Understanding the landscape of inherited mitochondrial diseases

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The term "inherited mitochondrial diseases" could potentially describe defects affecting any of the approximately 1200 proteins in the known mitochondrial proteome but is usually restricted to disorders of oxidative phosphorylation (OXPHOS), which is how we define it here. OXPHOS comprises five enzyme complexes embedded in the inner mitochondrial membrane and OXPHOS disorders can affect any organ system, alone or in combination. They are the most common group of inherited metabolic diseases, affecting at least 1 in 5000 births, but comprise over 200 different monogenic disorders, encoded on autosomes, the X chromosome or mitochondrial DNA (mtDNA). Mechanistically, they comprise defects affecting subunits or assembly factors for individual OXPHOS complexes, defects of mtDNA maintenance or expression, nucleotide synthesis or transport, membrane composition or dynamics and other aspects of OXPHOS biogenesis and quality control. Their clinical and genetic diversity makes genetic diagnosis by Sanger sequencing of single genes highly inefficient. Our centre has provided a national focus for diagnosis of paediatric OXPHOS disease for over 2 decades. Analysis of body fluids for metabolites can provide diagnostic support but has poor sensitivity and specificity. Mutation analysis of relatively "non-invasive" samples such as blood or urine has traditionally been restricted to testing for mtDNA mutations and typically provides a diagnosis for <10% of children suspected of an OXPHOS disorder.

Most paediatric diagnoses have thus relied on muscle biopsy. Ragged red fibres and enzyme histochemical defects are rare in children but measuring OXPHOS enzymes has allowed us to diagnose over 600 cases and guided subsequent analysis of candidate genes. Massively parallel sequencing of mitochondrial DNA, gene panels, exomes or genomes is now transitioning from research into clinical practice. These approaches have allowed us to identify mutations in 60 genes causing OXPHOS defects in over 300 children.