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Fund “Nauka” Project № 24001 Resume – Special competition-based session 2024:

“Investigation of biomarkers of mitochondrial dysfunction in patients with RASopathies”

Project leader: Chief assist. prof. Yuliya Rumenova Bazdarska, MD, PhD

The RASopathies are a group of rare genetic diseases caused by mutations in the Ras/MAPK signaling cascade and characterized by multiorgan damage, including increased malignant potential. Despite the interest in the RASopathies in recent years, the pathogenetic mechanisms of multisystem involvement remain largely unclear. The RASopathies have a number of clinical similarities with another group of congenital conditions – mitochondrial diseases. The Ras/MAPK cascade has a role in the regulation of mitochondrial functions.

The aim of the current project is to investigate biomarkers for mitochondrial dysfunction in patients with RASopathies, thereby searching for new pathogenetic mechanisms.

Forty patients aged 0-25 who are followed up at least once a year in the Pediatric Clinics, in the Endocrinology Clinic of UMHAT “St. Marina” - Varna and the Endocrinology, Diabetes and Genetics Clinic at SHATCD “Prof. Dr. Ivan Mitev” – Sofia will be included, as well as 40 healthy controls matched as much as possible for gender, age, auxological indicators and other characteristics. Clinical, laboratory and imaging studies will be performed to assess endocrine functions, metabolic and cardiovascular status, neuropsychological development. Classical and innovative biomarkers (FGF-21, GDF-15, gelsolin) for mitochondrial dysfunction will be investigated. A correlation between their values and the severity of clinical manifestation in the patients will be sought, thus searching for hitherto unknown pathogenetic mechanisms. In the course of the study, a multidisciplinary team with expertise in working with patients with RASopathies will be formed. The results of the study will be published in Bulgarian and international scientific journals with an impact factor, will be presented at scientific events, and will serve to plan future scientific research.

Research tasks:

1. Complete assessment of clinical and functional parameters and markers in well-defined patients with a clinical and/ or genetic diagnosis of “RASopathy”;
2. Search for data on mitochondrial dysfunction in patients with RASopathies by studying established biomarkers for the diagnosis of mitochondrial diseases, as well as innovative ones;
3. Search for correlations between the values of the studied biomarkers and the severity of the phenotypic manifestation of RASopathies;

4. Search for correlations between the values of the studied biomarkers and the established genetic mutation in patients with a view to discovering new genotype-phenotypic correlations;
5. Assessment of psychological features and quality of life, and correlations with clinical-genetic and laboratory parameters;
6. Development of an algorithm for early assessment and monitoring of multi-organ disorders and markers of mitochondrial dysfunction in patients with RASopathies;
7. Expanding and disseminating knowledge in the field of rare diseases from the RASopathies group through publications and participation in scientific forums;
8. Searching for future directions for scientific research, as well as possible pharmacological and therapeutic interventions in mitochondrial dysfunction in patients with RASopathies.

Expected results:

1. For the first time in the country, a patient population with clinical and/ or genetic data for a RASopathy will be identified, for whom a complex assessment will be performed within the study by a multidisciplinary team of specialists using various physical, laboratory, imaging and functional methods;
2. The comparison between classical and innovative biomarkers will enable to determine the markers with the highest sensitivity for mitochondrial dysfunction;
3. Establish correlations between classical and innovative biomarkers for mitochondrial dysfunction with the severity of the clinical manifestation of the genetic disease (retardation in physical and neuropsychological development, cardiovascular status, disorders in the musculoskeletal system, presence and severity of neurological affect etc.) is expected. This will allow relevant biomarkers to be used with predictive value since early childhood in patients;
4. Carrying out genetic studies in the patients will allow the establishment of additional genotype-phenotype correlations and has the potential to discover new genetic variants in patients with RASopathies;
5. Establishing correlations between the results of psychological assessment in the patients and the investigated biomarkers for mitochondrial dysfunction;
6. Development of an algorithm for assessment and follow-up in patients with RASopathies aiming at early detection of multiorgan disorders and presence of markers of mitochondrial dysfunction;
7. The proposed innovative methods for assessing the energy metabolism, physical and neuropsychological development, neurological and cardiovascular status in the patients with RASopathies will enrich the knowledge of the members of the project in the field of RASopathies. The work on the project will increase the expertise of different specialists – geneticists, endocrinologists, cardiologists, neurologists, clinical laboratory specialists, who are engaged in the multidisciplinary care for the patients;

8. The new knowledge obtained about the role of mitochondrial dysfunction in the pathogenesis of the RASopathies may serve to search for new therapeutic options for the patients by acting on mitochondrial functions;
9. If successful and as a continuation of the current work, transcriptomic genetic studies may be planned in the future to discover gene products suitable for evaluation in early pharmacological intervention, molecular cellular mechanisms and causes of specific dysfunctions in RASopathies. These results can be used in preclinical studies and the experimental design of transgenic animal models, e.g. laboratory mice with specific human mutations, conditional deletions or insertions, and changes in the quantity of gene products in selected cell types or tissues. The created models will be suitable for research and evaluation of the action of innovative molecules to improve the clinical condition and quality of life of patients with RASopathies and other similar conditions;
10. The dissemination of the results will improve the visibility of the team and the basic organization among the scientific community in our country and around the world and will contribute to the early recognition of the conditions from the RASopathy group and the improvement of multidisciplinary patient care. The results of the project will be published in scientific journals, incl. 2 articles in Scripta Scientifica Medica as well as 1-2 journal publications with an impact factor. This will enrich the existing scientific knowledge on the matter. Medical University in Varna has an open access system to its scientific resources and will help to spread knowledge and results (https://library.mu-varna.bg/). The authority of the Scientific Institute at MU-Varna will increase;
11. The project will lead to the defense of at least one PhD dissertation, which will increase the capacity of scientific units in Bulgaria.