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Original Communication

Dystonia and Parkinsonism in COA7-Related Disorders: Expanding the Phenotypic Spectrum

Author information

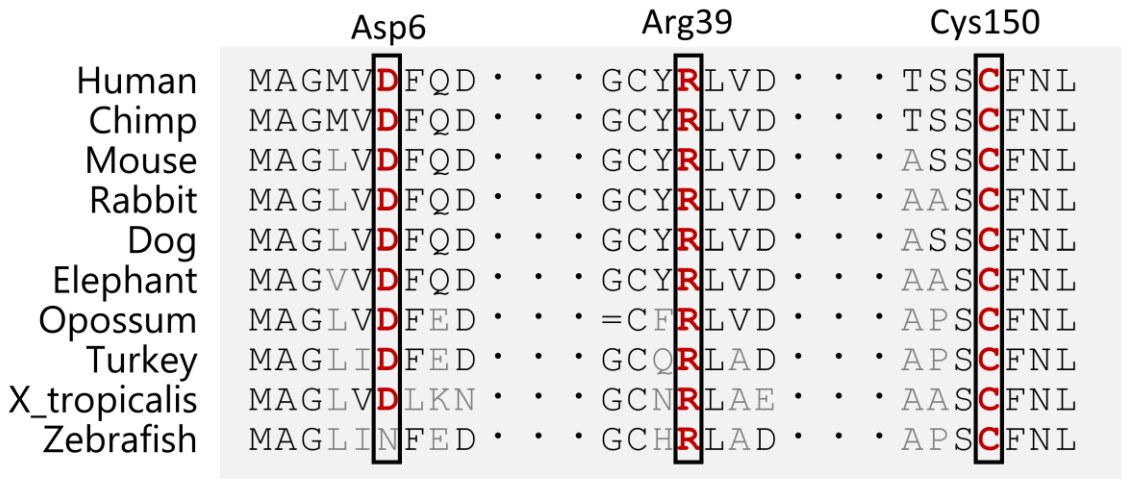
Yujiro Higuchi, MD, PhD[1)], Masahiro Ando, MD, PhD[1)], Fumikazu Kojima, MD [1)], Junhui Yuan, MD, PhD[1)], Akihiro Hashiguchi, MD, PhD[1)], Akiko Yoshimura, PhD[1)], Yu Hiramatsu, MD, PhD[1)], Satoshi Nozuma, MD, PhD[1)], Shinobu Fukumura, MD, PhD[2)], MD, PhD, Hiroyuki Yahikozawa, MD, PhD[3)], Erika Abe, MD, PhD[4)], Itaru Toyoshima, MD, PhD[4)], Masashiro Sugawara, MD, PhD[5)], Yuji Okamoto, MD, PhD[1)6)], Eiji Matsuura, MD, PhD[1)], and Hiroshi Takashima, MD, PhD[1)*].

1) Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan
2) Department of Pediatrics, Sapporo Medical University School of Medicine, Sapporo, Japan
3) Yahikozawa Internal Medicine and Neurology Clinic, Nagano, Japan
4) Department of Neurology, National Hospital Organization Akita National Hospital, Yurihonjo, Japan
5) Department of Neurology, Akita University Graduate School of Medicine, Akita, Japan
6) Department of Physical Therapy, School of Health Sciences, Faculty of Medicine, Kagoshima University, Kagoshima, Japan

Corresponding author: Hiroshi Takashima, Email: thiroshi@m3.kufm.kagoshima-u.ac.jp

Supplementary Information

Supplementary figure 1: Conservation analysis



Comparison of *COA7* across different species. Asparatic acid 6, Arginine 39 and Cystein 150 are highly conserved among listed species.

Supplementary figure 2: Evaluation of the structural model of COA7 mutant p.Cys150Tyr by SWISS-MODEL.

Results

The SWISS-MODEL template library was searched for evolutionary related structures matching the target sequence in Table T1. For details on the template search, see Materials and Methods. Overall 1 templates were found (Table T2).

