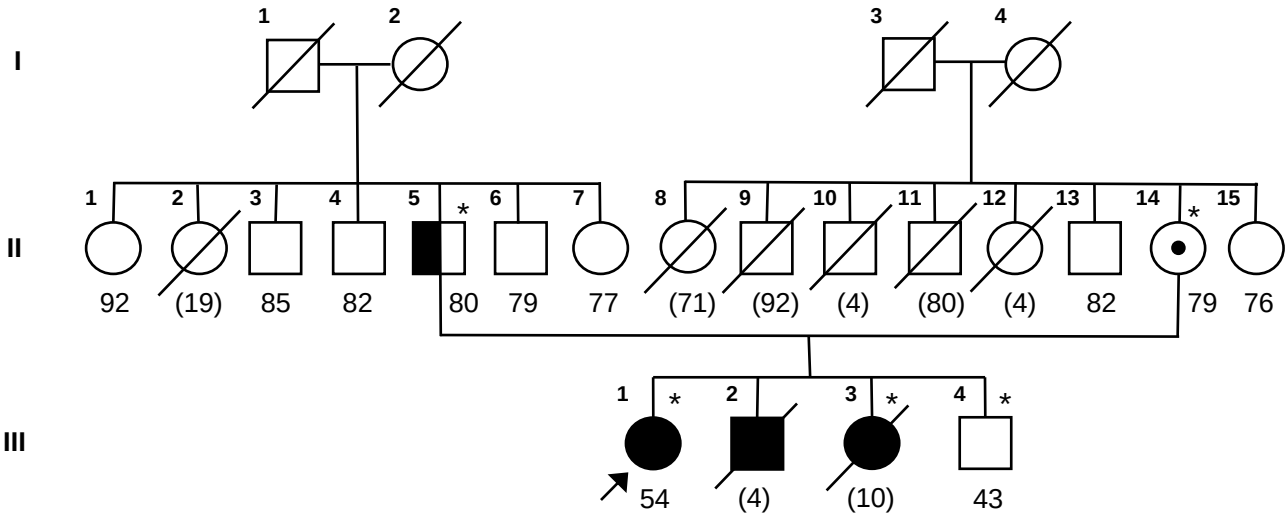
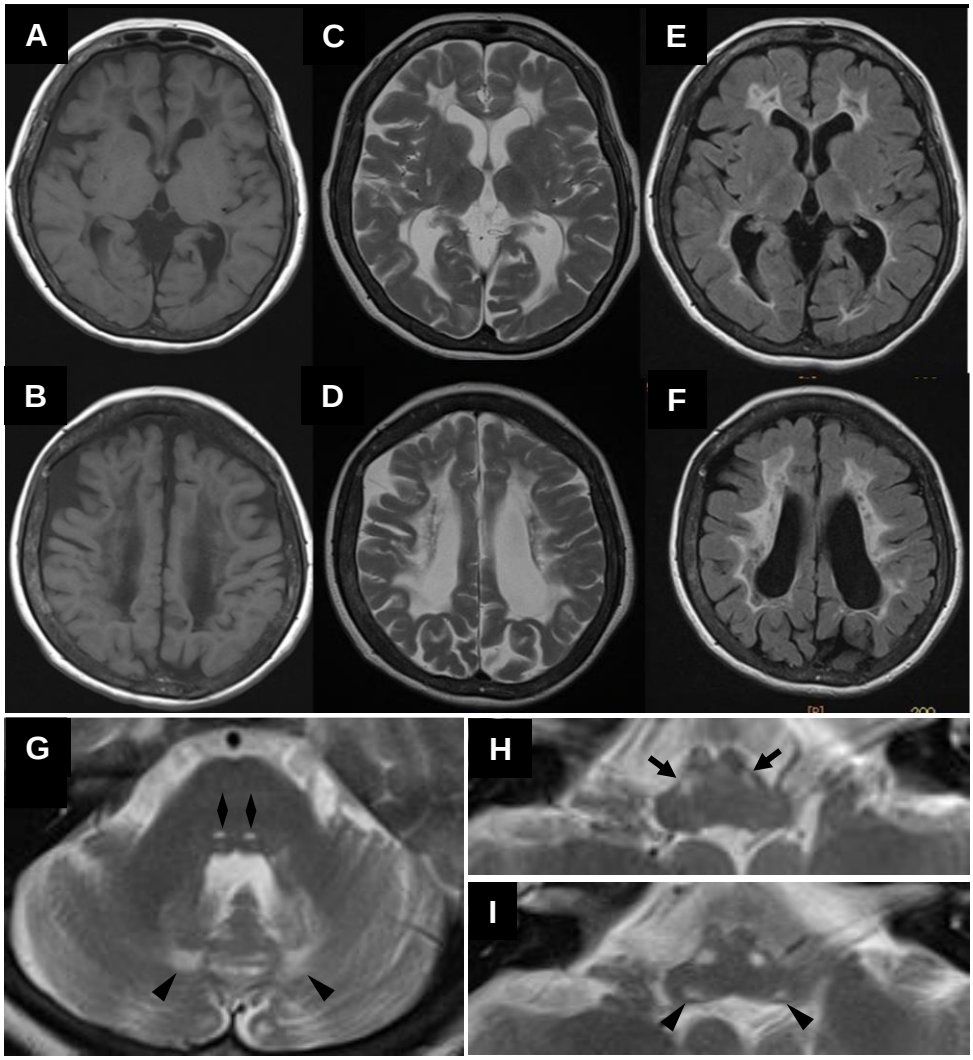
Supplementary eFigure 1



