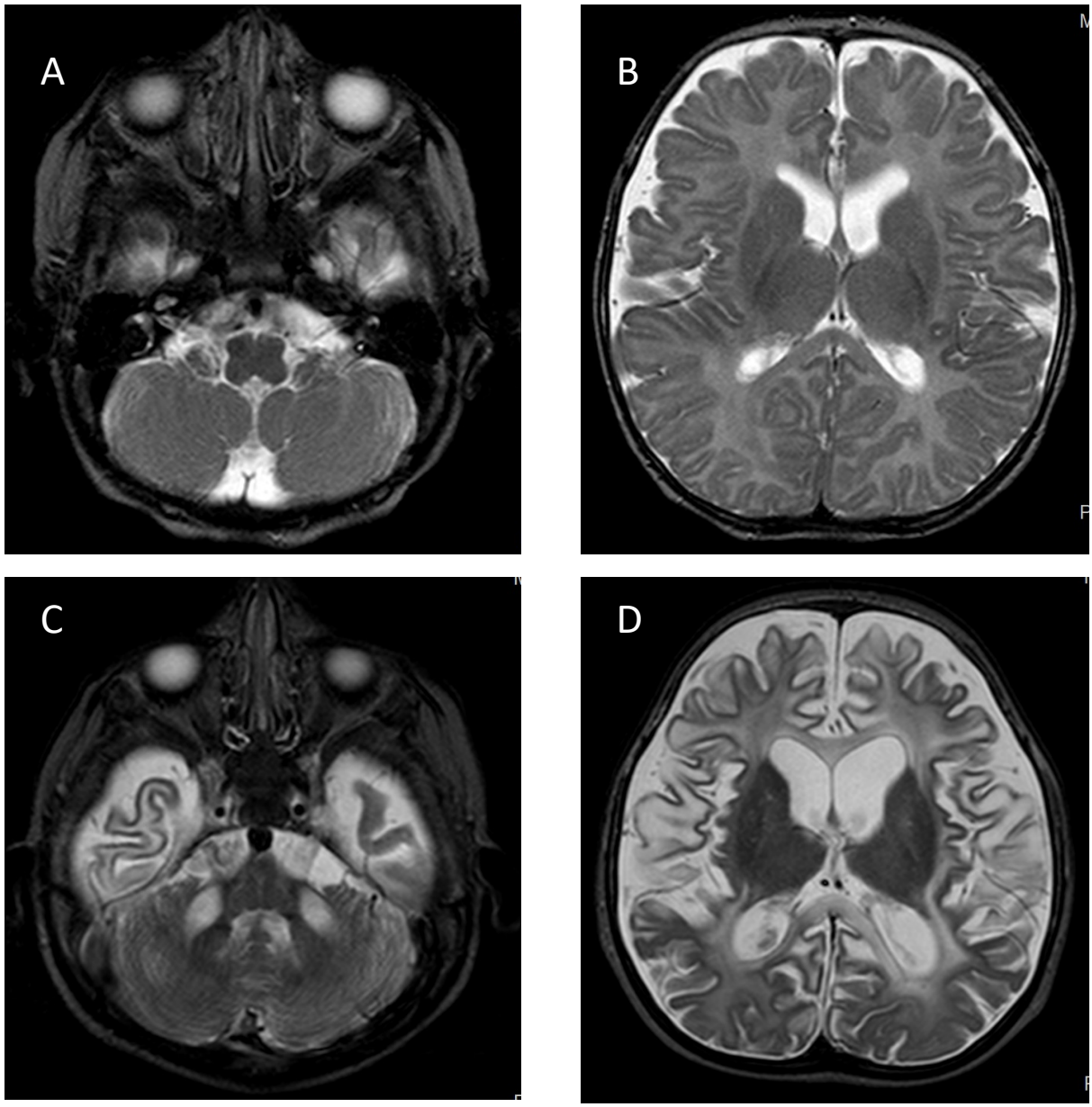

Figure S1. Patient X1 MRI imaging. Axial MRI at 2.5 months (A, B) and 6.3 months (C, D), shows progressive volume loss, dentate nucleus lesions, and diffuse white matter disease, with relative preservation of the basal ganglia. MRS was normal at 2.5 months, and technically failed at 6.3 months.

