“The floppy child syndrome” is a term that describes the spectrum of clinical symptoms with predominant decreased muscle tone called hypotonia present in infancy and early childhood. The etiology of this disease is complex and involve environmental factors like viral or bacterial infections that lead to neurological symptoms (so called acquired hypotonia) as well as genetic factors like chromosomal aberrations or point mutations in specific genes, that encode proteins building or important for the proper function of peripheral nerve or muscle cells. The mutations in these specific genes leads to the decrease of the muscle tone and in consequence to hypotonia. Actually, hypotonia is the main clinical sign observed in so called neuromuscular disorders – diseases of lower motor neuron, peripheral nerve cells, neuromuscular junctions and muscular cell itself. The majority of neuromuscular disorders have the genetic background and the most frequent disease in this group and the most frequent cause of floppy child phenotype is spinal muscular atrophy (SMA) caused by mutations in *SMN1* gene. The molecular analysis of *SMN1* gene is one of the first diagnostic tests performed for children with floppy child syndrome with excluded acquired hypotonia. The lack of mutation in *SMN1* gene is an indication to the extension of molecular tests that is highly challenging due to the similar symptomatology of neuromuscular disorders and huge genetic heterogeneity. The same clinical symptoms can be caused by mutations in different genes, as well as mutations in the same gene might result in distinct clinical phenotype depending for example from the mutation type or the localization of mutation in specific region of the gene. Such high genetic and clinical heterogeneity, as well as the lack of systematized diagnostic algorithm for the management of patients with floppy child syndrome were the basis to undertake the research on molecular background of the disease.

The main project objective is the identification of the floppy child syndrome background with the special emphasis on neuromuscular disorders with genetic background In our studies the next generation sequencing technique will be applied that allows to for the simultaneous analysis of the sequence of all coding regions (so called exome sequencing). The application of this method will enable the identification of new genes that mutations were not described previously in relation to particular known clinical entities, It seems, that the additional effect of the project will be the phenotypic expansion – description of new phenotypes associated with mutations in disease associated genes.

Our results will assess the role of molecular analyses, especially those performed with modern techniques, including next generation sequencing, in the diagnostic approach dedicated to children with early hypotonia. They will also show whether there is a possibility to limit the invasive diagnostic procedures (eg. muscle biopsy). The proposed project is also important because of the fact that the molecular studies of floppy child syndrome associated with neuromuscular disorders are highly limited due to the complex genetic heterogeneity. This impedes the proper management offered to the patient, including the genetic counselling for the patent and his family. The practical aim of the project will be the establishment of diagnostic scheme of childhood hypotonia, that will enable the proper medical care offered for patients and their families.