Models

The following model was built (see Materials and Methods "Model Building"):

Model #01	File	Built with	Oligo-State	Ligands	GMQE	QMEANDisCo Global
	PDB	ProMod3 3.2.1	monomer	None	0.97	0.91 ± 0.06

Template	Seq Identity	Oligo-state	QSQE	Found by	Method	Resolution	Seq Similarity	Range	Coverage	Description
7mqz.1.A	99.52	monomer	-	USER ALIGNMENT	X-ray	2.39Å	0.63	1 - 209	1.00	Cytochrome c oxidase assembly factor 7

The template contained no ligands.

```
Target    EEQVKSFLENMEVECNYHCYHEKDPDGCYRLVDYLEGIRKNFDEAAKVLKFNCEENQHSDSCYKLGAYYVTGKGGLTQDL
7mqz.1.A  EEQVKSFLENMEVECNYHCYHEKDPDGCYRLVDYLEGIRKNFDEAAKVLKFNCEENQHSDSCYKLGAYYVTGKGGLTQDL

Target    KAAARCFLMACEKPGKKSIAACHNVGLLAHDGQVNEDGQPDLGKARDYYTRACDGGYTSSYFNLSAMFLQGAPGFPKDMD
7mqz.1.A  KAAARCFLMACEKPGKKSIAACHNVGLLAHDGQVNEDGQPDLGKARDYYTRACDGGYTSSCFNLSAMFLQGAPGFPKDMD

Target    LACKYSMKACDLGHIWACANASRMYKLGDGVDKDEAKAEVLKNRAQQLH
7mqz.1.A  LACKYSMKACDLGHIWACANASRMYKLGDGVDKDEAKAEVLKNRAQQLH
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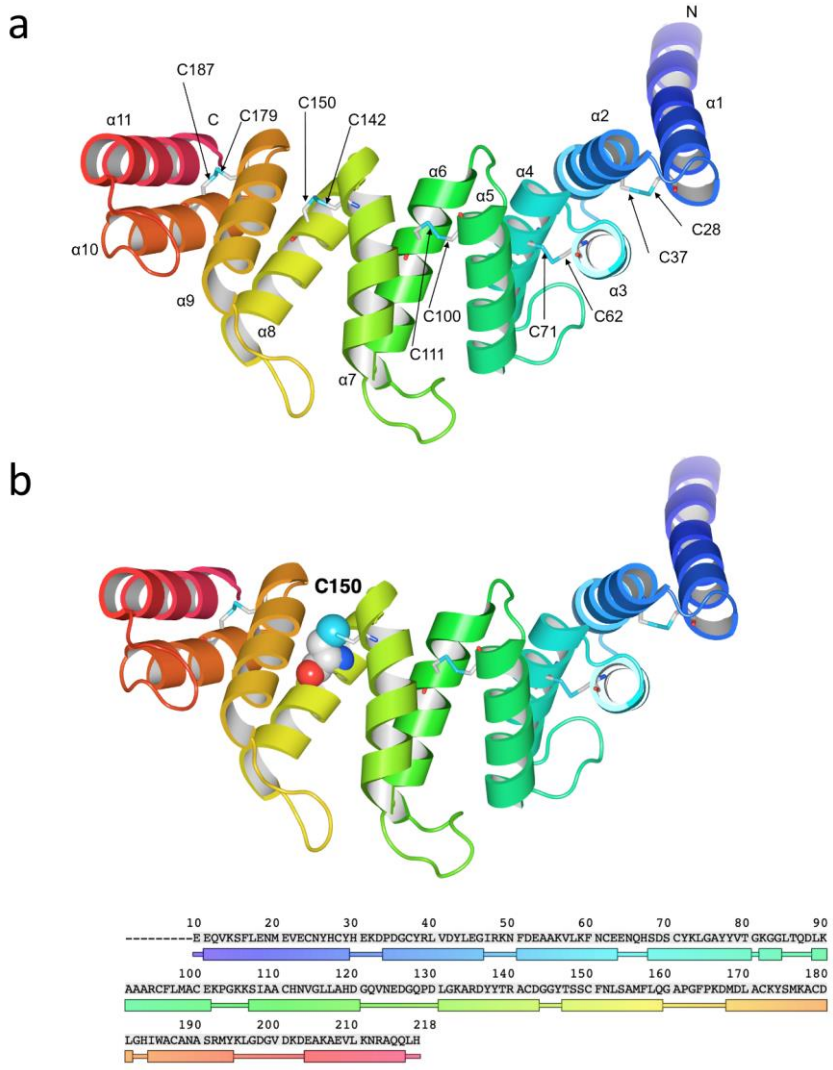
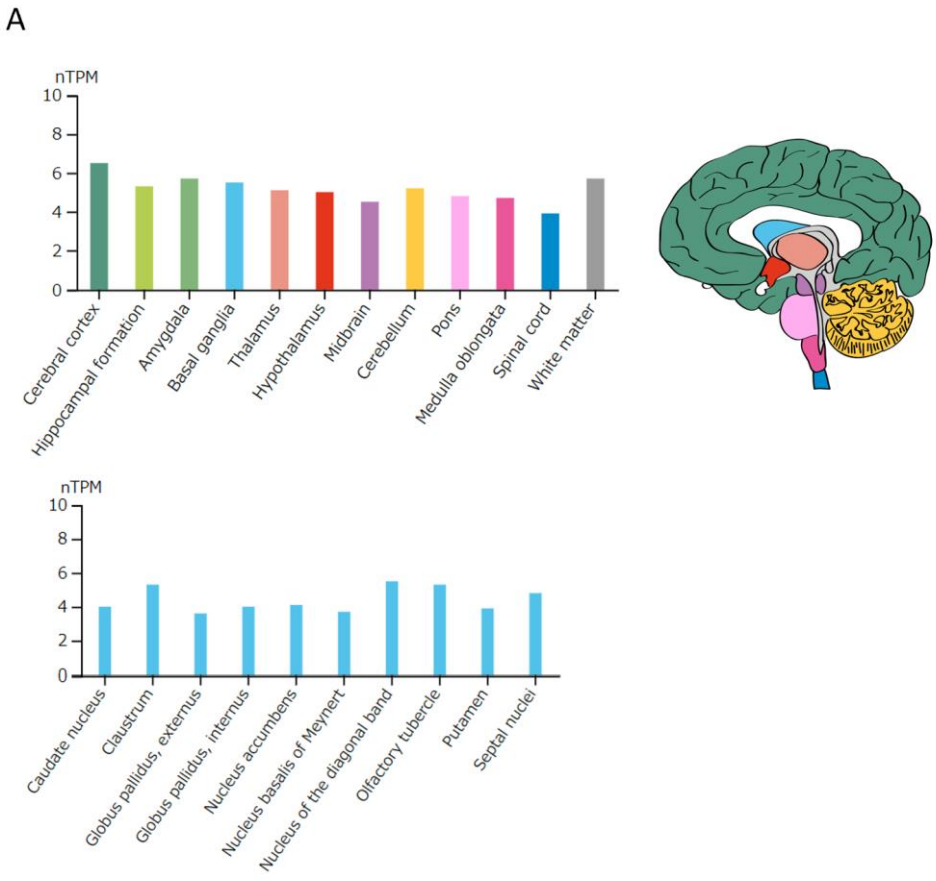
The quality of the structural model generated by SWISS-MODEL is evaluated using the QMEANDisCo Global score, which is 0.91±0.06 (recommended threshold: 0.5 or higher), indicating that the constructed model met the reliability criteria for modelling.

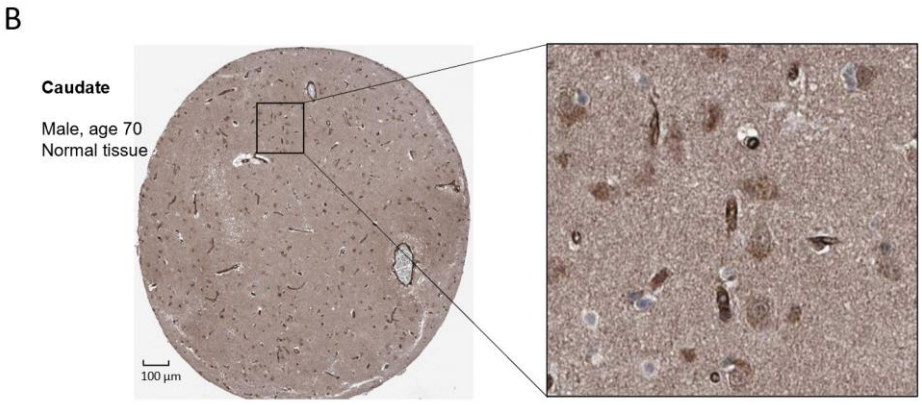
Supplementary figure 3: Disulfide bond and position of Cys150 on the three-dimensional structure of human COA7