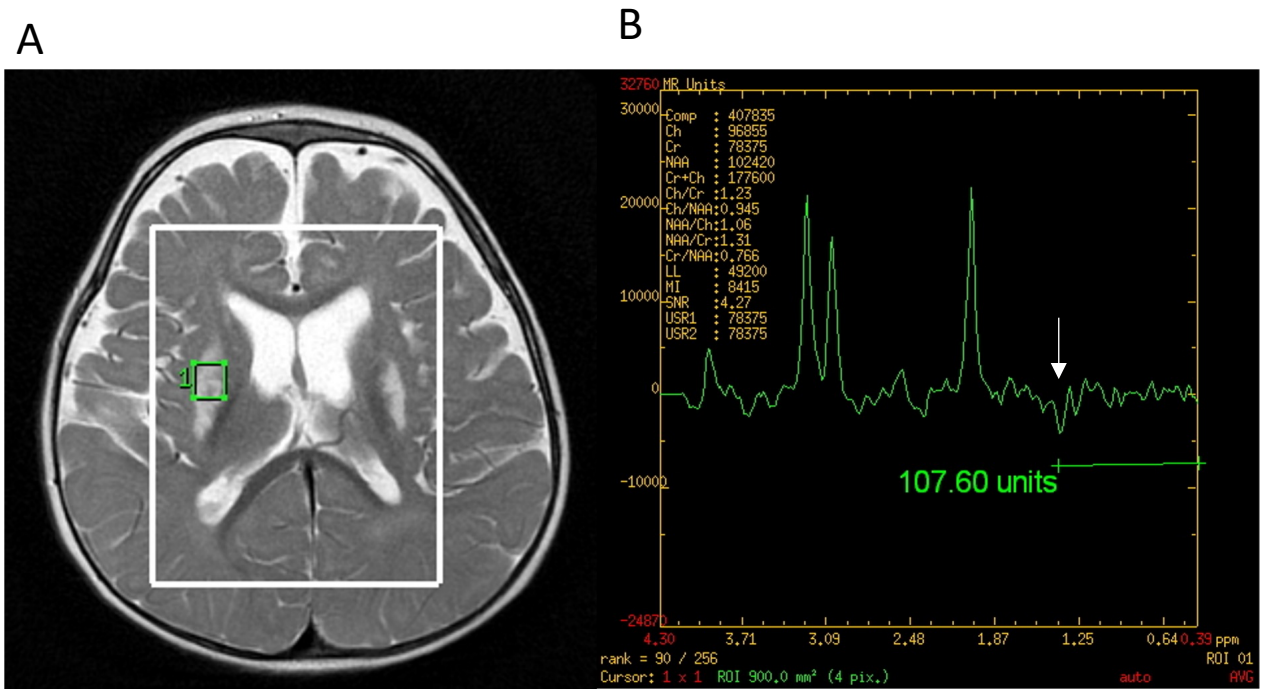

Figure S2. Individual X2 MRI imaging. (A) Axial T2-weighted image at the basal ganglia level shows bilateral hyperintensity, mainly in the lentiform nuclei (green square). Relatively prominent Sylvian fissure and frontal extra-axial space with mild brain atrophy can also be seen. (B) Single voxel spectrum acquired from the region of interest (green square) showing increased lactate with a level of 107.60 arbitrary units (the inverted doublet at 1.33 ppm). p.p.m., parts per million.

