ABSTRACT

Mitochondrial disorders are a clinically, biochemically and genetically heterogeneous group of inherited disorders with a prevalence of about 1:5 000 live births. A common sign of those disorders is disruption of mitochondrial energetic metabolism. To this day, more than 400 genes have been associated with mitochondrial disorders, but 45% of patients are still without a genetic diagnosis. Using next-generation sequencing, new candidate genes or variants are found. To confirm the causality of those newly found genes or variants, biochemical characterisation using a plethora of various methods is necessary.

The first aim of this thesis was to study the function of ACBD3 protein on mitochondrial energetic metabolism in non-steroidogenic cells HEK293 and HeLa and to confirm the causality of the *ACBD3* gene in a patient with combined oxidative phosphorylation (OXPHOS) deficit. The second aim was to confirm the causality of two novel variants in *MT-ND1* and *MT-ND5* genes, which encode structural subunits of complex I (CI) of the respiratory chain. The third aim of the thesis was to study the formation of supercomplexes (SCs) in patients with rare metabolic diseases.

Using functional studies, we showed in this thesis that ACBD3 protein has no essential function in mitochondria but plays an important role in the maintenance of Golgi structure. Moreover, the causality of two novel variants in *MT-ND1* and *MT-ND5* genes was successfully confirmed and a hypothesis about the impact of the mutation in the *MT-ND1* gene on the mechanism of CI function was formulated. Furthermore, a cohort of Czech and Slovak patients with CI deficit caused by mutations in mitochondrial DNA-encoded structural subunits of CI was characterised. Last but not least, it was shown that in patients with congenital disorders of glycosylation the formation of SCs is increased.

Keywords: mitochondria, mitochondrial disorders, ACBD3, *MT-ND1*, *MT-ND5*, supercomplexes