The three-dimensional structure of COA7 (PDB ID: 7MQZ) is shown in ribbon format with a blue-to-red gradient from the N-terminus to the C-terminus. The cysteine residues involved in disulfide bond formation are depicted in stick format, with carbon atoms in gray, oxygen atoms in red, nitrogen atoms in blue, and sulfur atoms in cyan. Figure a shows the positions of the disulfide bonds, while Figure b displays Cys150 in a space-filling model (top) and the amino acid sequence (bottom). Human COA7 is composed of 11 alpha helices (α1-α11), including five helix-turn-helix repeats (α/α repeats) and a single alpha helix at the C-terminus. Each of the 13 cysteine residues in COA7, of which 10 form disulfide bonds (Cys28-Cys37, Cys62-Cys71, Cys100-Cys111, Cys142-Cys150, Cys179-Cys187) between alpha helices in the α/α repeats. Supplementary Figure 3b shows the position of Cys150 in the three-dimensional structure of COA7. Cys150 is located in alpha helix 8 of the fourth α/α repeat (repeat_4) of COA7 and forms a disulfide bond with Cys142 in alpha helix 7 of the same repeat_4.

Supplementary figure 4: COA7 expression data in the central nervous system obtained from the Human Protein Atlas project





(A) Normalized RNA expression levels (nTPM) of COA7 in brain. RNA expression is widely observed in the brain including cerebral cortex, cerebellum, brain stem, basal ganglia and spinal

cord. It is also expressed in caudate nucleus, globus pallidus and putamen. RNA expression summary shows the consensus data based on normalized expression (nTPM) values from two different sources: internally generated Human Protein Atlas (HPA) RNA-seq data and RNA-seq data from the Genotype-Tissue Expression (GTEx) project. Color-coding is based on tissue groups, each consisting of tissues with functional features in common.

