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PhD thesis: Novel insights into the pathophysiology of growth retardation and other endocrine conditions: Lessons learned from consanguineous and non-consanguineous families

PhD candidate: MUDr. Anne Tharindi Shenali Dias Amaratunga

Evaluation report

This thesis focuses on elucidating the genetic architecture of three complex human conditions encountered in the pediatric endocrinology practice. Dr. Amaratunga explored the genetic basis of congenital hyperinsulinism, pediatric diabetes mellitus (DM), and short stature and contributed significantly to understanding these traits.

The thesis is based on a collection of 6 original reports, one review paper (all published in peer-reviewed journals), and one manuscript prepared for submission. The publications are accompanied by 22 pages of introduction, methods, hypothesis, and aims, and four pages of discussion, summary, and conclusion. One paper was published in a journal in the first decile of WoS JCR, and the rest were published in journals in the first and second quartiles, demonstrating the high quality of the candidates' research. From the formal point of view, the overall structure, formatting, language, and style are excellent, with minimal typographical errors. The only minor formal drawback is the tiny size of the fonts in Figures 2 and 4.

Dr. Amaratunga analyzed exome in patients with the three abovementioned traits in her studies. She hypothesized that these traits in the inbred Kurdish and panmictic Czech populations would have different genetic architecture and that studies of consanguineous kindreds might facilitate the discovery of novel mechanisms causing these disorders. The published works confirmed the original hypothesis and brought a wealth of novel information on the genetic makeup of studied conditions in populations with differing degrees of consanguinity. The diagnostic yield of whole exome sequencing (WES) was inversely correlated with the complexity of the studied conditions. The WES analysis of congenital hyperinsulinism explained the genetic cause in all patients, while the same approach in DM1 elucidated the genetic background in ≈83% of cases. In subjects with short stature, the diagnostic yield was lower and varied considerably depending on the type of population, subgroup, and the pathway studied. Moreover, these studies support the notion that genes regulating the growth plate may play a more prominent than expected role in human growth and final height.

In summary, Dr. Amaratunga's work substantially expanded the overall knowledge of the genetic architecture of three common pediatric endocrine conditions. Publications in high-ranked peer-reviewed journals demonstrate her contribution to the field. Data generated during her Ph.D. study provide an insight into disease mechanisms, thus offering the opportunity for personalized management of these conditions.

Conclusion: This work meets more than sufficiently the required PhD thesis standards.

Questions to the Candidate:

1. The thesis mentioned the reasons for the high consanguinity rate in specific populations. Please comment on the social and cultural drivers (and possible social advantages) that maintain high consanguinity occurrence despite the population burden due to the high frequency of rare disorders with an AR type of inheritance.
2. Interpreting the pathogenicity of newly described genetic variants in complex traits is intriguing, especially when functional tests are unavailable. Consanguineous families may share large chromosomal segments with multiple homozygous variants, even within a single gene. Have you encountered difficulties distinguishing between (likely) pathogenic and (likely) benign missense variants when multiple homozygous variants were found in the propositus?
3. Can you please hypothesize on the possible molecular consequences of the rare first-codon pathogenic variant p.Met1Val in the *KCNJ11* gene in paper 7.2)?
4. Publication 7.3 reports on a patient with DM2 and a very rare inherited metabolic disease mucolipidosis III. Is there any plausible mechanism associating MLIII and DM2, or is this association random?

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