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Fund “Nauka” Project № 18015 Resume – Competitive-based Session 2018:
“DNA analysis in children with unknown rare genetic disorders”
Project leader: Prof. Lyudmila Boncheva Angelova, MD, PhD

The aim of the research is to reveal the molecular-genetic basis of unexplained rare genetic conditions in childhood and to improve the care of these patients.

The main task of this project is to start new DNA technologies for the diagnosis of microdeletion and microduplication syndromes, as well as screening a high-risk group of children with neurodevelopmental disorders to detect FRAXA syndrome with molecular genetic techniques. It is planned to organize and create a protocol for clinical and genetic assessment in children with unexplained rare genetic diseases, as well as a register and a specific database through photo and video documentation. An important task within the project will be the creation of a biobank – with the isolation of biological material (DNA) from the patient and his first degree relatives.

The tests in the project will be conducted on children with unspecified genetic diagnoses pre-selected according to certain criteria. For this purpose, retro- and prospective study of children who passed through the Genetics Unit at the University Hospital “St. Marina”-Varna with unspecified cause of multiple congenital anomalies and/ or developmental delay and/ or dysmorphic features will be made.

The methods that will be used are: clinical (documentary, clinical-genetic assessment of the phenotype), laboratory (DNA extraction, conventional PCR, MLPA fragment analysis), statistical methods.

Expected results:

1. Detection of mutations associated with the clinical picture in patients with unclear diagnosis;
2. Improving care for patients with rare genetic conditions;
3. Implantation of new molecular genetic techniques;
4. Establishment of a DNA bank with the potential to conduct subsequent research projects;
5. Defending a doctoral thesis “Genetic-diagnostic research in children with hereditary pathology who have visited the Genetics Unit”.

Results:

As a result of the project activities, a total of 97 children were selected – 70 boys and 27 girls, hospitalized in the children's clinics of the University Hospital “St. Marina” or passed the genetic center of the Laboratory of Medical Genetics - Varna.

One of the tasks of the project is to screen a high-risk group of children with neurodevelopmental disorders with molecular genetic techniques (PCR) for the detection of FRAXA syndrome. The main criteria in the selection were: unexplained developmental delay/intellectual disability with or without congenital anomalies in persons under 18 years of age. The boys had an advantage in the selection due to the significantly higher frequency of this condition compared to the girls. 52 children were selected who met the criteria – 45 boys and 7 girls and a pathological variant – an increased number of CGG recurrences was found in 3 boys – 5.7% of all subjects.

26 of the children with a normal FRAXA test result and the other 45 of the initially selected 97 children were selected for one or both of the other analyzes: MLPA for common microdeletion/ microduplication syndromes, MLPA for subtelomeric microdeletion/ microduplication disorders. As a result of the applied algorithm of selective MLPA analysis, 6 (8.45%) microdeletions/ microduplications (3 syndromic and 3 subtelomeric disorders) were detected, associated with a phenotype overlapping with the clinical manifestation in the patient.

The present study was the first attempt for molecular genetic screening for *FMR1* gene mutations in a high-risk group of children with ID/developmental delay from the region of Northeastern Bulgaria. Even though FXS is a well-known cause of intellectual disability, sometimes it could be difficult to be recognized, especially at an early age. This demonstrates the importance of screening for FXS, as it provides a definitive diagnosis for the family and facilitates genetic counseling of the affected individual and relatives.

As a result of the project activity, new DNA technology was launched for the genetic laboratory at the University Hospital “St. Marina”-Varna – MLPA analysis, for the diagnosis of microdeletion and microduplication syndromes. A register and a specific database have been created through photo and video documentation for patients with unexplained rare syndromes. A biobank has been established – by isolating biological material from patients with unclear genetic conditions, with the potential to conduct subsequent research projects.