(B) Immunohistochemical (IH) staining with an anti-COA7 antibody (HPA028154) shows moderate expression of COA7 (brown) in neuronal cells in the caudate, but low in glial cells. Human Protein Atlas project: http://www.proteinatlas.org

Supplementary table 1: Targeted CMT/IPN-related gene panels for DNA microarray and NGS.

Microarray Chip sequencing (28 genes)	*AARS1*	*APTX*	*DNM2*	*EGR2*	*GAN1*	*GARS*	*GDAP1*	*GJB1*
	HSPB1	*HSPB8*	*LITAF*	*LMNA*	*LMNA*	*MFN2*	*MPZ*	*MTMR2*
	NDRG1	*NEFL*	*PMP22*	*PRX*	*RAB7*	*SBF2*	*SETX*	*SH3TC2*
	SLC12A6	*SOX10*	*TDP1*	*YARS1*				

1st CMT gene panel (60 genes)	*AARS1*	*APTX*	*ARHGEF10*	*DHH*	*DNM2*	*EGR2*	*FGD4*	*FIG4*
	GAN	*GARS*	*GDAP1*	*GJB1*	*HARS*	*HK1*	*HOXD10*	*HSPB1*
	HSPB8	*KARS*	*LITAF*	*LMNA*	*MARS*	*MED25*	*MFN2*	*MPZ*
	MTMR2	*NDRG1*	*NEFL*	*PMP22*	*PRPS1*	*PRX*	*RAB7A*	*SBF2*
	SETX	*SH3TC2*	*SLC12A6*	*SOX10*	*TDP1*	*TRPV4*	*TTR*	*YARS*
	20 candidate gene							

2nd CMT gene panel (72 genes)	*AARS*	*APTX*	*ARHGEF10*	*COA7*	*DHH*	*DNM2*	*EGR2*	*FGD4*
	FIG4	*GAN*	*GARS*	*GDAP1*	*GJB1*	*HARS*	*HK1*	*HOXD10*
	HSPB1	*HSPB8*	*KARS*	*LITAF*	*LMNA*	*MARS*	*MED25*	*MFN2*
	MPZ	*MTMR2*	*NDRG1*	*NEFL*	*PMP22*	*PRPS1*	*PRX*	*RAB7A*
	SBF2	*SETX*	*SH3TC2*	*SLC12A6*	*SOX10*	*TDP1*	*TRPV4*	*TTR*
	YARS	*BSCL2*	*DCTN1*	*DHTKD1*	*DYNC1H1*	*FBLN5*	*FBXO38*	*GJB3*
	GNB4	*HSPB3*	*IGHMBP2*	*INF2*	*KIF1A*	*LRSAM1*	*PDK3*	*REEP1*
	SBF1	*SLC5A7*	*TFG*	*TRIM2*	*DCAF8*	*MME*	*SURF1*	*SACS*
	GALC	*PLEKHG5*	*6 Candidate genes*					

3rd CMT gene panel (103 genes)	*AARS1*	*AIFM1*	*ATP1A1*	*BSCL2*	*COX6A1*	*DCTN1*	*DHTKD1*	*DYNC1H1*
