TABLE 85e-3 MITOCHONDRIAL DISEASES DUE TO MTDNA POINT MUTATIONS AND LARGE-SCALE REARRANGEMENTS

Disease	Phenotype	Most Frequent mtDNA Mutations	Homoplasmic (usually)	Maternal
NARP, Leigh disease	Loss of central vision leading to blindness in young adult life	m.1778G>A, m.14484T>C, m.3460G>A	Heteroplasmic	Maternal
MELAS	*M*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes; may manifest only as diabetes mellitus	Point mutation in $tRNA^{leu}$	Heteroplasmic	Maternal
MERRF	*M*yoclonic *e*pilepsy, *r*agged *r*ed *f*ibers in muscle, ataxia, increased CSF protein, sensorineural deafness, dementia	Point mutation in $tRNA^{lys}$	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics	m.1555A>G mutation in 12S rRNA	Homoplasmic	Maternal
	Nonsyndromic sensorineural deafness	m.7445A>G mutation in 12S rRNA	Homoplasmic	Maternal
Chronic progressive external ophthalmoplegia (PEO)	Late-onset bilateral ptosis and ophthalmoplegia, proximal muscle weakness, and exercise intolerance	Single deletions or duplications	Heteroplasmic	Mostly sporadic, somatic mutations
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis	Large deletion	Heteroplasmic	Sporadic, somatic mutations
Kearns-Sayre syndrome (KSS)	External ophthalmoplegia, heart block, retinal pigmentation, ataxia	The 5-kb "common deletion"	Heteroplasmic	Sporadic, somatic mutations

Abbreviations: CSF, cerebrospinal fluid; NARP, neuropathy, ataxia, and retinitis pigmentosa.

Neuropathy, ataxia, and retinitis pigmentosa (NARP) is characterized by moderate diffuse cerebral and cerebellar atrophy and symmetric lesions of the basal ganglia on magnetic resonance imaging (MRI). A heteroplasmic m.8993T>G mutation in the ATPase 6 subunit gene has been identified as causative. Ragged red fibers are not observed in muscle biopsy. When >95% of mtDNA molecules are mutant, a more severe clinical, neuroradiologic. and neuropathologic picture (Leigh syndrome) emerges. Point mutations in the mtDNA gene encoding the 12S rRNA result in heritable nonsyndromic hearing loss. One such mutation causes heritable ototoxic susceptibility to aminoglycoside antibiotics, which opens a pathway for a simple pharmacogenetic test in the appropriate clinical settings.

Kearns-Sayre syndrome (KSS), sporadic progressive external ophthalmoplegia (PEO), and Pearson syndrome are three disease phenotypes caused by large-scale mtDNA rearrangements including partial deletions or partial duplication. The majority of single large-scale rearrangements of mtDNA are thought to result from clonal amplification of a single sporadic mutational event, occurring in the maternal oocyte or during early embryonic development. Because germline involvement is rare, most cases are sporadic rather than inherited. KSS is characterized by the triad of onset before age 20, chronic progressive external ophthalmoplegia, and pigmentary retinopathy. Cerebellar syndrome, heart block, increased cerebrospinal fluid protein content, diabetes mellitus, and short stature are also part of the syndrome. Single deletions/duplication can also result in milder phenotypes such as PEO, characterized by late-onset progressive external ophthalmoplegia, proximal myopathy, and exercise intolerance. In both KSS and PEO, diabetes mellitus and hearing loss are frequent accompaniments. Pearson syndrome is also characterized by diabetes mellitus from pancreatic insufficiency, together with pancytopenia and lactic acidosis, caused by the large-scale sporadic deletion of several mtDNA genes.

Two important dilemmas in classic mtDNA disease have benefited from recent important research insights. The first relates to the greater involvement of neuronal, muscular, renal, hepatic, and pancreatic manifestations in mtDNA disease in these syndromes. This observation has appropriately been mostly attributed to the high energy utilization of the involved tissues and organ systems and, hence, greater dependency on mitochondrial ETC integrity and health. However, because mutations are stochastic events, mitochondrial mutations should occur in any organ during embryogenesis and development. Recently, additional explanations have been suggested based on studies of the common m.3243A>G transition. The proportion of this mutation in peripheral blood cells was shown to decrease exponentially with age. A selective process acting at the stem cell level with a strong bias against the mutated form would have its greatest effect to reduce the mutant mtDNA only in highly proliferating cells, such as those derived from the hematopoietic system. Tissues and organs with lower cell turnover, such as those involved with mtDNA mutations, would not benefit from this effect and, thus, would be the most affected.

The other dilemma arises from the observation that only a subset of mtDNA mutations accounts for the majority of the familial mtDNA diseases. The random occurrence of mutations in the mtDNA sequence should yield a more uniform distribution of disease-causing mutations. However, recent studies using the introduction of one severe and one mild point mutation into the female germline of experimental animals demonstrated selective elimination during oogenesis of the severe mutation and selective retention of the milder mutation, with the emergence of mitochondrial disease in offspring after multiple generations. Thus, oogenesis itself can act as an "evolutionary" filter for mtDNA disease.

THE INVESTIGATION OF SUSPECTED MTDNA DISEASE

The clinical presentations of classic syndromes, groupings of disease manifestations in multiple organ systems, or unexplained isolated presentations of one of the disease features of a classic mtDNA syndrome should prompt a systematic clinical investigation as outlined in Fig. 85e-6. Indeed, mitochondrial disease should be considered in the differential diagnosis of any progressive multisystem disorder. Despite the centrality of disruptive oxidative phosphorylation, an elevated blood lactate level is neither specific nor sensitive because there are many causes of blood lactic acidosis, and many patients with mtDNA defects presenting in adulthood have normal blood lactate. An elevated cerebrospinal fluid lactate is a more specific test for mitochondrial disease if there is central nervous system involvement. The serum creatine kinase may be elevated but is often normal, even in the presence of a proximal myopathy. Urinary organic and amino acids may also be abnormal, reflecting metabolic and kidney proximal tubule dysfunction. Every patient with seizures or cognitive decline should have an electroencephalogram. A brain computed tomography (CT) scan may show calcified basal ganglia or bilateral hypodense regions with cortical atrophy. MRI is indicated in patients with brainstem signs or stroke-like episodes.

For some mitochondrial diseases, it is possible to obtain an accurate diagnosis with a simple molecular genetic screen. For examples, 95% of patients with LHON harbor one of three mtDNA point mutations (m.11778A>G, m.A3460A>G, or m.14484T>C). These patients have very high levels of mutated mtDNA in peripheral blood cells, and