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## Genetic variability in the activation of brown-like adipocytes pathway and the risk of severe obesity

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**Statement of the Problem:** Regular physical activity has an important role in the prevention of the development of obesity; however the molecular aspects are still unknown. During exercise, PPARGC1 is overexpressed in skeletal muscles, stimulating an increase in FNDC5 expression. This gene encodes a muscle membrane protein which is cleaved to release a newly discovered hormone into the bloodstream, termed irisin. This novel myokine appears to act on white adipose tissue in humans, stimulating browning through an increase in UCP1 expression. As a result, irisin activates adipocyte thermogenic programs, leading to mitochondrial heat production and energy expenditure. The aim of this study was to assess whether genetic variants in genes related to browning are associated with severe obesity and related features.

**Methodology & Theoretical Orientation:** This case-control study comprised 400 participants, in which 208 were severely obese (BMI:45.6[40.5;52.2]) and 192 were normal-weight subjects (BMI:22.8[21.1;23.9]). Genomic DNA was extracted and genotypes for PPARGC1 (rs8192678, rs3736265, rs2970847 and rs3755863) and UCP1 (rs6536991 and rs12502572) polymorphisms were analyzed using real time PCR. Screening of exons 3, 4 and 5 (including their intron-exon boundaries) of FNDC5 gene was carried out by automatic sequencing. These exons were selected in order to screen the region which encodes the irisin hormone.

**Findings:** Our results demonstrate that genotype and allele frequencies of rs2979847 and rs12502572 differed significantly between the groups. Individuals carrying the rs12502572(A) and rs2979847(C) allele had a 1.35-2.01 fold increased risk for severe obesity. Additionally, these polymorphisms were associated with body weight, BMI, waist and hip circumference. After adjusting for gender and age, rs12502572 was also associated with HDL-cholesterol. Furthermore, five rare mutations were identified in FNDC5, one of which is a novel missense mutation.

**Conclusion & Significance:** This study suggests that genetic variants in the browning pathway influence severe obesity susceptibility as well as body fat distribution.

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