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Prevalence of mutations in *LEP*, *LEPR*, and *MC4R* genes in individuals with severe obesity

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ABSTRACT. Obesity is a major public health concern; despite evidence of high heritability, the genetic causes of obesity remain unclear. In this study, we assessed the presence of mutations in three genes involved in the hypothalamic leptin-melanocortin regulation pathway (leptin, *LEP*; leptin receptor, *LEPR*; and melanocortin-4 receptor, *MC4R*), which is important for energy homeostasis in the body, in a group of patients with severe obesity. For this study, we selected 77 patients who had undergone bariatric surgery and had a pre-operative body mass index (BMI) >35 kg/m^2, early onset and a family history of being overweight.

Candidate genes were screened by direct sequence analysis to search for rare genetic variations. The common *LEP* -2548 G/A polymorphism was also evaluated for its influence on the BMI (in obesity patients) and for obesity risk, using a case-control study involving 117 healthy individuals. Two different non-synonymous alterations in *MC4R* were found in two patients: the p.(Thr112Met), previously described in the literature as a probable gene involved in the obesity phenotype, and the novel p.(Tyr302Asp) variant, predicted to be pathogenic by *in silico* evaluations and family segregation studies. The *LEP* -2548 G/A polymorphism was not associated with the BMI or obesity risk. In conclusion, we have reported a novel mutation in *MC4R* in a family of Italian patients with severe obesity. Screening for *MC4R* could be important for directing the carriers of mutations towards therapy including partial agonists of the *MC4R* that could normalize their appetite and inhibit compulsive eating. Next-generation sequencing could be used to clarify the genetic basis of obesity in the future.

Key words: Obesity; Leptin; Leptin receptor; Melanocortin-4 receptor; Polymorphism