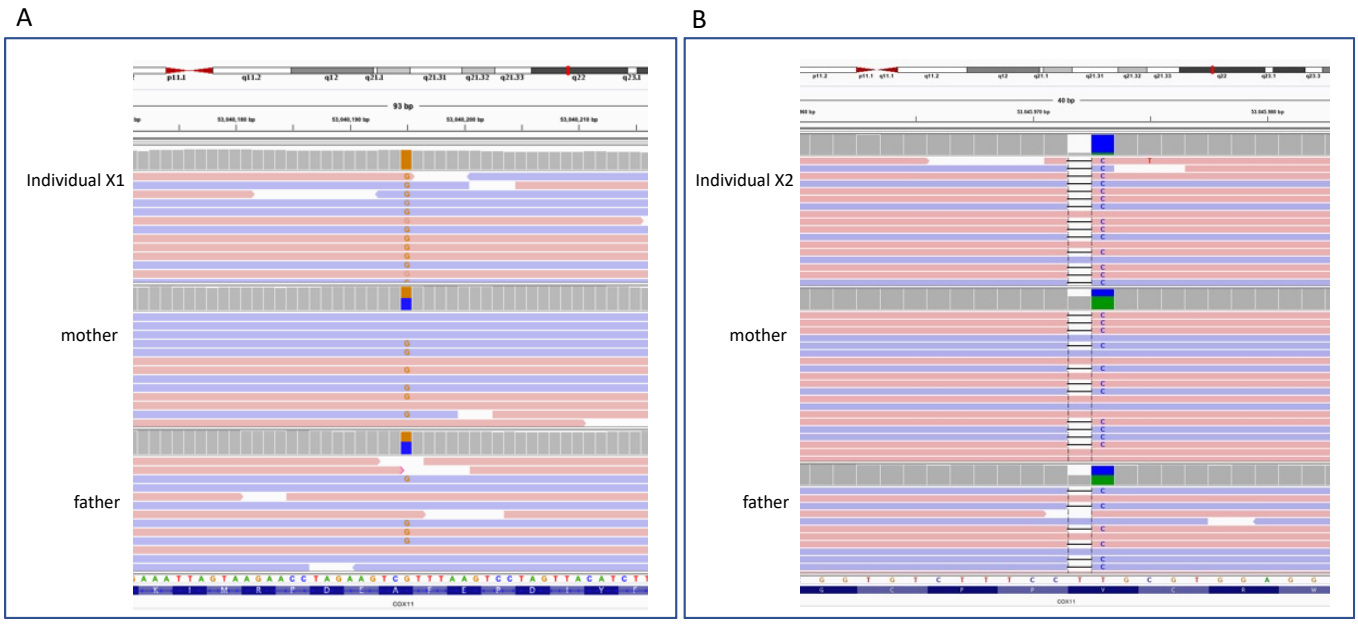

Figure S3. Integrative Genomics Viewer (IGV) screenshot of sequence alignment in *COX11*. (A) Trio GS identified a homozygous variant NM_004375.4:c.730G>C NP_004366.1:p.(Ala244Pro) in individual X1 with both parents being heterozygous. (B) Trio ES identified a homozygous variant NM_004375.4:c.35_36delinsG NP_004366.1:p.(Val12Glyfs*21) in individual X2, with both parents being heterozygous.

