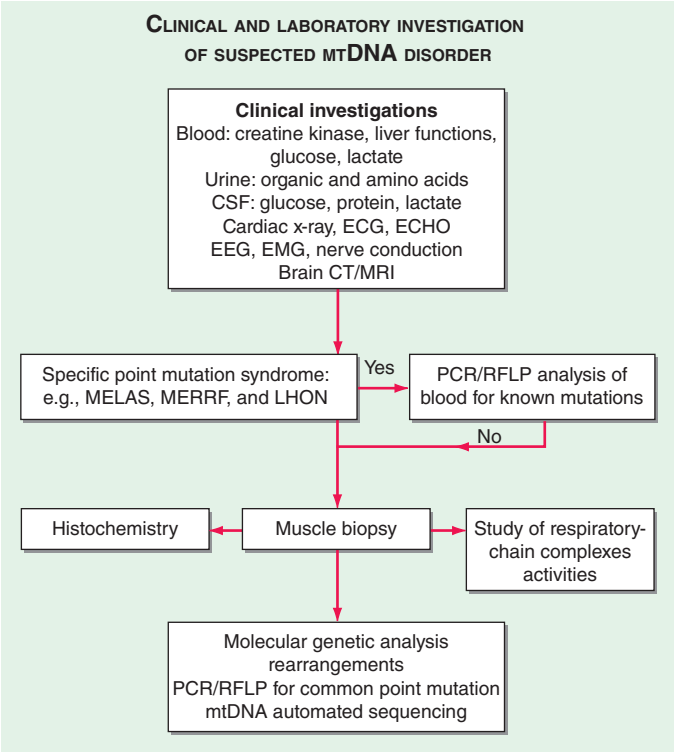

FIGURE 85e-6 Clinical and laboratory investigation of a suspected mitochondrial DNA (mtDNA) disorder. CSF, cerebrospinal fluid; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; EEG, electroencephalogram; EMG, electromyogram; LHON, Leber's hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stoke-like episodes; MERFF, myoclonic epilepsy with ragged red fibers; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

therefore, it is appropriate to send a blood sample for molecular genetic analysis by polymerase chain reaction (PCR) or restriction fragment length polymorphism. The same is true for most MERRF patients who harbor a point mutation in the lysine tRNA gene at position 8344. In contrast, patients with the m.3243A>G MELAS mutation often have low levels of mutated mtDNA in blood. If clinical suspicion is strong enough to warrant peripheral blood testing, then patients with a negative result should be investigated further by performing a skeletal muscle biopsy.

Muscle biopsy histochemical analysis is the cornerstone for investigation of patients with suspected mitochondrial disease. Histochemical analysis may show subsarcolemmal accumulation of mitochondria with the appearance of ragged red fibers. Electron microscopy might show abnormal mitochondria with paracrystalline inclusions. Muscle histochemistry may show cytochrome c oxidase (COX)–deficient fibers, which indicate mitochondrial dysfunction (Fig. 85e-5). Respiratory chain complex assays may also show reduced enzyme function. Either of these two abnormalities confirms the presence of a mitochondrial disease, to be followed by an in-depth molecular genetic analysis.

Recent evidence has provided important insights into the importance of nuclear-mtDNA genomic cross-talk and has provided a descriptive framework for classifying and understanding disorders that emanate from perturbations in this cross-talk. Although not strictly considered as mtDNA genetic disorders, manifestations do overlap those highlighted above (Fig. 85e-7).

IMPACT OF HOMOPLASMIC SEQUENCE VARIATION ON HERITABLE TRAITS AND DISEASE

The relationship among the degree of heteroplasmy, tissue distribution of the mutant mtDNA, and disease phenotype simplifies inference of a clear causative relationship between heteroplasmic mutation and disease. With the exception of certain mutations (e.g., those causing most cases of LHON), drift to homoplasmy of such mutations would be precluded normally by the severity of impaired oxidative phosphorylation and the consequent reduction in reproductive fitness. Therefore, sequence variants that have reached homoplasmy should be neutral in terms of human evolution and, hence, useful only for tracing human evolution, demography, and migration, as described above. One important exception is in the case of one or more of the homoplasmic population-level variants, which designate the mtDNA haplogroup J, and the interaction with the mtDNA mutations causing LHON. Reduced disease predilection suggests that one or more of the ancient sequence variants designating mtDNA haplogroup J appears to attenuate predisposition to degenerative disease, in the face of other risk factors. Whether or not additional epistatic interactions between population-level mtDNA haplotypes and common health conditions will be found remains to be determined. If such influences do exist, then they are more likely to be relevant to health conditions in the postreproductive age groups, wherein evolutionary filters would not have had the opportunity to censor deleterious effects and interactions and wherein the effects of oxidative stress may play a role. Although much has been written about the possible associations of population-level common mtDNA variants and human health and disease phenotypes or adaptation to different environmental influences (e.g., climate), a word of caution is in order.

Many studies that purport to show such associations with phenotypes such as longevity, athletic performance, and metabolic and neurodegenerative disease are limited by small sample sizes, possible genotyping inaccuracies, and the possibility of population stratification or ethnic ancestry bias. Because mtDNA haplogroups are so prominently partitioned along phylogeographic lines, it is difficult to rule out the possibility that a haplogroup for which an association has been found is simply a marker for differences in

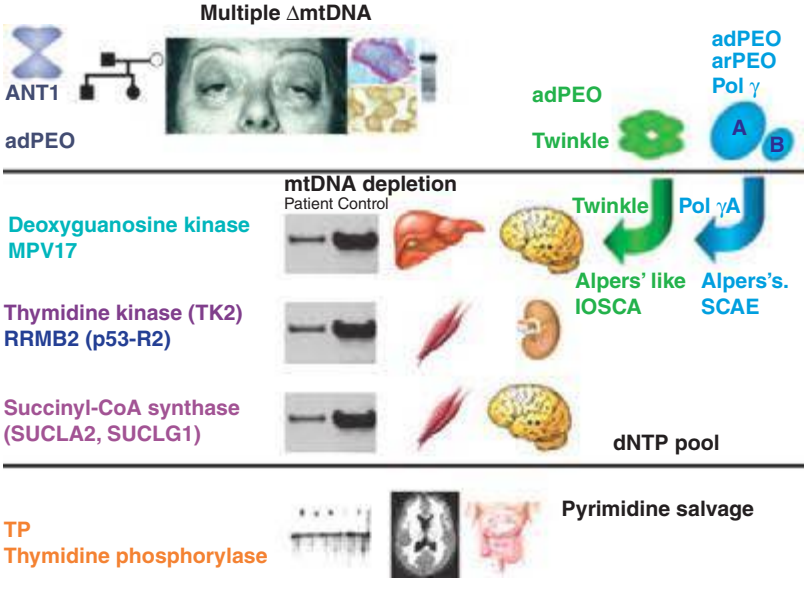

FIGURE 85e-7 Disorders associated with perturbations in nuclear-mitochondrial genomic cross-talk. Clinical features and genes associated with multiple mitochondrial DNA (mtDNA) deletions, mtDNA depletion, and mitochondrial neurogastrointestinal encephalomyopathy syndromes. ANT, adenine nucleotide translocators; adPEO, autosomal dominant progressive external ophthalmoplegia; arPEO, autosomal recessive progressive external ophthalmoplegia; IOSCA, infantile-onset spinocerebellar ataxia; SCAE, spinocerebellar ataxia and epilepsy. *(Reproduced with permission from A Spinazzola, M Zeviani: Disorders from perturbations of nuclear-mitochondrial intergenomic cross-talk. J Intern Med 265:174, 2009.)*