Limb-girdle muscular dystrophy (LGMD) refers to a group of rare inherited diseases that cause weakness and wasting of the muscles in the arms and legs. The muscles most affected are those closest to the body, especially the muscles of the shoulders, upper arms, pelvic area, and thighs. The severity, age of onset, and features of LGMD vary among the many subtypes of this condition and may be variable even within the same family. First symptoms may appear at any age and usually worsen with time. As the condition progresses, people with limb-girdle muscular dystrophy may eventually require wheelchair assistance.

Understanding of LGMD pathogenesis comes from molecular genetics. Most of LGMD-causative genes are involved in muscle structure. Some encode proteins of the myofibril, some of the cytoskeleton, some play role in muscle membrane repair. In recent years, with the progress of the next generation sequencing techniques like whole exome sequencing (WES), several new genes causing LGMD or similar phenotypes have been revealed. WES allows to analyze DNA sequence of all the protein-coding genes in an individual genome. This makes it quicker to screen known genes for the mutation, and allows to look for novel genes involved in the disease. Although the genetics of LGMD has been partially defined, still over 50% of patients are left without genetic diagnosis. This suggests that some genes are still to be discovered, however this could also mean that we might have been looking for the causal mutations not exactly where is the highest chance to find those.

The aim of the proposed study is to further increase our knowledge on LGMD genetics, and especially to determine if mosaicism (genetic variation present only in the subset of cells / tissues) can lead to the disease. Additional aim of the project is to assess the influence of found mutations on clinical course of the disease of particular patients.

We are planning to apply whole exome sequencing (WES) technique to compare DNA sequence from affected muscle tissue and blood of 10-20 carefully selected patients. Muscle specific mutations will be analyzed bioinformatically to assess pathogenicity. Family members and healthy controls will be screened for the presence of found mutations.

The novelty of the proposed research project is based on the determination of whole exome profile of selected patients not only in the DNA isolated from blood, but especially in the DNA isolated from the affected tissue. The results could not only present the significance of genetic mosaicism for the clinical course of the particular patients, but could also influence myopathy diagnostic procedures with regards to DNA collection method. Also it could be speculated that mosaic mutations could be found in the genes currently not known to be associated with LGMD. Possible identification of novel genes associated with the disease could expand our knowledge on LGMD pathogenesis which in future may lead to novel therapies, and influence patients' quality of life.