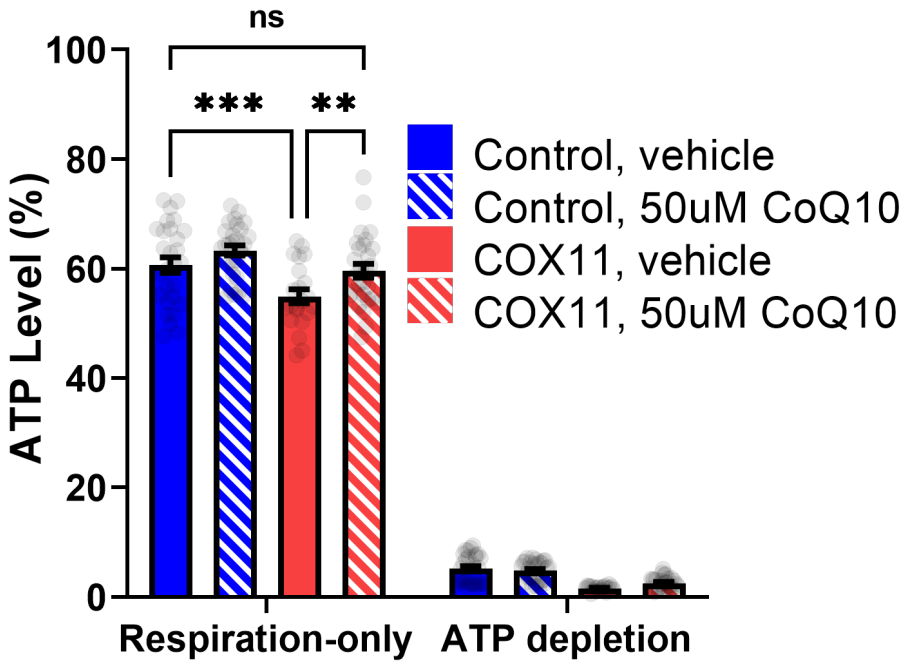

Figure S4 COX11 patient cells have decreased respiration-derived ATP levels, which can be restored with CoQ_{10}. Patient X1 (*COX11*) fibroblasts were treated with either 50 μM CoQ_{10} in dimethylformamide or vehicle control for 5 days, prior to treating the cells in either basal, respiration-only, or ATP-depleting conditions for 8 hours, before measuring ATP content using the CellTiter-Glo 2.0 luciferase assay for ATP. The ATP levels presented are relative to their respective basal ATP levels (100%). Vehicle-treated patient X1 fibroblasts had significantly reduced ATP in respiration-only conditions compared to vehicle-treated control cells ($p<0.001$), while CoQ_{10} supplementation significantly increased ATP levels in patient X1 cells ($p=0.0029$). Data show mean ± SEM; n=22-28 wells per condition, compiled from six independent experiments. ***$p<0.001$, **$p<0.01$ by two-way ANOVA with Tukey's multiple comparison's

test.

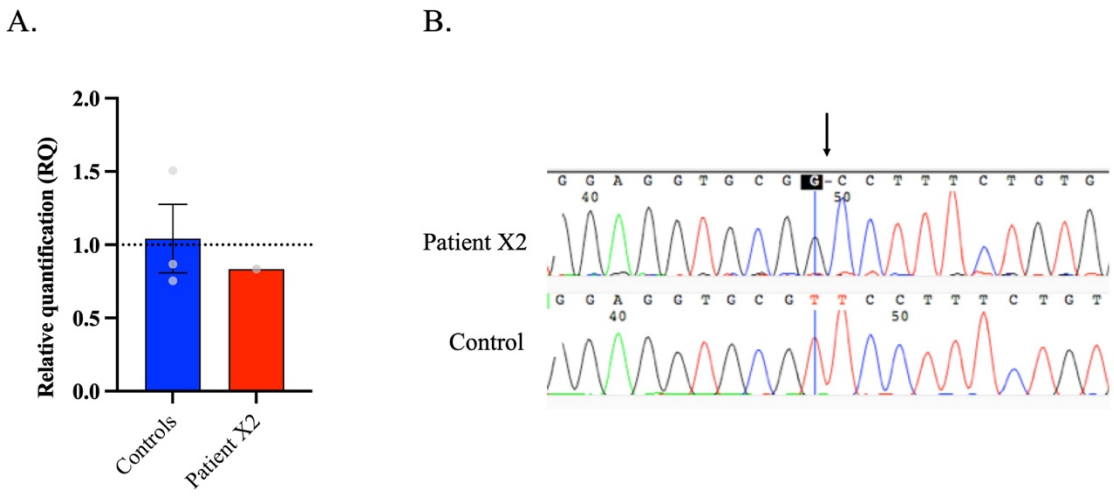

Figure S5 Relative expression of *COX11* in patient X2 and cDNA sequencing.

