Mitochondrial disorders due to mutations in the nuclear genome. Leigh syndrome can be caused by mutations in mitochondrial DNA (mtDNA), pyruvate dehydrogenase complex (PDHC) deficiency, or mutations in nuclear genes affecting the synthesis, structure or assembly to the mitochondrial respiratory chain. Disorders of mtDNA maintenance are a major cause of disease due to a nuclear gene defect affecting the amount or quality of mtDNA, which causes mtDNA depletion or secondary multiple mtDNA deletions. This group includes mutations in the mtDNA polymerase gene \textit{POLG} and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). Disorders of intramitochondrial protein synthesis can be due to primary mutations of mtDNA, or a wide range of different nuclear gene defects (see text). Other nuclear-encoded mitochondrial diseases include disorders of mitochondrial protein import (including the Mohr–Tranebjaerg syndrome) and disorders of the lipid membranes (including Barth syndrome), and disorders of coenzyme Q10 biosynthesis. The latter are particularly important to recognize because they are potentially treatable.

Copyright © 2015 Elsevier Inc. All rights reserved.
Fig. 24-2. **MRI findings in Leigh syndrome.** High signal in the caudate and putamen seen on T1- and T2-weighted images in a patient with the homozygous SCO2 mutation p.E140K. (With thanks to Prof Rita Horvath, Newcastle University).

Copyright © 2015 Elsevier Inc. All rights reserved.
Fig. 24-3A. MRI findings in POLG encephalopathy. (A) Sagittal T1 image showing cerebellar atrophy. (B) Axial T2 image showing dentate atrophy (arrow). (C) Axial T2 image showing cerebellar white matter hyperintensity. (D) Axial T2 image showing bilateral olivary lesions. The olives appear enlarged and hyperintense. (E) Axial T2 fluid-attenuated inversion recovery image showing bilateral thalamic and cortical occipital lesions. (F) Axial diffusion-weighted image (b = 1000) showing acute stroke-like lesions in the right cerebellar cortex. (G) Axial T1 image showing linear, gyriform hyperintensity in the right medial occipital cortex (cortical laminar necrosis). (With thanks to Prof Laurence Bindoff, University of Bergen.)

Copyright © 2015 Elsevier Inc. All rights reserved.
Fig. 22-3B. Replication of human mtDNA. (A) The "asynchronous, strand displacement" model. Replication of the parental mtDNA (thick solid lines are heavy H strands; thin solid lines are light L strands) proceeds from O₁, in the D-loop region (clockwise beginning at "1 o'clock") until daughter strand synthesis (heavy dashed line) reaches O₂, at which point daughter light-strand synthesis (light dashed line) initiates in a counterclockwise direction. (B) The "synchronous, strand-coupled" model. Replication proceeds bidirectionally on the leading and lagging strands, as in classic bacterial DNA "theta" replication, but with some modifications. Most notably, preformed RNA incorporation throughout the lagging strand (RITOLS) (dashed lines) are "threaded" through the advancing DNA polymerase complex, hybridizing with the displaced H-strand in the 3′–5′ direction, until an upstream RNA processing site (or a transcriptional start site) is encountered. In both models, following completion of synthesis of the two daughter strands, the two progeny molecules, which are initially catenated circles (not shown), are unlinked; the "relaxed" circles are then supercoiled by topoisomerase. See text for further description.
Fig. 24-3C. **MRI findings in POLG encephalopathy.** (A) Sagittal T1 image showing cerebellar atrophy. (B) Axial T2 image showing dentate atrophy (arrow). (C) Axial T2 image showing cerebellar white matter hyperintensity. (D) Axial T2 image showing bilateral olivary lesions. The olives appear enlarged and hyperintense. (E) Axial T2 fluid-attenuated inversion recovery image showing bilateral thalamic and cortical occipital lesions. (F) Axial diffusion-weighted image (b = 1000) showing acute stroke-like lesions in the right cerebellar cortex. (G) Axial T1 image showing linear, gyriform hyperintensity in the right medial occipital cortex (cortical laminar necrosis). (With thanks to Prof Laurence Bindoff, University of Bergen.)
Fig. 24-3D. **MRI findings in POLG encephalopathy.** (A) Sagittal T1 image showing cerebellar atrophy. (B) Axial T2 image showing dentate atrophy (arrow). (C) Axial T2 image showing cerebellar white matter hyperintensity. (D) Axial T2 image showing bilateral olivary lesions. The olives appear enlarged and hyperintense. (E) Axial T2 fluid-attenuated inversion recovery image showing bilateral thalamic and cortical occipital lesions. (F) Axial diffusion-weighted image (b = 1000) showing acute stroke-like lesions in the right cerebellar cortex. (G) Axial T1 image showing linear, gyriform hyperintensity in the right medial occipital cortex (cortical laminar necrosis). (With thanks to Prof Laurence Bindoff, University of Bergen.)
Fig. 24-3E. MRI findings in POLG encephalopathy. (A) Sagittal T1 image showing cerebellar atrophy. (B) Axial T2 image showing dentate atrophy (arrow). (C) Axial T2 image showing cerebellar white matter hyperintensity. (D) Axial T2 image showing bilateral olivary lesions. The olives appear enlarged and hyperintense. (E) Axial T2 fluid-attenuated inversion recovery image showing bilateral thalamic and cortical occipital lesions. (F) Axial diffusion-weighted image (b = 1000) showing acute stroke-like lesions in the right cerebellar cortex. (G) Axial T1 image showing linear, gyriform hyperintensity in the right medial occipital cortex (cortical laminar necrosis). (With thanks to Prof Laurence Bindoff, University of Bergen.)
Fig. 24-3F. MRI findings in POLG encephalopathy. (A) Sagittal T1 image showing cerebellar atrophy. (B) Axial T2 image showing dentate atrophy (arrow). (C) Axial T2 image showing cerebellar white matter hyperintensity. (D) Axial T2 image showing bilateral olivary lesions. The olives appear enlarged and hyperintense. (E) Axial T2 fluid-attenuated inversion recovery image showing bilateral thalamic and cortical occipital lesions. (F) Axial diffusion-weighted image (b = 1000) showing acute stroke-like lesions in the right cerebellar cortex. (G) Axial T1 image showing linear, gyriform hyperintensity in the right medial occipital cortex (cortical laminar necrosis). (With thanks to Prof Laurence Bindoff, University of Bergen.)
Fig. 24-3G. **MRI findings in POLG encephalopathy.** (A) Sagittal T1 image showing cerebellar atrophy. (B) Axial T2 image showing dentate atrophy (arrow). (C) Axial T2 image showing cerebellar white matter hyperintensity. (D) Axial T2 image showing bilateral olivary lesions. The olives appear enlarged and hyperintense. (E) Axial T2 fluid-attenuated inversion recovery image showing bilateral thalamic and cortical occipital lesions. (F) Axial diffusion-weighted image (b = 1000) showing acute stroke-like lesions in the right cerebellar cortex. (G) Axial T1 image showing linear, gyriform hyperintensity in the right medial occipital cortex (cortical laminar necrosis). (With thanks to Prof Laurence Bindoff, University of Bergen.)
Fig. 24-4. **Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).** Left: Axial T2-weighted MRI of the brain showing leukoencephalopathy. Right: intravenous contrast-enhanced computed tomography (CT) of the abdomen and pelvis, revealing multiple loops of small bowel with fluid and gas distension but no transition point, suggestive of ileus/intestinal dysmotility.