PACS2-related disorder is an ultra-rare disease and its' true prevalence is not known. As of now, about 32 cases have been reported in the literature and about 100 in total diagnosed world-wide. This disease is caused by some mutations in the *PACS2* gene encoding PACS2 protein (phosphofurin acidic cluster sorting protein 2). Mutations in *PACS2* gene are responsible for neurodevelopmental disorder consisting of early-onset seizures, autistic features, mild facial dysmorphism, cerebellar dysgenesis with folia abnormalities and other systemic malformations. In humans, *PACS2* gene localized on the 14th chromosome encodes PACS2 protein which is a multifunctional cytosolic membrane trafficking protein playing crucial role in mitochondria-endoplasmic reticulum (ER) membranes tethering. The mitochondria-endoplasmic reticulum contact sites could be isolated as subcellular fraction called mitochondria associated membranes (MAM). This cusses that PACS2 modulates communication between the ER and mitochondria especially by influencing calcium ion homeostasis. Two mutations in *PACS2* gene (c.625 G > A and p.Glu211Lys) responsible for the development of PACS2-related disorder have been identified. They affect PACS2 phosphorylation, what impairs MAM integrity, resulting in a reduction of mitochondrial Ca^{2+} uptake.

Unfortunately, the literature is relatively scarce regarding the association between *PACS2* gene mutations and cellular dysfunction. The manifestation of *PACS2* gene mutations at the cellular level still remains elusive. Which cellular functions or parameters altered as a result of *PACS2* gene mutations play a crucial role in disease development is largely unknown. Therefore, the general goal of this project is detailed characterization of the alterations in cellular homeostasis (at the proteomic, metabolomic and functional level) that could be responsible for the observed clinical phenotype of PACS2 patients. Specifically, we will focus on alterations in metabolism, i.e., cellular bioenergetics, metabolites levels, redox status with manifestation o oxidative stress, calcium homeostasis and its relationship to total cellular proteomic profiles as well as MAM proteomic and lipidomic profiles in order to characterize metabolic alterations responsible for clinical phenotype of this ultra-rare disease in patients. We will study these relationships at different complexity levels: metabolomics and proteomics, isolated subcellular structures as mitochondria and MAM fraction, *in vitro* model using PACS2 patients' fibroblasts and *in vivo* study using mouse model of PACS2-related disorder. We believe that we will identify PACS2 protein as a regulator of cell fate in PACS2-related disorders. We will identify altered metabolic processes, the restoration of which not only rescues altered metabolism and diminishes oxidative stress but also may slow the disease development. On this basis, we will investigate which cellular processes or individual proteins could be potentially considered as a target for possible pharmacological intervention.

The main significance of this project is based on the fact that there is no approved pharmacological therapy for PACS2 patients. Our project is potentially of great importance for future clinical trials aimed at looking for biomarkers and possible molecules that could be used in the treatment of PACS2 disorder. Proposed actions of this grant application have also strong societal impact, especially for PACS2 patients and their families (rare diseases are often regarded as negligible diseases). This causes that the treatment of such diseases is often considered unprofitable due to the high costs of their development and the limited patient population.