The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

eJIFCC

NGS for metabolic disease diagnosis

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Key words:
inborn errors of metabolism,
next generation sequencing

LETTER TO THE EDITOR

Inborn errors of metabolism (IEM) comprise heterogeneous and rare genetic diseases with a variety of overlapping or unspecific clinical phenotypes. Multiple proteins with enzymatic, transporter, regulatory and other functions participate in the complexity of metabolic pathways.

The breakdown of the normal function of some of these proteins may impair the metabolic state of an organism. These disruptions can generally be assessed biochemically through the detection of metabolites in different biological fluids.

However, the specificity and sensitivity of some of these biomarkers are not always high. IEM are, generally, severe diseases, and the accurate identification of the molecular basis of these diseases is important for appropriate patient treatment and genetic counselling.

Thus, even though the establishment of an IEM diagnosis is supported by clinical suspicion and biochemical investigations, genetic investigations also play a significant role. Genetic diagnosis in clinical practice has substantially changed in the past decade. The incorporation of next generation sequencing (NGS) technologies allows researchers, depending on the

selected strategy, to obtain the molecular sequence of the desired genes simultaneously, offering high-quality data. The utility of NGS in the clinical field has been widely demonstrated in different groups of diseases (1,2,3), but the actual debate encompasses two main points: the reinterpretation of the classical diagnostic algorithms and the chosen NGS strategy.

Today, regarding NGS strategies, targeted gene panels have been progressively replaced with larger panels, including all known disease-associated genes, or directly by whole exome sequencing (WES) (4).

In terms of rare genetic diseases, the identification of the genetic basis of disease is reached in 20 to 40% of patients using WES (5). Some of the reasons why up to 70% of patients might remain unsolved are explained by methodological issues like incomplete coverage of the exome and genetic mutations elusive to the technology itself. However, in most of the cases, the disease-causing variant is within the WES data, but there is insufficient evidence to support a definitive diagnosis (5).

Whole genome sequencing (WGS) is the ideal framework, in which a unique approach provides the most complete knowledge of an individual genetics, offering the possibility to analyze and interpret the genomic data along with the advances of scientific learning (6).

In a recent work, we demonstrate the importance of biomarkers as a key clue for genetic diagnosis achievement (7). In spite of this, the most common picture in IEM is represented by a patient with unspecific clinical features and also unspecific biomarkers. Although accurate characterization of clinical, biochemical and pathological patterns of patients are immensely valuable to understand genetic findings, NGS technology can be a step forward in terms of diagnostic issues. Some IEM are straight ahead to the causative gene, but others are not so easy to solve.

One of the most evident examples are CoQ deficiency syndromes, which are defects of the energy metabolism system. Several proteins with unclear molecular functions facilitate CoQ biosynthesis through unknown mechanisms, and multiple steps in this pathway are catalyzed by currently unidentified proteins (8).

This intricate metabolic process implies unidentified enzymes and, there are several genes that remain to be identified as essential for CoQ biosynthesis regulation. Furthermore, negative findings in COQ genes do not completely discard the possibility of a CoQ primary deficiency.

Thereby, biochemical measurements maintain a significant role in the diagnostic strategy. The heterogeneity of clinical and biochemical patterns in this specific mitochondrial disease reinforces the idea of using widespread NGS strategies like huge genic panels or whole exome sequencing to reach molecular diagnosis.

In conclusion, analysis and comprehension of genomic data must be closely connected to all the hints that classical biomarkers can offer, which is crucial information to guide the interpretation of an individual's exome or genome.

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