EXPERT OPINION

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Internal member of the Scientific Juri for Medical University Varna No. P-109-133/05.04.2024

Regarding: Dissertation defense procedure entitled:

"GENOTYPE - PHENOTYPE CORRELATION IN PATIENTS WITH CYSTIC FIBROSIS" for the awarding scientific and educational degree "Doctor" in the doctoral program "Pediatrics" from **MARGARITA IVANOVA NIKOLOVA,** PhD, in the field of higher education 7. "Health and sports", by profession direction 7.1. "Medicine" and scientific specialty "Pediatrics".

Professional development and qualities of the candidate:

Dr. Margarita Ivanova Nikolova, is a full-time PhD student in Department of Pediatrics, Medical University, Varna. She completed her higher education in the Medicine at Medical University-Varna in 2017. Since 2017 until now she is a resident in pediatric pulmonology at the Second Children's Hospital "St. Marina", Varna. In 2017 she was appointed as an assistant to the Department of Pediatrics, Medical University "Prof. Dr. Paraskev Stoyanov", Varna.

Dr Nikolova presents 5 articles in refereed Bulgarian journals. She is an active participant in international and national congresses, conferences and symposia with posters and reports.

Dissertation work

The dissertation is written on 141 standard typewritten pages. The text contains 32 tables, 16 figures and 2 appendices. It is organized in to 9 parts - introduction, literature review, materials and methods, results, discussion, conclusions, contributions, appendices and reference. The literature reference includes 285 titles - 16 in Cyrillic and 269 in Latin. The reference is up-to-date as over 85% of the sources are from the last 10 years.

In her dissertation work, Dr. Nikolova aims to investigate the existence of a genotype-phenotype correlation in patients with cystic fibrosis from North-Eastern Bulgaria, who are followed up and treated at the St. Marina Hodpital.

The severity of hereditary diseases is determined by the interaction of three factors: the nature of the genetic defect; genetic background and environmental influences. The contribution of the first component can be assessed by examining the relationship between genetic defects and disease severity. The genotype-phenotype correlation in cystic fibrosis patients is complex, despite its being a monogenic disorder. Factors that contribute to variability among individuals with the same genotype are an area of intense study. Long-term observations have shown that different tissues require different levels of CFTR function in order to have no clinical manifestation of the disease. Molecular analysis of disease-associated mutations identified through genotype-phenotype studies provides a mechanistic framework for genotype-based therapeutic approaches and pharmaceutical interventions. The literature review provides a broad and comprehensive review of our knowledge of the disease historically, the classes of mutations, the phenotypic manifestations, the diagnostic algorithm, and the new methods of treatment with CFTR modulators. The importance of targeted search and recognition of the phenotypic manifestations of the disease, for countries without neonatal screening, as an important, first step before genetic tests to confirm the diagnosis is emphasized.

The assigned tasks are chosen correctly and consistently to achieve the set goal.

All research was carried out after obtaining informed consent, attached to the dissertation work, which was accepted without objections by the Ethics Commission of MU- Varna.

The study was undertaken in 45 patients aged 5 months to 37 years, followed for a period of 5 years. In 44 of them were found both mutations. The results are described very thoroughly and presented graphically, with an individual and detailed assessment of genotype-phenotype correlation by classes of mutations in relation to lung function, structural lung changes, colonization with Ps. aeruginosa and Staph. aureus, BMI, gastrointestinal manifestations and liver involvement.

As an important conclusion, it is noted that the genotype-phenotype correlation is more demonstrative in terms of manifestations from the gastrointestinal tract, and patients with respiratory problems are diagnosed at older age. The main part of the dissertation work is a diagnostic algorithm based on phenotypic manifestations, for early recognition of cystic fibrosis in countries without neonatal screening, as well as in the period after its introduction, in which there will still be newly diagnosed, undetected patients.

Conclusions are clearly written and correspond to the presented work.

Based on the obtained results and conclusions, Dr. Nikolova defines five original contributions of her dissertation work, which I fully accept.

In connection with the dissertation work, Dr. Nikolova has made 5 full-text publications in refereed journals, 16 participations in national and international scientific conferences and congresses. Her scientific output meets the requirements of Appendix 4 of ZRAS and PURPNSZAD MU-Varna for the acquisition of the scientific degree "Doctor".

In conclusion, based on all that has been said, I believe that the proposed dissertation work of Dr. Margarita Ivanova Nikolova, "GENOTYPE - PHENOTYPE CORRELATION IN PATIENTS WITH CYSTIC FIBROSIS" meets the requirements of ZRAS and PURPNSZAD MU-Varna, by voting positively and with conviction, I recommend to the respected Scientific Jury to vote for the acquisition of the scientific degree "Doctor" in the field of higher education 7. "Health and Sports", by professional direction 7.1. "Medicine" and scientific specialty "Pediatrics".

15.05.2024 Assoc. Dr. S. Mileva,

Sofia