Mitochondrial Genetics, Disease and Inheritance

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Mitochondrial disease is principally a chronic loss of cellular energy, where a failure to meet cellular energy demand results in a clinical phenotype. The clinical spectrum of mitochondrial disease is diverse; however, tissues where there is a high metabolic demand, such as the central nervous system (CNS) or heart, are typically affected. The broad clinical spectrum of mitochondrial dysfunction, coupled with the heterogeneity of mtDNA variation, makes the prevalence of mitochondrial DNA (mtDNA) difficult to calculate.

Mitochondria are dependent upon the nuclear genome for the majority of the OXPHOS system and also for maintaining and replicating mtDNA as well as organelle network proliferation and destruction. To date, 92 structural OXPHOS subunit genes have been identified: 13 encoded by mtDNA and 79 encoded by the nuclear genome.

Mitochondrial dysfunction should be considered in the differential diagnosis of any progressive, multisystem, disorder. However, clinical diagnosis can be difficult if patients do not present with 'classical mitochondrial disease. A detailed family history is important; a clear maternal inheritance indicates a primary mtDNA defect, whilst an autosomal inheritance pattern is indicative of nDNA interaction. In many cases blood and/or CSF lactate concentration, neuroimaging, cardiac evaluation and muscle biopsy for histological or histochemical evidence can indicate mitochondrial disease. However, establishing a molecular genetic diagnosis is preferred.

Molecular genetic testing can be carried out on DNA extracted from blood but DNA extracted from the affected tissue is preferred. Genetic Disgnosis of Leber hereditary optic Neuropathy (LHON), Non-syndromic and aminoglycoside-induced sensorineuronal hearing loss, Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), Myoclonus epilepsy with ragged red fibres (MERRF), Kearns–Sayre syndrome (KSS), Pearson's bone-marrow–pancreas syndrome, will be provide from mtDNA.

Nuclear–mitochondrial disease can be classified into four distinct groups: (i) disorders resulting from a reduction in mtDNA stability; (ii) disorders resulting from mutations in nuclear-encoded components or assembly factors of the OXPHOS system; (iii) disorders resulting from mutations affecting mitochondrial translation and (iv) disorders due to defects in genes controlling mitochondrial network dynamics.

Keywords: Children; Mitochondrial disease; Genetic Study; Inheritance

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