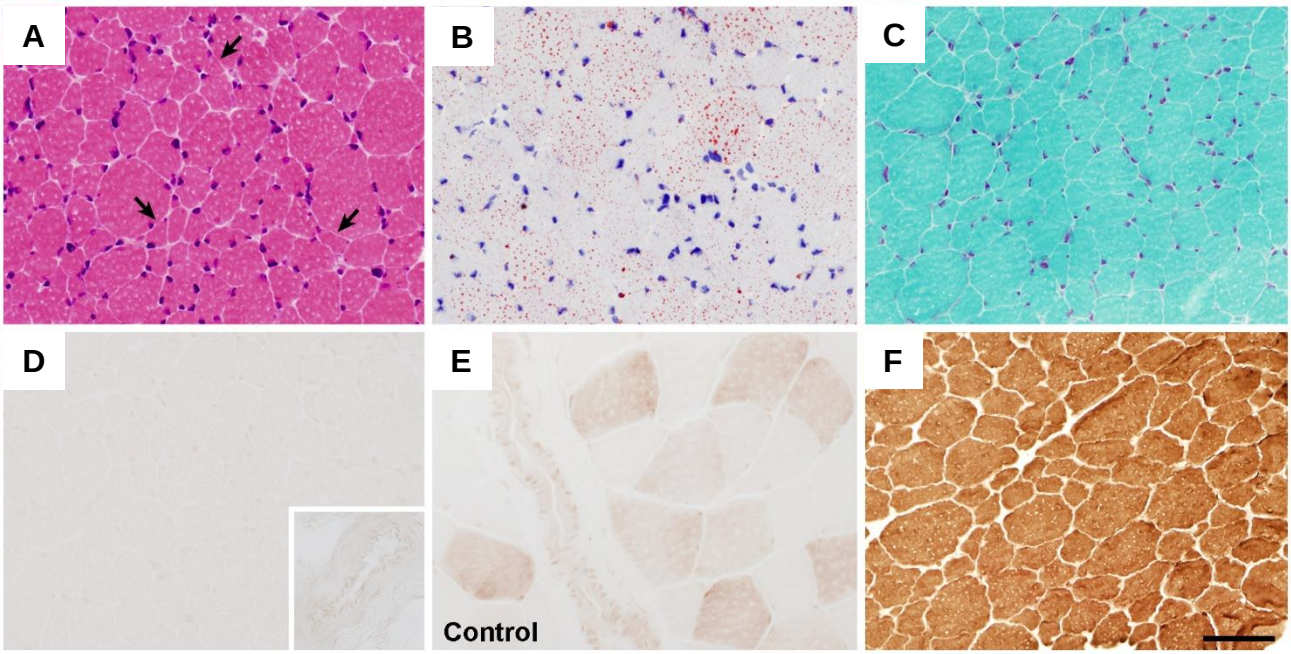
eFigure 1. Family pedigree
Black shaded: patients with Leigh syndrome; half shaded: a patient with pressure neuropathy. Arrow: proband; shaded: deceased; numbers: age; numbers in parentheses: age at death. Asterixis indicates subjects who underwent genomic DNA analysis. A central dot in a symbol denotes an asymptomatic carrier.

