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Commentary

Revealing the Complexity of Mitochondrial DNA-Related Disorders

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Mitochondrial diseases are an extraordinarily complex group of disorders caused by impairment of the respiratory chain. Among them, disorders due to mitochondrial DNA (mtDNA) mutations are unique in human genetics. Indeed, the rules of inheritance for genes located in mitochondria are different than for nuclear genes. MtDNA point mutations don not follow the Mendelian laws of inheritance, and are inherited according to the rules of mitochondrial genetics (maternal inheritance, heteroplasmy and the threshold effect, mitotic segregation), differently from mtDNA large-scale single deletions which are sporadic and not inheritable (DiMauro et al., 2013).

Each cell contains multiple copies of mtDNA (polyplasmy), which in healthy individuals are identical to one another (homoplasmy). Heteroplasmy refers to the coexistence of two populations of mtDNA, normal and mutated. Mutated mtDNA in a given tissue has to reach a minimum critical number before oxidative metabolism is impaired severely enough to cause dysfunction (threshold effect). The pathogenic threshold varies from tissue to tissue according to the relative dependence of each tissue on oxidative metabolism (DiMauro et al., 2013). Differences in mutational load surpassing the pathogenic threshold in some tissues but not in others may contribute to the heterogeneity of phenotypes. Because of the mitotic segregation (random share-out of mutated and non-mutated mitochondria between the daughter cells), the mutation load can change from one cell generation to the next and, with time, it can either surpass or fall below the pathogenic threshold (DiMauro et al., 2013). Other factors, including gender (Kirkman et al., 2009), nuclear genetic background, mtDNA polymorphisms and additional mtDNA mutations (Swalwell et al., 2008) may influence the expression of mtDNA mutations. Gene-environment interactions, including smoke (Kirkman et al., 2009) and drugs (Mancuso et al., 2012), could have a role as well.

The effects of mutations which affect the respiratory chain may therefore be multisystemic, with possible involvement of visual and auditory pathways, heart, central nervous system and skeletal muscle. The "red flags" are myopathy with exercise intolerance, eyelid ptosis, ophthalmoparesis, axonal neuropathy, sensorineural hearing loss, pigmentary retinopathy, optic neuropathy, diabetes mellitus, hypertrophic cardiomyopathy, migraine, short stature (DiMauro et al., 2013).

For the above reported reasons, studying genotype-phenotype relationship in mitochondrial disorders is a complex task. The clinical variability is large even in individuals with the same genotype and the statistical power is low in single-center studies given the rarity of these conditions. In order to better define the clinical phenotypes associated with mtDNA mutations, there is a strong need of nation-wide, and even international, studies on large cohorts of patients. For instance, the Italian Network had the opportunity to redefine the clinical features of some mtDNA mutations, including the m.8344A>G (Mancuso et al., 2013) and m.3243A>G (Mancuso et al., 2014) substitutions.

The m.8344A>G mutation was previously associated with "MERRF" (myoclonic epilepsy with ragged-red fibers). The Italian group studied 42 patients carrying this mutation, observing that the great majority did not have full-blown MERRF syndrome (Mancuso et al., 2013). Myoclonus was present in 1 of 5 patients, whereas myopathic signs and symptoms, generalized seizures, hearing loss, eyelid ptosis, and multiple lipomatosis represented the most common clinical features. Some asymptomatic mutation carriers have also been observed. Interestingly, myoclonus was more strictly associated with ataxia than generalized seizures, suggesting that MERRF could be better defined as a myoclonic ataxia rather than a myoclonic epilepsy (Mancuso et al., 2013).

The phenotypes associated to the m.3243A>G "MELAS" (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) mutation were also revised by the Italian Network, which studied 126 patients and confirmed the high clinical heterogeneity of this mutation (Mancuso et al., 2014). Hearing loss and diabetes were the most frequent clinical features, followed by stroke-like episodes. "MIDD" (maternally-inherited diabetes and deafness) and "PEO" (progressive external ophthalmoplegia) were nosographic terms without any real prognostic value, because these patients could be even more prone to the development of multisystem complications such as stroke-like episodes and heart involvement. The "MELAS" acronym seemed convincing and useful to denote patients with histological, biochemical and/or molecular evidence of mitochondrial disease who experience stroke-like episodes. Of note, it was observed for the first time that male gender could represent a risk factor for the development of stroke-like episodes in Italian m.3243A>G carriers (Mancuso et al., 2014).

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By using a similar approach, in this issue of EBioMedicine, Ng et al. (2018) described a rarer mtDNA mutation, previously reported only in three cases of Leigh Syndrome (LS), a devastating pediatric encephalopathy (Lake et al., 2015). This mutation, the m.13094T>C substitution in the mitochondrial *MT-ND5* gene, encodes a subunit of complex I of the oxidative phosphorylation system (Rodenburg, 2016). In this retrospective international cohort study 20 clinically affected individuals and four asymptomatic carriers were identified in 13 families (Ng et al., 2018). Clinical variability was higher than previously thought also for this mutation. In fact, nine patients manifested with LS, one with MELAS, whereas ten patients presented with either overlapping syndromes or isolated neurological symptoms (including one with isolated optic neuropathy) (Ng et al., 2018). Interestingly, abnormalities within the basal ganglia (common in other forms of LS) (Lake et al., 2015) were rare in these patients, studied by neuroimaging and in two cases by neuropathological examination. Furthermore, muscle biopsy, including respiratory chain activity analysis, was normal in most patients (Ng et al., 2018).

The authors have concluded that whole mtDNA genome sequencing should be performed in all patients with undiagnosed complex neurological disorders (in clinically relevant tissues, not just in blood). Once again, the observed clinical heterogeneity, apparent lack of maternal inheritance, normal histological and biochemical muscle biopsy findings and variability in tissue segregation underscore the diagnostic challenges of mtDNA-related diseases (Ng et al., 2018).

Marked clinical heterogeneity with a continuous spectrum of overlapping symptoms was associated with the m.13094T>C mutation (Ng et al., 2018). In mitochondrial medicine, the concept of "spectrum" should probably be highlighted (Mancuso et al., 2015). We don't fully know mitochondrial disorders yet, but at least we are beginning to unravel their complexity.

Disclosure

The authors declared no conflicts of interest.

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