State the objective of the project.

The aim of the project is to explain the pathomechanism of cognitive impairments including memory, language skills in patients with molecularly confirmed Noonan syndrome.
We will perform accurate neuropsychological assessment as well as MRI examination of brain structures, resting state functional connectivity and white matter connectivity in association with molecular defects in genes encoding proteins in the RAS/MAPK (RAS – mitogen activated protein kinase) signaling pathway.

The basic research to be carried out.

The intendent studies will be carried out in the group of patients, with molecularly confirmed Noonan syndrome, who are followed up at the Counselling Unit of the Department of Medical Genetics at the Institute of Mother and Child. Neuropsychological evaluation will be performed in around 45 patients divided into three age groups. In the next stage a neuroimaging functional phenotype will be examined in around 30 participants older than 8 years.
A psychological evaluation will include intellectual abilities testing using the Raven Progressive Matrices, language skills using the Test of Language Development for younger children as well as the Test of Words Understanding for adolescents and adults, as well as executive function and working memory tasks using the Working Memory Test. The psychological tests and an analysis of their results will be performed in cooperation with the Department of Child and Family Clinical Psychology of the University of Warsaw.
After the comprehensive psychological evaluation of cognitive functions, the structural and functional analysis of the brain will be obtained in individuals older than 8 years with confirmed cognitive impairments. In order to discover the possible neurological mechanism of cognitive abnormalities observed in patients with Noonan syndrome resting-state functional magnetic resonance imaging (rs-fMRI), diffusion tensor imaging and voxel based morphometry will be performed..
Structural and functional analysis of particular regions of the central nervous system will be carried out at the World Hearing Center at the Institute of Physiology and Pathology of Hearing in Warsaw.

Reasons for choosing the research topic.

Noonan syndrome is one of the most common genetic conditions inherited in autosomal dominant manner. Distinctive facial features as well as short stature, congenital heart defect, chest malformation, skin difference, osteoarticular defects, visual impairments and variable developmental delay are the most typical clinical symptoms of Noonan syndrome. In addition, increased risk of malignancy including haematoproliferative diseases are observed. Noonan syndrome is caused by mutations in particular genes of the RAS/MAPK signaling pathway which is one of the basic cellular signaling pathways responsible for the signal transduction form of the outer cell membrane to the nucleus and plays an essential role in the regulation of cell function.
In the last few years, there has been an increasing interest in cognitive impairments described including memory deficits, verbal skills and social functioning impairments. The etiology leading to cognitive deficits in some patients with Noonan syndrome is not yet well known. Based on current knowledge about an essential impact of the RAS/MAPK signaling pathway on human brain function, we cannot exclude the relation between molecular defects and cognitive impairments. We hypothesize that cognitive deficits are result of structural and/or functional abnormalities of particular brain regions or networks caused by disturbances in RAS/MAPK signalling cascade.