Supplementary eFigure 2



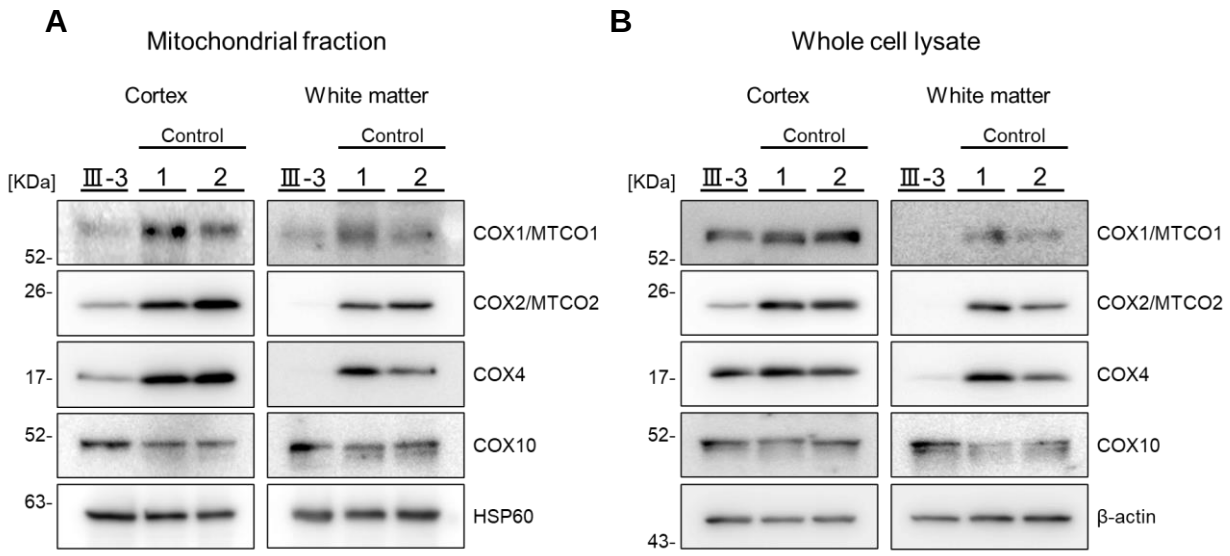
eFigure 2. Brain MRI findings (patient 1)
Brain 1.5 Tesla MR image of patient 1 at age 51 **(A–I)**. T1-weighted axial image, TR/TE 2,000/8.4 ms **(A,B)**. T2-weighted axial image, TR/TE 4,000/85 ms **(C,D)**. FLAIR axial image, TR/TE 10,000/120 ms **(E,F)**. MR image shows diffuse T2- and FLAIR high-intensity lesions in the white matter with coarsening and vacuolization reminiscent of cavitating leukoencephalopathy **(A–F)**. T2-weighted axial image at age 51 demonstrates new symmetrical lesions in the cerebellar dentate nucleus (arrowhead), central tegmental tract (rectangle), and inferior olivary nucleus (arrow). **(G,H)** T2-weighted axial image after placement under ventilator management at age 53 revealed new symmetrical lesions appearing in the dorsal medulla oblongata (arrowhead) **(I)**.

