FULL-LENGTH ARTICLE NPub.org/3xsum5

Use of Whole-Genome Sequencing for Mitochondrial Disease Diagnosis

Ryan L. Davis, PhD, Kishore Raj R. Kumar, MBBS, FRACP, PhD, Clare Puttick, MStat, et al.

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Correspondence
Dr. Sue
carolyn.sue@sydney.edu.au

Study Question

Does whole-genome sequencing (WGS) provide a single comprehensive genetic test that can detect mitochondrial disease–causing variants and simplify the diagnostic paradigm for mitochondrial disease?

What Is Known and What This Paper Adds

Mitochondrial diseases are the commonest group of heritable metabolic disorders. Phenotypic diversity can make molecular diagnosis challenging, and disease-causing genetic variants may reside in either mitochondrial or nuclear DNA. This study showed that WGS can comprehensively detect mitochondrial disease–causing variants in either genome, providing a single genetic test that simplifies the diagnostic paradigm for mitochondrial disease.

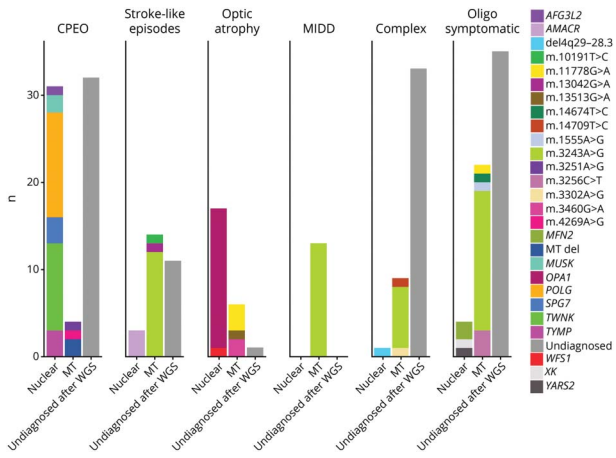
Methods

To determine the diagnostic utility of WGS for mitochondrial disease, we prospectively recruited 242 patients from the Mitochondrial Disease Clinic at Royal North Shore Hospital, Sydney, Australia, between 2014 and 2020. Patients were recruited if they satisfied clinical mitochondrial disease (Nijmegen) criteria; 62 patients had "definite," 108 had "probable," and 72 had "possible" mitochondrial disease. We performed WGS on blood DNA, followed by genetic analysis for known pathogenic mitochondrial disease–associated variants and disease mimics. Nuclear DNA variants were detected using a GATK best practices pipeline for single nucleotide variants and indels, while copy number and structural variants were detected using *ClinSV*. To enable the reliable detection of mitochondrial DNA variants, even at very low heteroplasmic levels, we developed a sensitive variant calling tool named '*mity*'. Genetic diagnoses were classified using the American College of Medical Genetics and Genomics (ACMG) 2015 guidelines.

Results and Study Limitations

Genetic diagnoses were made for 130 patients, regardless of the location of the causative genetic variants, giving an overall diagnostic rate of 53.7%. The diagnostic rate varied depending on the presenting clinical phenotype (Figure), with mitochondrial disease–causing variants identified in 23 of 24 patients with optic atrophy (95.8%), 17 of 28 patients presenting with stroke-like episodes (60.1%), and 35 of 67 patients with a chronic progressive external ophthalmoplegia phenotype (52.2%). Limitations of this study include the conservative restriction of variant calling to known disease-relevant variants and a stringent pathogenicity classification. A number of patients remain undiagnosed and may have variants in novel disease genes yet to be discovered or associated with mitochondrial disease.

Figure Genetic Diversity of Clinical Phenotypes



WGS determined the genetic heterogenity in patients with specific clinical phenotypes by identifying both nuclear and mitochondrial (MT) genetic diagnoses (color coded) using a single blood sample. Undx = undiagnosed.

WGS detected causative mitochondrial disease variants in DNA from blood to precisely diagnose patients with MD, thus simplifying diagnosis, enabling precise treatment, restoring reproductive confidence, and informing the risk of genetic transmission.

Study Funding and Competing Interests

This work was funded by a NSW Health Collaborative Genomics Grant. The authors report no competing interests. Go to Neurology.org/N for full disclosures.