Utility and diagnostic yield of whole-exome sequencing (WES) for patients with suspected genetic disorders in Penang Hospital

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ABSTRACT

Introduction: Genetic disorders occur at a rate of 40 - 82 per 1000 live births worldwide. Investigations available for patients referred to genetic clinic include karyotyping, metabolic analysis and single gene testing. Chromosomal microarray is not routinely available due to lack of funding. Multigene panel testing in private labs is only available to patients who can afford out-of-pocket expenses; hence, many patients remain undiagnosed for years. **Methods:** This retrospective study was conducted in genetic clinic, Penang Hospital. 513 patients with suspected genetic disorders without a molecular diagnosis who were seen over a period of 17 months from August 2020 to December 2021 were included. Proband-only WES was performed and the results were analysed. **Results:** A total of 85.0% (435/513) paediatric patients, including 26 neonates and 78 adults presented with a wide range of phenotypes. 174 patients received positive results with pathogenic or likely pathogenic variants and 240 patients received negative results. 81 of 99 patients with inconclusive results had probable genetic diagnosis as 90/115 variants of uncertain significance (VUS) were potentially causal. Four patients received dual molecular genetic diagnoses and 11 patients had copy number variants (CNV). Inheritance pattern of diagnosed disorders were 65.0% autosomal dominant (167/259), 25.0% autosomal recessive (66/259) and 10.0% X-linked (26/259). Of the 78.0% (401/513) of patients opted for receiving secondary findings, 6.5% (26/401) received a positive result, mainly in cardiac disease-related genes. **Conclusion:** 50.0% (255/513) received a genetic diagnosis by WES. This supports the importance of prompt and accurate molecular diagnosis at an early stage to identify potential treatments, provide anticipatory guidance, prognosis and genetic counselling.