Making sense of whole-exome sequencing (WES) results

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ABSTRACT

Introduction: WES is increasingly used to clinch an accurate molecular diagnosis and inform patient care in a timely manner for patients suspected with rare genetic disorders. Patients and treating physicians are challenged by the relatively high cost of test and interpretation of variants of uncertain significance (VUS) and secondary findings. **Methods:** This retrospective study was conducted in genetic clinic, Penang Hospital. Proband-only WES was performed from August 2020 to December 2021. Of total 513 patients, 273 patients received positive or inconclusive results with 35.0% (115/330) being VUS. Remaining 240 patients (46.8%) with negative results were subjected to automated daily reanalysis. **Results:** For 99 patients who received inconclusive results, further genotype-phenotype correlation, disease pathomechanism evaluation and variant segregation studies suggested that 90 of the 115 VUS could potentially be causal. Through additional phenotype information and reanalysis, 11 of 240 WES-negative patients, eventually received an updated report with detection of variant in a new disease gene and reclassification of VUS to pathogenic or likely pathogenic (P/LP). 78.0% (401/513) opted to receive secondary findings of which 6.5% (26/401) was positive with majority in genes for cardiovascular disorders (65.0%, 15/23) and cancers (26.0%, 6/23). As these were medically actionable variants, genetic counselling including reproductive planning and cascade screening, initiation of appropriate surveillance, avoidance of unnecessary investigations and change of treatment were provided. **Conclusion:** Positive WES results provide tremendous benefits to patient management. Initial negative results may become positive later through reanalysis and periodic phenotypic review, hence increasing diagnostic yield. VUS resolution and secondary finding management may entail additional medical cost and clinical burden.