A) The relative expression of *COX11* mRNA extracted from blood from patient X2 was similar to controls (n=3). The expression level was normalized to *HPRT1* and expressed relative to the average of controls. Samples were analyzed from a single blood draw, with three technical replicates. Data show mean ± SD. B) Partial electropherogram showing *COX11* cDNA Sanger sequencing from blood, showing a NM_004375.4:c.35_36delinsG NP_004366.1:p.(Val12Glyfs*21) homozygous variant in patient X2.

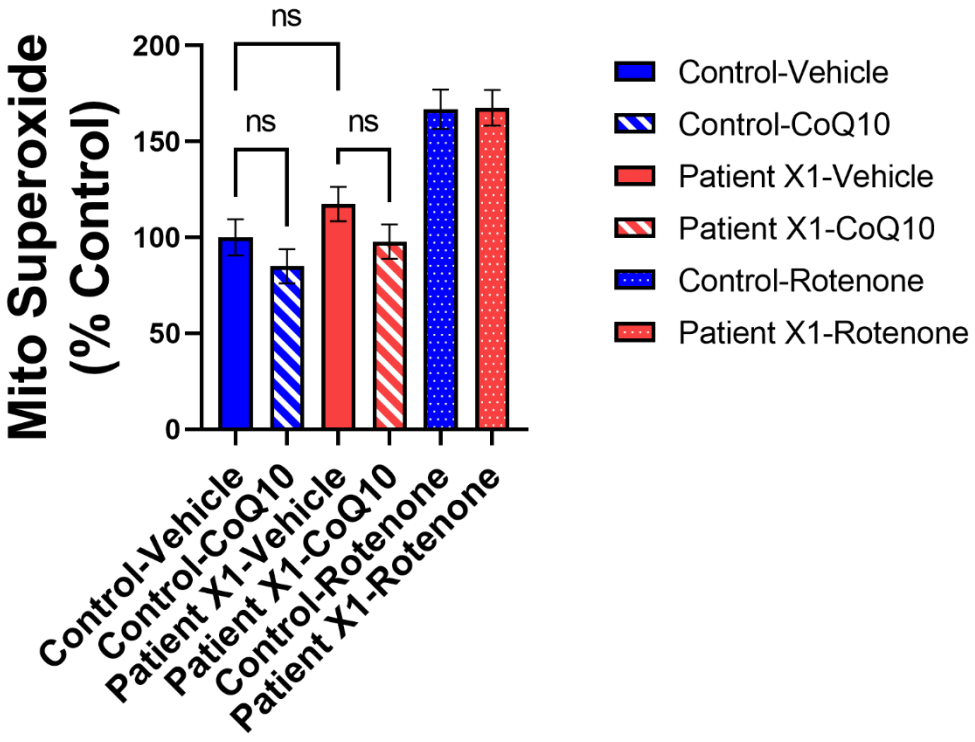

Figure S6 Mitochondrial superoxide is not significantly altered with CoQ_{10} treatment. Control and Patient X1 fibroblasts were incubated with 50 uM CoQ_{10} or vehicle control for 5 days, before staining with 2.5 uM MitoSOX to measure mitochondrial superoxide. While there was a slight MitoSOX decrease with CoQ10 treatment, this did not reach significance. Data shown are mean MitoSOX fluorescence measured by flow cytometry compiled from two experiments, n = 2, error bars are mean ± SEM, n.s is not significant by one-way ANOVA with Tukey's multiple comparisons test. Data shown are mean MitoSOX fluorescence measured by flow cytometry compiled from two experiments, error bars are mean ± SEM.

