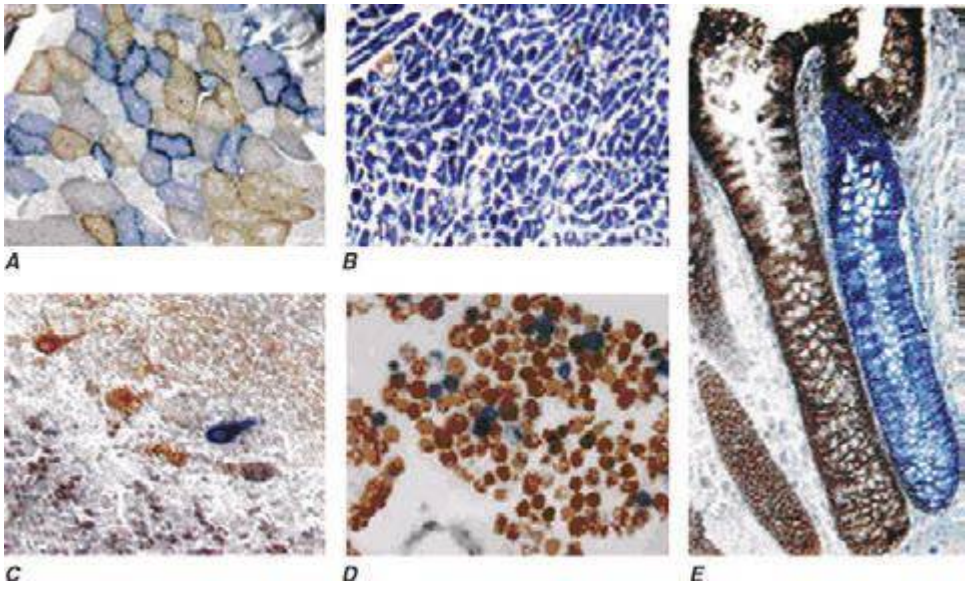

FIGURE 85e-5 Cytochrome c oxidase (COX) deficiency in mitochondrial DNA (mtDNA)–associated disease. Transverse tissue sections that have been stained for COX and succinate dehydrogenase (SDH) activities sequentially, with COX-positive cells shown in *brown* and COX-deficient cells shown in *blue*. ***A.*** Skeletal muscle from a patient with a heteroplasmic mitochondrial tRNA point mutation. The section shows a typical "mosaic" pattern of COX activity, with many muscle fibers harboring levels of mutated mtDNA that are above the crucial threshold to produce a functional enzyme complex. ***B.*** Cardiac tissue (left ventricle) from a patient with a homoplasmic tRNA mutation that causes hypertrophic cardiomyopathy, which demonstrates an absence of COX in most cells. ***C.*** A section of cerebellum from a patient with mtDNA rearrangement that highlights the presence of COX-deficient neurons. ***D, E.*** Tissues that show COX deficiency due to clonal expansion of somatic mtDNA mutations within single cells—a phenomenon that is seen in both postmitotic cells (***D***; extraocular muscles) and rapidly dividing cells (***E***; colonic crypt) in aging humans. *(Reproduced with permission from R Taylor, D Turnbull: Mitochondrial DNA mutations in human disease. Nat Rev Genetics 6:389, 2005.)*