Supplementary eFigure 3



eFigure 3. Histological and histochemical findings in a biopsy muscle (patient 1)
(A) A biopsy specimen taken from the vastus lateralis muscle showed variability of muscle fiber diameter. **(B)** Moderate lipid increase in muscle fibers. **(C)** Absence of ragged-red fibers. **(D)** Diffuse reduction in COX activity in muscle fibers and a small artery (inset). **(E)** An image of specimen taken from a normal subject stained simultaneously with a section shown in **(D)**. **(F)** Uniform type 2 fiber staining pattern. **(A–F)** Vastus lateralis muscle. **(A)** Hematoxylin and eosin, **(B)** oil red O, and (**C**) modified Gomori trichrome staining, **(D,E)** COX histochemistry, **(F)** ATPase histochemistry at pH 10.6. Bar = 20 μm.

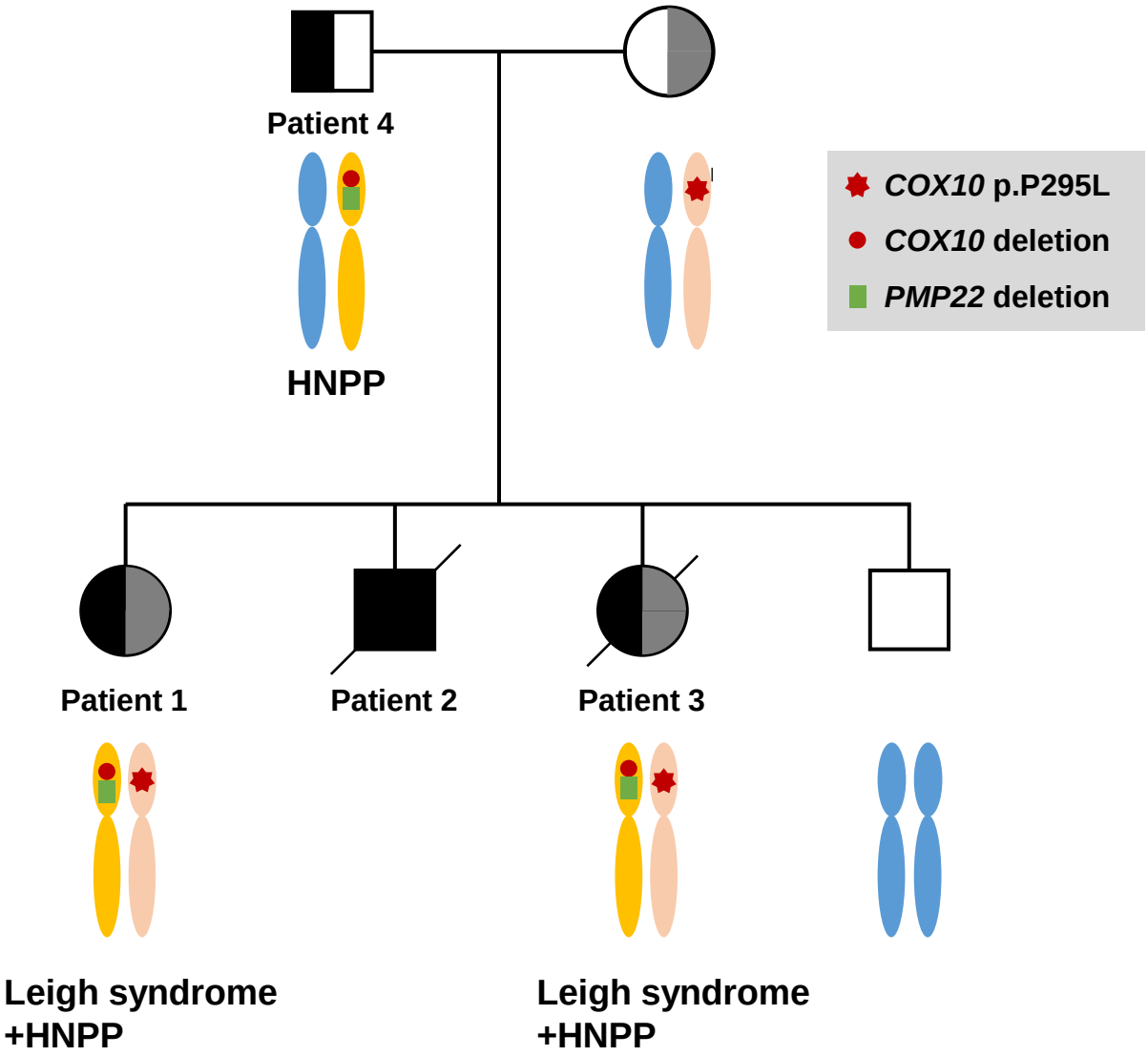
Supplementary eFigure 4



