Mitochondrial Diagnostics: Challenges in the genomic era

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Next generation sequencing (NGS) has been a very promising technology for medical diagnoses. Use of NGS in diagnosing mitochondrial disorders (MD) has a positive yield of up to 60%. Duchess of Kent Children's Hospital is a tertiary / quaternary referral centre for the diagnosis and management of MD in this locality. In collaboration with the Radboud Centre for Mitochondrial Medicine (Nijmegen), a total of 46 patients, recruited from 2009 to 2017, with the clinical suspicion of MD underwent NGS from a gene panel analysis to the opening of the whole exome if the former was negative. There was a positive diagnostic yield of 26% including 5 and 7 patients confirmed to have MD and non-mitochondrial neurogenetic disorders respectively. Significant clinical phenotypic overlap occurred in patients with MD and non-MD, necessitating the inclusion of a group of MD mimickers in the gene panel analysis. The phenotypic spectrum of our patients with a confirmed diagnosis will be illustrated including a non-specific cerebral palsy-like clinical picture. 6 patients had variants of uncertain clinical significance and further functional studies are ongoing. The power of NGS may have an impact on the use of conventional tissue biopsies for respiratory chain enzymologies as a first-line mitochondrial diagnostic test. On the other hand, functional analyses including respiratory chain enzymologies are still essential to validate some variants found by NGS. Recently, several biomarkers were found to be both sensitive and specific for MD including fibroblast growth factor 21 (FGF21) and growth and differentiation factor 15 (GDF15). However, our data suggested that these markers were not as specific as previously thought. They could be raised in other non-MD including channelopathies. A proposed diagnostic algorithm for MD would be discussed, followed by some novel treatment strategies. Hope will be the future of mitochondrial medicine.