Singapore Undiagnosed Research Endeavour (SUREKids): Investigating Splice-altering Genomic Variants in Pediatric Patients

Chaerish Eint Myet Chae Htoo1, Jeannette Goh1, Xavier Roca2, Saumya Shekhar Jamuar3, Jiin Ying Lim1, Sylvia Kam1 1Department of Genomic Medicine, KK Women's & Children's Hospital, Singapore, Singapore, 2School of Biological Sciences, Nanyang Technological University, Singapore, Singapore, 3Maternal and Child Health Research Institute, Singhealth Duke-NUS, Singapore, Singapore

Background: More than 300 million individuals worldwide live with rare diseases. For many of these patients and their families, the journey to discovering the underlying cause is often a long and arduous process involving multiple specialists and misdiagnoses. The Singapore Undiagnosed Research Endeavour (SUREKids) leverages genomic technologies, including whole-exome sequencing (WES), whole-genome sequencing (WGS), and long read sequencing (LRS), to provide a diagnosis to more patients to help bridge the diagnostic gap and shorten the diagnostic odyssey from an average of 7 years to as short as 10 days. However, genomic sequencing may identify variants of uncertain significance (VUS), leading to ambiguity in genetic diagnoses. Out of these VUS, many are predicted to be splice-altering variants that disrupt canonical RNA splicing but are often not well characterised. Method: Utilising genomic sequencing, including RapidSeq (accelerated WES), WGS and LRS, with supportive in silico tools that predict splicing patterns and downstream effects on protein products, as well as minigene splicing functional analyses, we have characterised over 30 clinical variants in 2 years, comprising both novel variants and previously identified VUS. Results: Here we report 3 clinical case studies of paediatric patients with splice-altering variants in TCF4, ROBO3 and TMEM63B gene respectively. Our investigation of these genomic variants confirms that these VUS have an effect of splicing, helping to reduce ambiguity to the diagnosis to inform further clinical decisions. Conclusion: This poster thus illustrates that WES data analysis with supportive in silico and functional analysis provide an effective approach to improve the diagnostic yield for unsolved clinical cases