Abstract

This master´s thesis is focused on determination of mutation spectrum and frequency representation of variants in genes involved in Melanocortin Receptor Type 4 Signaling Cascade. Mutation in genes connected to MC4R signalisation cascade may induce so called monogenic type of obesity, which is characterised not only by mutation in single gene but also by an early onset severe obesity and hyperphagia. Due to new means of medications being introduced its especially important to ascertain the frequency of mutations in Czech children and adolescent population.

Theoretic part of the thesis is devoted to description of energy homestasis and leptin-melanocortin pathway. Physiology of hunger and satiety and the most common causes of obesity and monogenic obesity are also included. There is also mention of population differences in genetical predisposition for monogenic obesity namely in genes *MC4R, POMC, SIM1* and *BDNF* which were the focal points of this thesis.

In practical part, genetical analysis of 1910 samples from Czech children and adolescent population was implemented. We identified twelve different, likely pathogenic causal variants via next generation sequencing. More precisely eight different MC4R variants, 2 POMC variants and 2 SIM1 variants. In those, two novel variants were found c.346 C> T (Gln116Ter) in *POMC* gene and c.460C> G (Arg154Gly) *SIM1* gene.

Molecular-genetic testing of obese children and adolescents may significantly improve the insight in mechanism of origin for monogenic and polygenic obesity as well as finding new potentially pathogenic variants. This thesis helped with mapping of population incidence in czech population.