictors of the onset and severity of obesity in carriers of pathogenic MC4R mutations.

The most common functional receptor defect found in individuals with pathogenic MC4R mutations is a reduction in the constitutive activity of the receptor.<sup>9</sup> Normal constitutive receptor activity results in basal cAMP generation in the absence of an agonist.<sup>12</sup> N-terminal sequences are responsible for the constitutive activity which is compromised if mutations arise within this domain.<sup>12</sup> Mutations of

this nature have only been identified in obese individuals, which implies that a loss of or decline in basal MC4R is likely to affect the regulation of body weight.<sup>12</sup> In 2008, a total of 100 mutations in the MC4R gene were described,<sup>8</sup> 30% of which comprised frameshift or nonsense mutations and 70% of which were missense mutations that impaired signalling through cyclic AMP *in vitro*.<sup>8</sup>

The identification of a mutation/polymorphism in the MC4R gene does not necessarily imply that it is involved in the pathogenesis of the disease. *In vitro* functional confirmation is required to demonstrate that a mutation is pathogenic.<sup>21</sup> Thus there are many MC4R polymorphisms that occur commonly in both obese and non-obese individuals that have no consequence for the function of the receptor and are referred to as non-pathogenic.<sup>19</sup> This highlights the importance of functional studies, especially when investigating the therapeutic potential of mutant receptors. It should be pointed out, however, that there are exceptions to this rule: normal receptor function has been observed in obese individuals and, conversely, loss-of-function mutations have been seen in the non-obese.<sup>21</sup>

### MC4R mutational prevalence and inheritance mechanisms

Obesity is most commonly considered to be a polygenic disease. However, monogenic forms of obesity do exist, and the affected genes described thus far include leptin, the leptin receptor, POMC, pro-hormone convertase-1 and MC4R.<sup>3</sup> Forty to seventy percent of an individual's body weight is genetically determined, with the remaining contribution coming from the quality and quantity of food that is consumed.<sup>20</sup> An investigation of monogenic obesity disorders, despite their rarity, is an important step in the destigmatisation of the disease, i.e. in highlighting the fact that there is an undisputed biological basis for its development.<sup>8</sup>

MC4R deficiency is one of the most common human monogenic disorders.<sup>22</sup> MC4R mutations have a population prevalence of at least 1 in 2 000 (0.05%),<sup>22,23</sup> are found in 0.5% to 1% of obese adults<sup>22,23</sup> and are accountable for 6% of all severe cases of the disease starting in childhood.<sup>10,22-24</sup> With regard to penetrance, carriers of MC4R mutations will pass these on to their offspring with an 82% frequency, and individuals that carry mutations that affect function have a 4.5-fold increased risk of developing obesity as opposed to non-carriers.<sup>12</sup> The accepted mode of inheritance of MC4R mutations is co-dominance with modulation of penetrance and expressivity.<sup>8</sup> This inheritance pattern explains why homozygous carriers are more obese than heterozygous carriers.<sup>25</sup> Finally, the frequency of MC4R mutations is dependent on the ethnicity of the study group.<sup>12</sup>

Two factors have thus been proposed to explain discrepancies in MC4R mutation phenotypic penetrance. First, ethnic background, and second, whether or not the mutation leads to a receptor-function defect.<sup>25</sup> Both of these factors impact on the severity of the phenotype, which is more extreme in those individuals that have complete loss of receptor function: individuals that harbour mutations that totally abolish MC4R function have a higher BMI than those that have mutations that retain partial receptor function.<sup>26</sup> A decrease in the amount of functional MC4R also has a direct causative effect on the control of body weight.<sup>17</sup> Consequently, persons that are homozygous carriers have a higher BMI than those that are heterozygous carriers for the same mutation.<sup>26</sup> The transmission of mutations leading

to either loss of function or reduced function occurred at a rate of 81.8%. In addition, all mutations were transmitted to offspring in favour of the wild-type alleles.<sup>12</sup> Arguments for an autosomal dominant segregation pattern have also been proposed.<sup>12</sup> It would seem, however, that this theory is questionable, as the observed phenotypes do not confirm its assumptions.

### Concluding remarks

Obesity has become a major health care problem in the last few decades and is an important contributor to the increasing rate of global mortality. Bariatric surgical treatment has consistently been shown to be a very effective means of achieving weight loss and to be effective in the resolution of co-morbidities. Identifying genetic mechanisms that contribute to the development of the disease and using them to implement therapeutic strategies at both pharmacological and surgical levels is likely to become important in the future. In cases of monogenic obesity, for example, the most effective form of management would be bariatric surgery at an earlier age, rather than the more conservative approaches to treatment. The genetically-induced malfunction of proteins such as MC4R, which are involved in appetite regulation and energy homeostasis, could be used as markers in diagnostic strategies, and as predictors for therapeutic outcome in obesity management once the pathogenesis has been confirmed.

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