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Oponent´s opinion on dissertation thesis

MUDr. **Anne Tharindi Shenali Dias Amaratunga**

NOVEL INSIGHTS INTO THE PATHOPHYSIOLOGY OF GROWTH RETARDATION AND OTHER ENDOCRINE CONDITIONS: LESSONS LEARNED FROM CONSANGUINEOUS AND NON-CONSANGUINEOUS FAMILIES

The submitted dissertation thesis of **MUDr. Anne Tharindi Shenali Dias Amaratunga, "Novel insights into the pathophysiology of growth retardation and other endocrine conditions: Lessons learned from consanguineous and non-consanguineous families"** was prepared at the Department of Paediatrics, 2nd Faculty of Medicine, Charles University and Motol University Hospital in Prague under the expert guidance of professor Jan Lebl. It summarizes results of the Ph.D. student's own scientific research activities. The text pages (logically quite brief) are actually a commentary on a set of her published papers, which are focused on genetic background in individuals with three paediatric endocrine conditions (congenital hyperinsulinism, monogenic diabetes and short stature) and are an integral part of the dissertation thesis. These include eight already published papers in journals with known impact factor (in three of them the candidate is the first author), and one manuscript ready for submission. The papers are attached in full version.

Hypothesis of the project: In children from consanguineous families with apparent phenotypes, it may be possible to identify novel variants of known causative genes, or even novel genes (due to a higher risk of recessive mutations). These findings might elucidate novel mechanisms and pathophysiological pathways causing endocrine conditions in children.

In addition, the spectrum of causative genes will be varied when comparing consanguineous and non-consanguineous populations.

The dissertation aims to compare findings in three pediatric endocrine conditions – congenital hyperinsulinism, monogenic diabetes, and short stature – performed in a unique cohort of children from a highly consanguineous region of Sulaimani, Kurdistan, Iraq (consanguinity rate 44%) with a non-consanguineous cohort from Prague, Czech Republic. With informed consent, DNAs of all probands were primarily analyzed by NGS methods followed by variant selection and verification by a set of connected algorithms (or blocks) that are executed in a predefined order to process and analyze next-generation sequencing (NGS) data (bioinformatic pipeline). In consanguineous individuals, the genetic cause of congenital hyperinsulinism was elucidated in 100%, monogenic diabetes in 74% and short stature in 65% of patients. Homozygous variants were the most prevalent, with the spectrum of causative genes and thus disease mechanisms differing considerably from nonconsanguineous individuals. In studies of non-consanguineous patients with growth hormone deficiency and those born small for gestational age, the rate of positive findings were 29% and 42% respectively with largely prevailing monoallelic (dominant) genetic conditions. In addition, this research produced the first ever papers describing large cohorts of children from consanguineous populations with diabetes and short stature. A statistical significance of consanguinity and the occurrence of syndromic diabetes was described. This research highlights the fundamental contribution of studies in consanguineous families to novel insights into disease origin and mechanisms.

Genetic disorders, although diverse, share a common complexity and impact, especially in the pediatric population. The high prevalence underscores the critical need for ongoing research leading to understanding these conditions and thus improving quality of life. The field of pediatric endocrinology is particularly affected because many conditions, although rare, can significantly affect a child's growth and development, child's metabolism and overall well-being. Despite are widely described in the literature, the exact pathophysiological, genetic and molecular mechanisms of many pediatric endocrine disorders are still the subject of detailed research.

The uniqueness and significance of the presented work is also evidenced by the extensive publication activity. The dissertation is based on several publication in peer-reviewed journals with high impact factor, including four publications, of which MUDr. Shenali Amaratunga is the first author. For the 2023 publication **Paediatric diabetes subtypes in a consanguineous**

population: a single-centre cohort study from Kurdistan, Iraq Shenali A. Amaratunga, was the winner of the Best International Publication in Pediatric Endocrinology awarded at 44th DDE in January 2024.

I have the following questions for the author:

1. What was your personal contribution in examining pediatric patients, processing their clinical data and possibly working in the genetics laboratory.
2. Does the level of consanguinity vary across European countries? If so, is it trending upwards or downwards? Is it possible to apply the results of genetic testing of consanguineous populations to populations with low consanguinity?

The submitted dissertation thesis of MUDr. Shenali Amaratunga meets all the criteria for its successful defence and awarding of the academic degree of Ph.D. according to § 47 Zákona o vysokých školách č. 111/1998 Sb.

In Olomouc, 30 January 2024 Doc. MUDr. Jiřina Zapletalová, PhD.