OTR.26 - Screening of monogenic obesity gene *MC4R* in Brazilian patients with morbid obesity

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Introduction:

Obesity is defined as an increased in body fat mass (Body mass index, BMI?30 kg/m2) that may impair health. The etiology of obesity is multifactorial, caused by an interaction of environmental factor with many genes variants of minor effect; however, rare monogenic forms were identified in human, which are caused by mutations with major effect in a single gene. Among the monogenic type of non-syndromic obesity, mutations in melanocortin-4 receptor gene (*MC4R*) are considered the most common cause of this disorder (OMIM*155541). Therefore, the aim of this study was to determine the prevalence of *MC4R* mutations in a cohort of morbidly obese adults.

Objective:

The aim of this study was to determine the prevalence of MC4R mutations in a cohort of morbidly obese adults.

Methodology:

This study comprised 158 unrelated adult participants. The inclusion criteria were patients with morbid obesity (BMI≥40.0) and the onset of obesity during childhood (0-11 years) or adolescence (12–21 years). The exclusion criteria were pregnancy, lactation, the use of medication to lose or gain weight, and the presence of monogenic obesity syndromes. Genomic DNA was extracted from peripheral blood for each participant and the coding region of *MC4R* was performed by direct sequencing.

Results:

Six rare *MC4R* variants were detected in this study in which two were novel. All individuals were heterozygous for these mutations. Four previously described *MC4R* mutations (Ser36Tre, Val193Ile, Ile98I= and Phe202Leu) were identified in 14 individuals. Additionally, two novel mutations were identified in

patients with early-onset obesity. One of them was a variation which disrupts the initiation codon ATG (Met1?) and the other was a missense mutation (Ala27Gly). Potential impact of rare variants was interpreted according to current standards and guidelines or *in silico* softwares. Our results showed the start lost variant was classified as pathogenic and the others as benign.

Conclusion:

This study showed that *MC4R* variants were identified in morbidly obese participants. Our results suggested the first Brazilian patient with monogenic obesity caused by *MC4R* deficiency; however, additional functional testing of the start lost mutation is required to confirm the findings.

Keywords: Monogenic Obesity; MC4R; Mutations