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DISEASE GENETICS

Sequencing for diagnosis

A recent paper discussing the application of next-generation sequencing (NGS) to study mitochondrial disease illustrates the potential and challenges of using NGS in clinical diagnosis. A crucial aspect of the clinical setting is that the aim may be to diagnose a single affected individual with no family history of the disease.

Human oxidative phosphorylation (OXPHOS) disease is a mitochondrial disorder for which 77 disease genes have been discovered so far, but many cases have no molecular diagnosis. Therefore, NGS is an attractive approach for improving its diagnosis. To explore this, Calvo *et al.* sequenced the entire mitochondrial genome and the exons of ~1,000 nuclear genes in 42 patients with undiagnosed infantile OXPHOS disease. This set of genes includes all of those that are known to encode mitochondrial proteins.

The authors prioritized rare nuclear genome variants that were predicted to modify protein function, mitochondrial and nuclear variants that were previously linked to disease and structural variants in the mitochondrial genome. Twenty-three patients (55%) had at least one prioritized variant; in ten of these, the variants were in genes that were previously associated with OXPHOS disease. Further study of the prioritized variants in 2 of the 13 identified novel genes suggested that they had identified the pathogenic mutations.

Calvo *et al.* explain several reasons why prioritized variants were not identified in the other 19 patients, perhaps the most likely of which is that the stringent filters rejected the causal variant. Overall, the authors emphasize the need for further development of clinical standards for interpreting genetic variants.

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ORIGINAL RESEARCH PAPER Calvo, S. E. *et al.* Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. *Sci. Transl. Med.* **4**, 118ra10 (2012)