A descriptive study of the genetic basis of rare undiagnosed disorders in a cohort of Sri Lankan patients

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Whole Exome Sequencing (WES) is a powerful tool for identifying the genetic basis of rare, undiagnosed disorders. It has reduced the diagnostic odysseys associated with such conditions and has replaced single gene and gene panel testing. This study describes the genetic findings in patients who underwent WES at the Center for Genetics and Genomics, Faculty of Medicine, University of Colombo. A prospective database of genotypic and phenotypic data from patients tested between November 2014 and April 2025 was retrospectively analyzed. Next Generation Sequencing was performed on an Illumina platform on patients referred due to a rare, undiagnosed disorder. Of 724 patients sequenced, the male-to-female ratio was 1.1:1, with ages ranging from neonates to 79 years. A definitive genetic diagnosis was established in 452 patients (62.4%), and 154 (21.3%) harboured novel variants. System-wise breakdown is as follows (number referred, diagnosed [%], novel variants): Multisystemic presentations: 226, 144 (63.7%), 50, Neurological: 174, 106 (60.9%), 37, Musculoskeletal: 69, 52 (75.4%), 17, Endocrine: 34, 20 (58.8%), 6, Renal: 24, 14 (58.3%), 6, Cardiovascular: 19, 12 (63.2%), 1, Eye: 19, 17 (89.5%), 7, Metabolic: 19, 13 (68.4%), 5, Blood/lymphoreticular: 13, 7 (53.8%), 2, Skin: 8, 5 (62.5%), 3, Gastrointestinal: 6, 3 (50%), 0. Among those with a confirmed diagnosis, 88 (71.5%) were from consanguineous families with 22 novel variants. WES enabled a molecular diagnosis in more than half of this cohort, demonstrating its clinical value in accelerating diagnosis which helped in guiding management, and identifying novel disease-causing variants in rare disorders.

Keywords: *Rare and undiagnosed disorders*, *Whole Exome Sequencing*, *Novel variants*