

In today's aging societies, the problem of neurodegenerative diseases is increasing. These diseases lead to a variety of symptoms affecting the nervous system, negatively impacting cognitive function and motor abilities of patients, thus making their daily, independent functioning challenging. Unfortunately, our current knowledge about these diseases is still limited, and we lack effective methods of their treatment. One significant aspect influencing the development of these diseases is called epigenetic dysregulation, which affects changes in the activity of our genes (gene expression) through structural and chemical modifications of DNA, without altering its sequence.

One of the neurodegenerative diseases is spinocerebellar ataxia type 7 (SCA7), which is associated with altered functions of ATXN7 protein, a part of the protein complex responsible for remodeling DNA structure. In this condition, a specific group of large cerebellar neurons, called Purkinje cells (PCs), undergo selective dysfunction. These cells form a distinct pattern of alternating stripes of positive and negative expression of the "Zeb1rin-II" protein, hence often referred to as a "zebrin" pattern. Our recent research has revealed that the loss of this pattern is a characteristic feature of ataxias.

The aim of this project is to investigate changes in the epigenetic profiles of Purkinje cells that contribute to their degeneration, with a particular focus on the Zeb1rin-II positive and negative populations. To achieve this, I will analyze Purkinje cells obtained from genetically modified SCA7 mice at both the early and late disease stages and compare them with healthy mice. I will utilize recently developed technologies and advanced data processing methods that allow for simultaneous analysis of multiple epigenetic modifications in individual neuronal cells. Through this approach, I will create a detailed epigenetic map of Purkinje cells in health and disease. By integrating this information with publicly available data on several neurodegenerative diseases, it will be possible to identify new markers and mechanisms influencing the degeneration of Purkinje cells and their subgroups. Additionally, I will conduct preliminary experiments to validate the significance of the identified markers, both for SCA7 and other neurodegenerative diseases.

The completion of this project will provide us with a better understanding of the processes leading to the death of Purkinje cells in SCA7 and other neurodegenerative diseases. The identification of new disease markers and underlying mechanisms in SCA7 will be a crucial step toward the development of effective therapies for these devastating diseases.