

Introduction: Today it is possible to detect the underlying genetic aetiology of rare and undiagnosed disorders using Whole Exome Sequencing (WES) without the need to sequence genes separately reducing the time from presentation to diagnosis. The objective of this study was to report the genetic aetiology of patients with rare undiagnosed disorders undergoing WES in the Human Genetics Unit, Colombo.

Methods: A database of patients tested in our unit consisting of phenotype and genotype data was maintained prospectively from 13th November 2014 to 26th March 2021 and analysed retrospectively. Genotype data was generated by Illumina HiSeq platform.

Results: 123 patients were sequenced. 75 (61%) were male. Age ranged from 14 days to 18 years. The genetic aetiology was confirmed in 58 (47.2%). 27 (22%) had novel variants. The systems affected, the total number and percentage of patients, the number and percentage of patients diagnosed and the total number with novel variants in each system respectively were: neurological, 66 (53.7%), 30 (45.5%), 17; musculoskeletal, 16 (13.0%), 7 (43.8%), 2; multisystem, 16 (13.0%), 5 (31.3%), 2; eye, 7 (5.7%), 6 (85.7%), 3; metabolic, 7 (5.7%), 5 (71.4%), 2; blood and lymphoreticular, 4 (3.3%), 0 (0%), 0; cardiovascular, 3 (2.4%), 2 (66.7%), 0; skin, 2 (1.6%), 2 (100%), 1; gastrointestinal, 1 (0.8%), 1 (100%), 0 and renal, 1 (0.8%), 0 (0%), 0. In those with a definitive diagnosis, a pathogenic variant related to an autosomal dominant condition was found in 30 (51.7%); an autosomal recessive condition in 23 (39.7%); an x-linked dominant condition in 2 (3.4%) and an x-linked recessive condition in 3 (5.2%)

Conclusion: The use of WES has made it possible to arrive at the genetic aetiology in nearly half of the patients with rare and undiagnosed disorders tested in our Unit. It has led to early diagnosis, accurate prognostication and appropriate treatment of these patients.