eFigure 4. Protein analysis

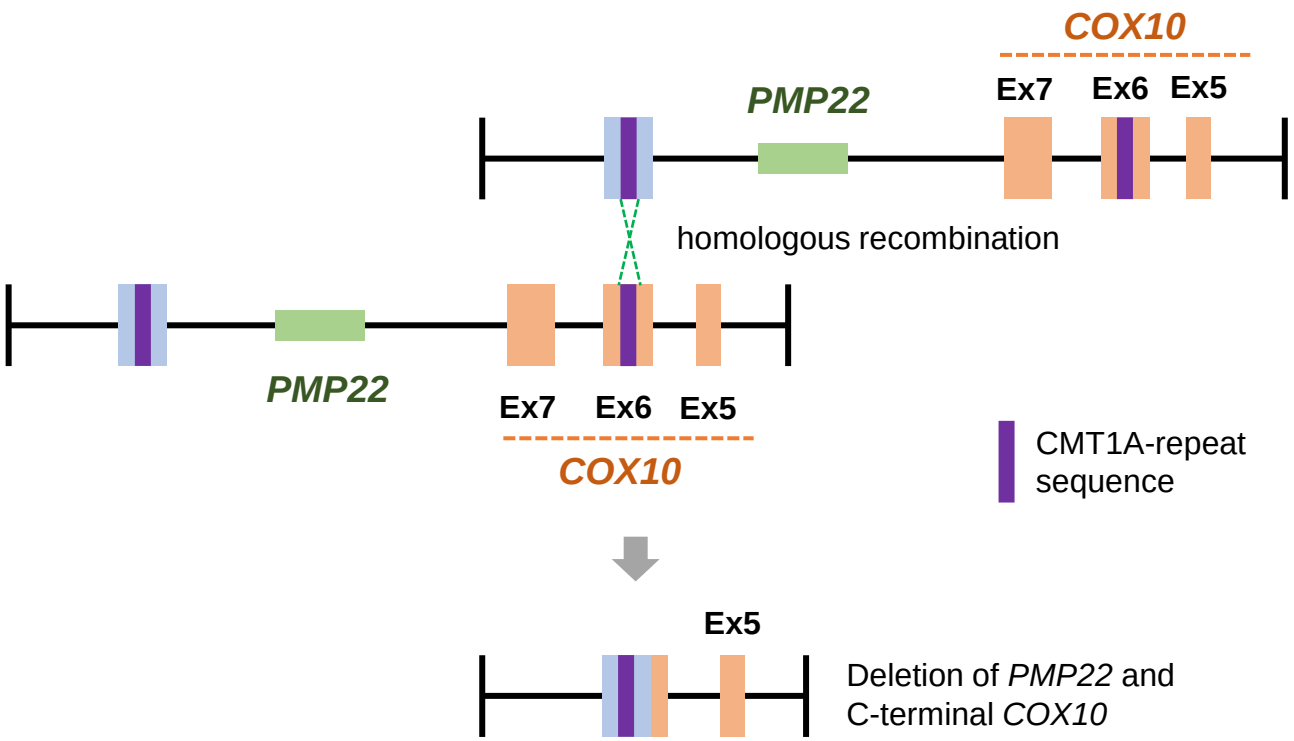
Protein lysates were extracted from the cerebral cortex and white matter of patient 3 (III-3) and two age-matched control subjects. Mitochondrial **(A)** and total lysate fractions **(B)** were separately examined by immunoblot analysis. Low expression levels of COX1/MT-CO1, COX2/MT-CO2, and COX4 complex IV subunits are observed. Samples from cerebral white matter exhibit expression levels that are prominently decreased relative to cortical samples. The level of COX10 protein migrating at 48 kDa, which derived from missense COX10 variant in patient 3 (III-3) was comparable to those of control subjects. Truncated COX10 protein lacking 130 amino acids derived from COX10 deletion was undetectable by the anti-COX10 antibody (HPA-032005) that recognizes N-terminal polypeptides of COX10.