Leber's hereditary optic neuropathy (LHON) is a common cause of maternally inherited visual failure. LHON typically presents during young adulthood with subacute painless loss of vision in one eye, with symptoms developing in the other eye 6–12 weeks after the initial onset. In some instances, cerebellar ataxia, peripheral neuropathy, and cardiac conduction defects are observed. In >95% of cases, LHON is due to one of three homoplasmic point mutations of mtDNA that affect genes encoding different subunits of complex I of the mitochondrial ETC; however, not all individuals who inherit a primary LHON mtDNA mutation develop optic neuropathy, and males are four to five times more likely than females to be affected, indicating that additional environmental (e.g., tobacco exposure) or genetic factors are important in the etiology of the disorder. Both the nuclear and mitochondrial genomic backgrounds modify disease penetrance. Indeed, a region of the X chromosome containing a high-risk haplotype for LHON was recently identified, supporting the formulation that nuclear genes act as modifiers and affording an explanation for the male prevalence of LHON. This haplotype can be used in predictive genomic testing and prenatal screening for this disease. In contrast to the other classic mtDNA disorders, it is of interest that patients with this syndrome are often homoplasmic for the disease-causing mutation. The somewhat later onset in young adulthood and modifying effect of protective background nuclear genomic haplotypes may have enabled homoplasmic pathogenic mutations to have escaped evolutionary censoring.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a multisystem disorder with a typical onset between 2 to 10 years of age. Following normal early psychomotor development, the most common initial symptoms are seizures, recurrent headaches, anorexia, and recurrent vomiting. Exercise intolerance or proximal limb weakness can be the initial manifestation, followed by generalized tonic-clonic seizures. Short stature is common. Seizures are often associated with stroke-like episodes of transient hemiparesis or cortical blindness that may produce altered consciousness and may recur. The cumulative residual effects of the stroke-like episodes gradually impair motor abilities, vision, and cognition, often by adolescence or young adulthood. Sensorineural hearing loss adds to the progressive decline of these individuals. A plethora of less common symptoms have been described including myoclonus, ataxia, episodic coma, optic atrophy, cardiomyopathy, pigmentary retinopathy, ophthalmoplegia, diabetes mellitus, hirsutism, gastrointestinal dysmotility, and nephropathy. The typical age of death ranges from 10 to 35 years, but some individuals live into their sixth decade. Intercurrent infections or intestinal obstructions are often the terminal events. Laboratory investigation commonly demonstrates elevated lactate concentrations at rest with excessive increase after moderate exercise. Brain imaging during stroke-like episodes shows areas of increased T2 signal, typically involving the posterior cerebrum and not conforming to the distribution of major arteries. Electrocardiogram (ECG) may show evidence of cardiomyopathy, preexcitation, or incomplete heart block. Electromyography and nerve conduction studies are consistent with a myopathic process, but axonal and sensory neuropathy may coexist. Muscle biopsy typically shows ragged red fibers with the modified Gomori trichrome stain or "ragged blue fibers" resulting from the hyperintense reaction with the histochemical staining for succinate dehydrogenase. The diagnosis of MELAS is based on a combination of clinical findings and molecular genetic testing. Mutations in the mtDNA gene *MT-TL1* encoding $tRNA^{leu}$ are causative. The most common mutation, present in approximately 80% of individuals with typical clinical findings, is an A-to-G transition at nucleotide 3243 (m.3243A>G). Mutations can usually be detected in mtDNA from leukocytes in individuals with typical MELAS; however, the occurrence of heteroplasmy can result in varying tissue distribution of mutated mtDNA. In the absence of specific treatment, various manifestations of MELAS are treated according to standard modalities for prevention, surveillance, and treatment.

Myoclonic epilepsy with ragged red fibers (MERRF) is a multisystem disorder characterized by myoclonus, seizures, ataxia, and myopathy with ragged red fibers. Hearing loss, exercise intolerance, neuropathy, and short stature are often present. Almost all MERRF patients have mutation in the mtDNA $tRNA^{lys}$ gene, and the m.8344A>G mutation in the mtDNA gene encoding the lysine amino acid tRNA is responsible for 80–90% of MERRF cases.

TABLE 85e-2 COMMON FEATURES OF MTDNA-ASSOCIATED DISEASES IN ADULTS

Neurologic: stroke, epilepsy, migraine headache, peripheral neuropathy, cranial neuropathy (optic atrophy, sensorineural deafness, dysphagia, dysphasia)
Skeletal myopathy: ophthalmoplegia, exercise intolerance, myalgia
Cardiac: conduction block, cardiomyopathy
Respiratory: hypoventilation, aspiration pneumonitis
Endocrine: diabetes mellitus, premature ovarian failure, hypothyroidism, hypoparathyroidism
Ophthalmologic: cataracts, pigment retinopathy, neurologic and myopathic (optic atrophy, ophthalmoplegia)