The substantial progress has been made in the research into the causes of inherited human diseases. We owe most of this information to the significantly expanded knowledge of the human genome, the identification of many novel markers of genetic variability, and the amazing technological advances in genomic analysis. In addition, many novel bioinformatics tools have been developed to mine the ever increasing amount of data. Currently, the mainstream in the field of genomic research, including the identification of new mutations, is slowly changing towards establishing molecular relationships between mutation and disease. However, the knowledge of this genotype-phenotype correlation is still very limited. The problem becomes more complicated if the mutations are located in non-coding, regulatory sequences of the genome, or concern multifactorial diseases. These disorders are more common than diseases caused by a defect in one gene, and most of them result from the combined small effects from numerous genetic and environmental factors. Also, changes in genomic sequence can affect several interacting networks that together influence susceptibility to complex traits. Therefore, these mutations may affect many targets such as changes in chromatin structure, gene expression and/or localization of expression.

This proposal focuses on studying the molecular basis of human hereditary limb disorder – Clubfoot. Studies on the etiology of this disease indicate that it is a multifactorial trait, therefore we want to confirm the hypothesis that defects in different genes/regions can cause the same patient phenotype. The main purpose of the presented work is to explain the genotype-phenotype correlation in Clubfoot disease. The first part of the project includes the functional characteristics of the newly discovered mutation in the members of the family with Clubfoot. The second research task concerns the identification of mutation(s) associated with the isolated form of Clubfoot in 3 families and confirmation of the significance of the discovered changes in the etiology of Clubfoot.