GeNeXpreSS

Exome to Genome Sequencing: Re-look Before You Leap!!

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Prospective annual reanalysis of whole exome sequencing in rare disorders (Nambot et al., 2018)

The widespread use of exome sequencing (ES) in clinical practice has revolutionized the diagnosis of Mendelian disorders. But 50 to 75% of patients undergoing ES still remain without a diagnosis. Whole genome sequencing is an option to fill this lacuna and has been reported to increase the detection rate by 15%. However, limitations like availability, costs and data mining challenges preclude its widespread clinical use at present. Nambot et al. studied the impact of re-analysis of WES data in a cohort of 416 patients with congenital anomalies and intellectual disability. The raw data of 156 patients with no conclusive diagnosis were re-analyzed with the latest bioinformatics pipeline. This exercise was done annually over a period of 3 years. They could detect a disease-causing variant in 24 (15.4%) additional patients. Twelve of these were attributed to new publications, reclassification of initially identified uncertain variants or detection of copy number variants. The other twelve patients were diagnosed through international data sharing and collaboration. This also yielded five novel genes.

New diagnosis emerging from old data (Wright et al., 2018)

Prioritization of variants in ES is based on application of certain filters. A balance between sensitivity and specificity has to be struck to detect the causative variant while keeping the false positives low. Hence a disease-causing variant may be missed due to various technical and analytical limitations. A Deciphering Developmental Disorders study reported a diagnostic yield of 27% in 2014 by trios ES of 1133 children. Wright et al. did a reanalysis of this cohort using improved and updated bioinformatics algorithm and variant filtering strategies. They were able to make a diagnosis in additional 182 patients, thus increasing the overall diagnostic yield to 40%. Most of these were due to new gene-disease associations reported in the interim. Also, 39 probands with a previous diagnosis were reclassified as uncertain or likely benign. This is the first large-scale report highlighting the potential utility of NGS data re-analysis and re-contact with the patients and health care providers.

Comprehensive iterative approach in diagnosing "exome negative" individuals (Shashi et al., 2018)

Standard reanalysis of ES resolves 10-15% cases with an initial negative report. This is mainly attributed to new gene-disease discovery. Other causes include resequencing of singletons to trios, analyzing for copy number variations and data sharing. The majority (~60%) of patients enrolled at the Duke/Columbia site of the Undiagnosed Disease Network had a negative ES. Trios ES was done in majority of these patients and reanalysis was also done in some. To further maximize the diagnostic yield, Shashi et al. proposed an iterative approach in 38 of these exome-negative patients. An individualized genomic-phenomic approach was used consisting of detailed phenotyping, reanalysis of FASTQ files with an updated bioinformatics pipeline, targeted molecular testing and genome sequencing. A diagnosis was obtained in 18 patients (47%). This was mainly due to better bioinformatics, phenotyping and targeted testing for variants undetected in the prior ES. A reanalysis of prior ES yielded a diagnosis in 25% individuals in this cohort. Genome sequencing

detected structural variants not identifiable in ES in 3/18 patients. Candidate genes were identified in additional eight individuals taking the overall diagnostic yield to 68%. They also identified two novel developmental disorders.

Responsibility of re-contact after re-interpretation (Carrieri et al., 2019; Bombard et al., 2019)

The emerging scientific evidence for regular re-interpretation of genomic testing results has necessitated the development of guidelines for re-contact. In the clinical setting, a few guidelines exist. The European Society of Human Genetics recently recommended that it is desirable for clinicians to re-contact patients regarding findings with clinical or established personal utility, yet there is no legal or professional responsibility to do so. They add that re-contacting is a shared responsibility between patients and laboratories and requests for reanalysis should be initiated by the patient, clinical laboratory or clinician. The American College of Medical Genetics and Genomics and American Academy of Pediatrics encourage re-contact if a variant is reclassified but leave it to the discretion of clinical laboratories to determine when to re-analyze data and when to re-contact patients. For the research setting the American Society of Human Genetics (ASHG) has published a position statement. They strongly recommend re-contact attempt, within 6 months, if the reclassified variant is related to the phenotype under study and if it is expected to alter clinical management. In cases where management is not expected to change, re-contact is advised if the classification has changed from or to pathogenic/likely pathogenic. The ASHG also states that there is no responsibility for researchers to hunt or scan genetic and genomic data or literature for changes in variant interpretation.

References

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