Cag/polyglutamine disease diagnostics

Impact

This research is the first of its kind to conduct integrated omics studies (genomic, proteomic and metabolomic) in Poly Q diseases (mainly HD and SCA) in Sri Lanka. Our objective in this section is to outline the societal impact of this project. During the study, the author and colleagues, led by Prof. Ranil de Silva as the Principal Supervisor in Sri Lanka, implemented the use of mobile clinics and home visits in Sri Lanka. Our service distinguishes itself with a distinctive approach of delivering doctors and researchers right to patients doorstep. This sets us apart from the pro-bono molecular genetic testing services in India and the West Indies that have been reported. The project accomplished the largest ever patient registry for Poly Q diseases, specifically focusing on HD and SCA, in Sri Lanka. The registry includes a total of 321 patients who indicate clinical symptoms associated with HD (n=87) and SCA (n=236) (Gonawala et al., 2024). An article was published in The Lancet Neurology (Wijekoon et al., 2020) that emphasizes the importance of the neuro-biobank established in Sri Lanka. This development has created exciting opportunities for potential collaborations.

Neurogenetic testing for Poly Q diseases is not readily available in Sri Lankan government hospitals and is only offered at high prices in a limited number of private sector institutes. In this thesis , we have presented a molecular diagnostic approach for SCA which has revealed the potential for cost reduction by narrowing down the number of SCA tests conducted per patient. This narrowing is based on geographical localization, specifically focusing on a cluster of patients with SCA1 in three villages in the southern region of Sri Lanka (n = 29/61). (Gonawala et al., 2024) (Wijekoon et al., 2023). Intriguingly, we could identify 45 HD patients in our cohort as amenable for future gene therapy approaches, providing a ray of hope for these patients and their family members.

In our research on proteomics in SCA, we made an interesting discovery. We found three previously unidentified proteins that are linked to the progression of SCA1 disease. We have conducted additional validation on these proteins using ELISA, demonstrating their potential as surrogate endpoints in SCA1. It has been noted in scientific literature that the absence of validated biomarkers in SCA poses a significant challenge to the success of clinical trials. Thereby, our findings will open up exciting opportunities to enhance the utilization of these novel protein biomarkers in SCA clinical trials.

In the Sri Lankan Poly Q disease cohort, n= 155 Patients were tested negative for common mutations in HD and SCA. These patients were found to be negative for common mutations in HD and SCA. It is crucial to consider the use of NGS panel/ WES/ WGS for further investigation. Despite the limited availability of funding, this study took a collaborative approach and examined two cases of individuals who tested negative for the typical mutations linked to SCA as a pilot study. This study has made an important finding in South Asia by identifying a new pathogenic variant in HSP known as DDHD2 (c.1982A>G), which causes SPG54. Additionally, a missense mutation called ZFHX3 (c.530C>T) has been found to be responsible for Spinocerebellar ataxia type 4. The unique variants identified by WES in this pilot study call for a thorough genetic analysis of these negative cases using WES. This analysis will assist in uncovering new genes, genes with overlapping phenotypes, and genetic modifiers that may vary based on region and population. Collaborations with experts in advanced genetic analysis from other countries are essential for this undertaking.