

Parkinson's disease is the second most common neurodegenerative disorder, affecting roughly 6,1 million people worldwide and one of the leading causes of disability. Symptoms include slowness of movement, tremor, and rigidity as well as depression and cognitive decline. While treatment options exist, they lose effectiveness over time and produce a plethora of side effects. In the brains of the patients, characteristic is the loss of neurons in the region called Substantia Nigra. This region consists of a very specific type of neurons – ones that secrete neurotransmitter dopamine. The reason for their loss is unknown, however, in the surviving neurons, a protein called alpha-synuclein accumulates. The exact role of alpha-synuclein in the disease's development as well as the reasons for its appearance is a subject of decades of research with no definitive conclusion.

NFE2L1 gene encodes a factor responsible for a variety of cellular functions among others the clearance of badly formed and unnecessary proteins. We have discovered that the deactivation of this gene in the nervous system causes accumulation of alpha-synuclein and subsequently neurodegeneration. However, we lack direct evidence of the NFE2L1 gene's involvement in the development of Parkinson's disease.

In this project, we wish to explore this possible involvement and investigate the responsible mechanism. We will deactivate the gene specifically in the dopamine secreting neurons and we will observe the effects on mice behavior. The appearance of Parkinson-related symptoms will confirm that NFE2L1's dysfunction could be the cause of Parkinson's disease.

We will further research how the accumulation of alpha-synuclein happens. The central nervous system will be examined under the microscope with a focus on Substantia Nigra. After extracting dopamine-secreting neurons, we will perform analyses to find out how NFE2L1's deactivation affects other genes' functions.

We will also perform these types of analyses on an in vitro model of neuronal development. Cells will be specially treated to cause their differentiation into neurons. The cells in which we have deactivated NFE2L1 will be compared to intact cells in the number of produced neurons, their growth, and other parameters.

This project will allow for a better understanding of Parkinson's disease development, delivering missing puzzle pieces. Alpha-synuclein accumulation has been a long-acknowledged defining feature of this disease but the mechanism in which it happens remains elusive. Our research can provide for unveiling this mystery. As such it can pave the way towards the creation of treatment and prevention.