ABSTRACT

Mitochondria are the key source of vital ATP molecules, which are largely produced within cells by a system of oxidative phosphorylation (OXPHOS). Genetic defects affecting any of the components of the oxidative phosphorylation system or the structure and function of mitochondria lead to mitochondrial disorders, which occur at an incidence rate of 1 in 5000 live births. Cytochrome c oxidase (COX) is the terminal enzyme and electron acceptor of a respiratory chain that catalyses oxygen to produce a water molecule. In addition to complex I deficiency, isolated or combined COX deficiency is the most common respiratory chain defect in paediatric patients, and it can arise from mutations located either in mitochondrial DNA or in nuclear genes encoding the structural subunits or corresponding assembly factors of the enzyme complex. However, the molecular basis of COX deficiency remains elusive in many patients despite advances in the identification of an increasing number of mutations and genes involved in the disease.

This thesis focuses on the identification of the genetic causes of mitochondrial diseases in a cohort of 60 unrelated Czech children with clinically and laboratory confirmed COX-deficiency. With the use of a high-resolution melting analysis mutation screen, four heterozygous sequence variants, located in *COX4I2*, *COX5A*, *COX7A1* and *COX10*, were found to be pathogenic and are suggested as candidate variants for future targeted-mutation screening in Czech COX-deficient children. The application of a DNA microarray SNP chip enabled the identification of rarely occurring but pathological large deletions in 4/16 patients affecting the *TYMP*, *SCO2* and *PUS1* genes, which were combined with causal missense mutations in *TYMP* and *SCO2*. The genomic DNA of 25/57 patients was analysed using next-generation sequencing targeted to the mitochondrial exome. The preliminary data analysis enabled the identification of pathological sequence variants in 5/25 patients, which affected the *AARS2*, *TSFM*, *TK2*, *AIFM1* and *MGME1* genes. Additional suspected disease-candidate variants were found in the *ACOX2*, *UQCRH*, *QARS*, *SUCLG2* and *ACBD3* genes of 5/25 patients, but their pathogenicity has yet to be confirmed experimentally. In conclusion, the genetic bases of COX deficiency have been clarified in nine paediatric patients.

Key words: mitochondria, mitochondrial disorders, laboratory diagnostics, inheritance, cytochrome c oxidase (COX) deficiency