Table S1. *In silico* Predictions for NP_004366.1:p.(Ala244Pro) variant in Individual X1

***In silico* tool**	**Predictions**
CADD	deleterious (25.7)
MetaRNN	damaging (0.6731)
REVEL	benign (0.162)
PolyPhen-2	probably damaging (0.961)
SIFT	tolerated (0.15)
MutationTaster	disease causing (0.9999)
EIGEN	pathogenic (0.7035)
FATHMM_MKL	damaging 0.9862

CADD (http://cadd.gs.washington.edu/) MetaRNN (http://www.liulab.science/metarnn.html) REVEL (https://sites.google.com/site/revelgenomics/) PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2), SIFT (http://sift.jcvi.org), Mutation Taster (http://www.mutationtaster.org), EIGEN (http://www.columbia.edu/~ii2135/eigen.html) , fathmm-MKL (http://fathmm.biocompute.org.uk).

Table S2. *In silico* Predictions of the Mitochondrial Targeting Sequence for Individual X2

***In silico* tool**	**Predictions**	**COX11 WT**	**COX11 p.(Val12Glyfs*21)**
MitoFates	Presequence predictions	Possessing mitochondrial presequence	No target sequence detected
	Probability for mitochondria localization (range 0-1)	0.996	0.112
	Predicted cleavage site	Amino acid 19	NA
TPpred 3.0	Protein localization prediction	Mitochondrion	No target sequence detected
	Predicted cleavage site	Amino acid 28	NA

NA= not applicable

MitoFates (https://mitf.cbrc.jp/MitoFates/cgi-bin/top.cgi), TPpred (https://tppred3.biocomp.unibo.it/welcome/default/index)

Table S3. Mitochondrial disease criteria

Features	Mitochondrial disease criteria (MDC)*	Max Score	Patient X1	Patient X2
Muscular	Myopathy	2	NA	NA
	Abnormal EMG		NA	NA
	Motor developmental delay		1	1
	Exercise intolerance		NA	NA
	TOTAL		**1**	**1**
Neurological	Developmental delay or ID	2	1	1
	Speech delay		NA	1
	Dystonia		1	0
	Ataxia		NA	0
	Spasticity		NA	0
	Neuropathy		NA	NA
	Seizures of encephalopathy		1	1
	TOTAL		**2 (max)**	**2 (max)**
Multisystem	Any GIT disease	3	1	1
	Growth delay or failure to thrive		1	1
	Endocrine		NA	0
	Immune		NA	0
	Eye (vision) or Hearing		1	NA
	Renal tubular acidosis		NA	0
	Cardiomyopathy		NA	0
	TOTAL		**3**	**2**
TOTAL CLINICAL		4	**4 (max)**	**4 (max)**
Metabolic	Lactate high at least 2x: (score 2)	4	2	2
	Alanine high at least 2x		0	0

	Krebs' cycle intermediates (alpha-ketoglutarate, succinate, fumarate)		0	0
	Ethyl malonic acid methyl malonic acid		0	0
	3 methyl glutaconic acid		0	0
	CSF lactate, alanine		1	0
Imaging/other	Leigh disease (score 2)		0	0
	Stroke like episodes (score 2)		0	0
	Lactate peak on MRS		NA	1
	Leukoencephalopathy with brainstem and spinal cord involvement		0	0
	Cavitating leukoencephalopathy		0	0
	Leukoencephaloparhy with thalamus involvement		0	0
	Deep cereberal white matter involvement and CCA		1	0
TOTAL METABOLIC & IMAGINING			**4 (max)**	**3**
TOTAL MDC score (clinical, metabolic, imaging)		8	**8 (max)**	**7**

EVALUATION	
TOTAL SCORE	**MITOCHONDRIAL DISORDER**
1	unlikely
2-4	possible
5-7	probable
8	definite

*Adopted from Witters et al (2018). Every element scores 1 unless indicated differently. The severity of each finding is not taken into account due to the progressive nature of the disease.NA- not applicable or not available.