Supplementary eFigure 5



eFigure 5. Correlation between the phenotypes and genotypes
Half shaded in black: subjects with *PMP* deletion and partial *COX10* deletion; half shaded in gray: subjects with *COX10* missense mutation. *PMP* deletion is associated with late-onset HNPP in Patient 4 and may modulate neuropathic phenotype in Patients 1 and 3 with Leigh syndrome. The discordant clinical phenotypes among family members could be explained by multiple genetic mutations within the pedigree.

Supplementary eFigure 6



eFigure 6. Homologous recombination of *COX10* and *PMP22* mediated by CMT1A-REP sequences

By homologous recombination between misaligned CMT-REP sequences, the deletion allele results in a truncation of COX10 lacking its C-terminus. Modified from Reiter *et al*.[7)]

Supplementary eTable 1. Results of NCV study

	Patient 1 (III-1)	Patient 3 (III-2)	Patient 4 (II-5)
Left Median nerve			
MCV (m/s)	**33.5**	**25.8**	63.3
Distal latency (ms)	**5.83**	-	**6.51**
CMAP (mV)	**1.24**	-	6.14
SCV (m/s)	N.E.	-	**48.0**
SNAP (μV)	N.E.	-	9.90
Left Tibial nerve			
MCV (m/s)	N.E.	-	44.9
Distal latency (ms)	N.E.	-	**5.60**
CMAP (mV)	N.E.	-	8.70
Left Sural nerve			
SCV (m/s)	N.E.	-	41.7
SNAP (μV)	N.E.	-	7.60

NCV, nerve conduction velocity; MCV, motor nerve conduction velocity; CMAP, compound muscle action potential; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential; N.E., not evoked; abnormal values are shown in **bold**.

Supplementary eTable 2. Respiratory chain activities in biopsied muscle and fibroblasts

		Co I	Co II	Co III	Co IV
Muscle	CS ratio (%)	44.1	98.2	72.3	**25.4**
	Co II ratio (%)	43.8		72.1	**24.5**
Fibroblasts	CS ratio (%)	68.5	64.4	61.7	**24.9**
	CoII ratio (%)	105.2		94.4	**37.6**

Co I, complex I, Co II, complex II; Co III, complex III; Co IV, complex IV; CS, citrate synthase. Abnormal values are shown in **bold.**

Supplementary eTable 3. *COX10* variants identified by whole exome sequence analysis

***COX10* variant**	**Nucleotide change***	***in silico* analyses**			**Allele frequency in publicly available database**			
		CADD	**Polyphen-2**	**SIFT**	**gnomAD**	**ExAC**	**ToMMo**	**HGVD**
p.Arg159Glu	c.476G>A	23.3	benign	tolerated	49.6%	49.5%	48.1%	49.1%
p.Pro295Leu	c.884C>T	27.8	probably damaging	deleterious	0.001%	0.002%	not registered	not registered

*Nucleotide numbering is based on NM_001303.4. Polyphen-2, http://genetics.bwh.harvard.edu/pph2/; SIFT, https://sift.bii.a-star.edu.sg/; gnomAD, https://gnomad.broadinstitute.org/; ExAC, https://gnomad.broadinstitute.org/; ToMMo, https://jmorp.megabank.tohoku.ac.jp/202102/variants; HGVD, https://www.hgvd.genome.med.kyoto-u.ac.jp/