Abstract

Next-generation (NGS) and third-generation (TGS) sequencing methods have played a key role in strategies of disease genes identification. Especially the exome sequencing increased the efficiency of causal variants identification up to tens of percent in study cohorts.

Rare neurodegenerative diseases are clinically and genetically heterogeneous and show a broad differential diagnostics. NGS and TGS technologies have been crucial in our understanding of the pathomechanism of rare neurodegenerative diseases. NGS and TGS, used by research laboratories, have been essential for many patients to determine a correct diagnosis, provide genetic counselling and reach an adequate treatment.

This thesis focuses on molecular mechanisms of selected rare neurodegenerative diseases, namely adult neuronal ceroid lipofuscinosis (ANCL), spinal muscular atrophy (SMA) and neuronal intranuclear inclusion disease (NIID). Modern DNA sequencing methods led to identification of causal lesions in ANCL suspect patients. We provide a concept of genetic testing for *SMN1* negative SMA patients and present a method for validation of tandem repeat expansion in NIID.

Key words: adult neuronal ceroid lipofuscinosis, spinal muscular atrophy, neuronal intranuclear inclusion disease, next-generation sequencing methods, *DNAJC5*