Editorial

Clinical Utility of Whole Genome Sequencing for Undiagnosed Rare Genetic Disorders

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Rare disorders contribute significantly to morbidity and mortality worldwide. Approximately three fifty million people are suffering from rare diseases globally[1]. Eighty percent of these diseases have either an exclusive genetic etiology or have genetic subtypes[2]. Patients of such diseases in spite of multiyear diagnostistic assessments are usually misdiagnosed[1]. The advent of whole exome sequencing (WES) has paved the way for an accurate and precise genetic diagnosis which is not only cost effective but also helps in clinical management of these rare disorders[3,4].

The treatment of these rare genetic diseases depends on clinical genetic diagnosis. But serial testing for specific phenotypes is required because of clinical heterogeneity. This approach is time consuming, expensive, has the probability of incomplete testing and may result in failure to reach a molecular diagnosis[5]. Strategies based on clinical hypothesis limit the focus of clinicians to a particular phenotype component or system and targeted gene sequencing may or may not provide the complete differential diagnosis. Even WES cannot cover the main causative genomic regions (e.g. intronic SNVs, structural variants, indels). Next generation sequencing (NGS) technology has made high throughput genome analysis of patients possible. It detects a broad range of pathogenic variants and has appeared as the first line of diagnostic test for the diagnosis of diseases in which clinicians face high probability of diagnostic uncertainty[6]. Clinical whole genome sequencing (cWGS) opens new horizons in molecular diagnostics and assures a single testing platform that permits concurrent investigation of reported causative genes and identification of copy number variants (CNVs), small insertions and/or deletions (indels), single nucleotide variants (SNVs), and some structural chromosomal abnormalities[5,7] Current literature supports the use of cWGS as a first-tier test for chromosomal or Mendelian disorders where diagnosis is impossible from clinical examination alone[5]. Combined with advances in molecular genetics and better understanding the pathophysiology of diseases, whole genome sequencing has changed public health and clinical practice by promising more refined, exact, and cost-effective genetic testing.

Unlike other NGS methods, WGS can overcome many technical limitations like more sensitivity for the identification of complex and structural variants[2], and better coverage[8]. Noncoding variants like mRNA splicing, noncoding RNAs contributing towards disease phenotype and mutant alleles disrupting regulatory regions can also be identified through WGS[9]. WGS is also being used for pharmacogenetic testing[10], calculation of polygenic risk scores[11] and HLA genotyping[12]. Segregation of clinically significant alleles in a many cohorts[13] proves the diagnostic supremacy of WGS over conventional testing in critically ill infants[14] and pediatric patients[3,9]. Due to its improved coverage and high diagnostic efficiency, WGS is replacing targeted NGS or WES and chromosomal microarray (CMA) for the characterization of subjects with a suspected genetic disorder[3,5].

Genomic sequencing has become a routine procedure in clinical medicine in developed world. WGS is now an important tool for identification of drug able targets in various types of malignancies, diagnosis of undiagnosed genetic disorders, preconception carrier screening prenatal diagnosis and screening of genetic susceptibility in healthy subjects to delay the onset of diseases. The genomic data available will facilitate further clinical innovation in the diagnosis and treatment of previously undiagnosed and incurable diseases. But there are challenges for all stakeholders ranging from standardization of variant interpretation strategies to the training of no geneticist physicians to use this wealth of genomic information in their clinical practice.

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