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Novel technologies

WIDENING THE SCOPE OF NEXT GENERATION SEQUENCING APPLICATIONS IN PEDIATRIC MEDICAL GENETICS.

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ABSTRACT

Advances in DNA sequencing technologies through Next Generation Sequencing (NGS) approaches have enabled genome-wide discovery of chromosomal copy-number variants and single-nucleotide changes. NGS technologies are rapidly expanding our ability to identify and better define disease-causing mutations and genotype-phenotype correlation. Pediatric patients may particularly benefit from the introduction of these new technologies. Pediatricians must keep up with all these new skills, both in their residency programs as well as in their continuing medical education programs.

1. Text

During the past decade, advances in DNA sequencing technologies through Next Generation Sequencing (NGS) approaches have enabled genome-wide discovery of chromosomal copy-number variants and single-nucleotide changes in patients with a wide range of clinical phenotypes (1). These technological advances - which include Whole Exome Sequencing (WES), Whole Genome Sequencing (WGS) and RNA sequencing (RNA-seq) - have transformed the approach to study disease-causing genes and genomic rearrangements.

Today NGS approaches are going to be applied in the clinical diagnostic arena (1) and pediatric patients may particularly benefit from the introduction of these new technologies. Most genetic diseases are diagnosed in pediatric age, but in many cases a long and complex clinical and diagnostic work-up is needed, requiring several genetic investigations and high costs.

Furthermore, WES has been recently proposed as a powerful tool for the diagnostic evaluation of critically ill infants with suspected monogenic disorders in the Neonatal and Pediatric Intensive Care Units and its use has a notable effect on clinical decision-making process (2).

WES is the most used approach for the discovery of disease-causing genes, as it has been estimated that 85% of the disease-causing mutations are located in the coding portion of the human genome. To date WES data are more often analyzed through in-house pipeline using integrated bioinformatics tools and their analyses are more focused on non-synonymous changes (i.e. non-synonymous, frame shift, splice acceptor/donor), rare variants (i.e. low frequency or absent from population databases) and those mutations predicted to be deleterious. In this view, and in order to achieve a more complete overview on variants and genes identified through WES, we need to expand our knowledge on several databases and annotation and prioritization tools. Functional annotations regarding either the variant or the gene can be investigated using SnpEff and dbNSFP utilities; variants' annotation can be obtained from publicly available databases using their frequency data; hence, to predict a variants' potential deleterious effect, several scores can be used such as Polymorphism Phenotyping v2, Sorting Intolerant From Tolerant, Combined Annotation Dependent Depletion, Deleterious Annotation of genetic variants softwares etc. Moreover, germline variants can be also annotated using public information on their pathogenicity through Human Gene Mutation Database. Because of its feasibility in terms of computational infrastructures, costs, and interpretation effort (3), WES is allowing us to investigate previous associated disease-causing genetic loci (4), a wide spectrum of single or associated congenital malformations (5) and their relationship with other intrauterine and/or environmental factors (6,7). Despite WES presents fundamental limitations compared to WGS (e.g. the inability to assess the impact of non-coding variants), it represents a well-justified strategy for discovering rare alleles underlying

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Mendelian phenotypes, as well as genetic variants associated to developmental disorder, enabling the growth of new diagnostic, prognostic and therapeutic tools (8).

In this view, while translation into pediatric rare disease-modifying treatments is still challenging, some disorders like inborn errors of metabolism would benefit of a NGS-based early diagnosis since many of these disorders are responsive to therapy that targets pathophysiological features at the molecular or cellular level (9). Regarding those conditions associated with a severe neonatal onset (10), an early and appropriate access to interventions has been the only so far demonstrated tool to gain patients' long-term outcomes and to reduce lifetime costs for individuals, families and society.

Recently, Tarailo-Graovac et al. (2016) through deep phenotyping and applying WES in 41 probands with intellectual developmental disorder and unexplained metabolic abnormalities were able to gain a diagnosis in 68%, to identify 11 candidate genes newly implicated in neurometabolic disease, and to achieve a change in treatment beyond genetic counseling in 44%(9). These numbers are certainly going to increase in few years in similar cohort of patients. Rare diseases have been highlighted as the most frequent reasons for medical referral and/or diagnostic workup to geneticists during the developmental age. NGS technologies are rapidly expanding our ability to identify and better define disease-causing mutations and genotype-phenotype correlation.

This information is particularly useful in addressing genetic counseling for parents and families of pediatric patients, in order to enable the making of decisions relating to patients with genetic diseases that are considered, responsible and rational. Pediatricians must keep up with all these new skills, both in their residency programs as well as in their continuing medical education programs.

The use of NGS technologies is expanding the current knowledge about molecular mechanisms underlying a wide range of rare disorders. Characterizing molecular bases underlying these conditions, through WES approaches, will open a new window in their physiopathology and on the dynamics that constantly shape and re-shape our genome.

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