	EGR2	*FGD4*	*FIG4*	*GARS1*	*GDAP1*	*GNB4*	*HSPB1*	*HSPB3*
	HSPB8	*IGHMBP2*	*INF2*	*KARS1*	*LITAF*	*LMNA*	*LRSAM1*	*MARS1*
	MCM3AP	*MFN2*	*MME*	*MORC2*	*MPV17*	*MPZ*	*MTMR2*	*NAGLU*
	NDRG1	*NEFH*	*NEFL*	*PDK3*	*PLEKHG5*	*PMP2*	*PMP22*	*PNKP*
	PRPS1	*PRX*	*RAB7A*	*REEP1*	*SBF1*	*SBF2*	*SH3TC2*	*SIGMAR1*
	SLC25A46	*SLC5A7*	*SORD*	*SPG11*	*SURF1*	*VCP*	*WARS1*	*YARS1*
	APTX	*ARHGEF10*	*COA7*	*DNM2*	*FBLN5*	*GALC*	*GAN*	*GJB1*
	GJB3	*HARS1*	*HOXD10*	*KIF1A*	*SACS*	*SETX*	*SLC12A6*	*TDP1*
	TFG	*TRPV4*	*TTR*	*BAG3*	*DRP2*	*HINT1*	*LMNA*	*PDXK*
	POLG	*SCO2*	*ABHD12*	*SLC52A3*	*ATL1*	*ATL3*	*DNMT1*	*NTRK1*
	PRDM12	*SCN11A*	*SCN9A*	*SPTLC1*	*SPTLC2*	*WNK1*	*BICD2*	*DNAJB2*
	LAMA2	*GNE*	*SOD1*	*FUS*	*3 Candidate genes*			

Supplementary table 2: Prediction scores and allele frequency of detected variants in the *COA7* gene

Mutation		c.17A>G	c.115C>T	c.449G>A
Protein		p.Asp6Gly	p.Arg39Trp	p.Cys150Tyr
Position (GRCh38)		chr1:52698310	chr1:52692859	chr1:52687967
Reference		T	G	G
Alternate		C	A	A
dbSNP ID		rs780572767	rs768084335	None
Prediction scores	SIFT	0.014 (damaging)	0.029 (deleterious)	0 (Damaging)
	Polyphen2	0.86 (possible damaging)	1.00 (probably damaging)	0.325 (benign)
	PROVEAN	-3.71(damaging)	-4.51(Damaging)	-10.61(Damaging)
	MutationTaster	1 (disease causing)	0.9999 (disease causing)	1 (disease causing)
	CADD (PHRED score)	23.7 (deleterious)	27.5 (deleterious)	26.1 (deleterious)
MAF	jMorp (ToMMo 38KJPN)	C=0.000542 (44/77,444) homozygous count = 0	C=0.000103 (8/77,444) homozygous count = 0	NE
	ExAC	C=0.000008 (1/120,268) homozygous count = 0	NE	NE
	gnomAD	C=0.000004 (1/248,356) homozygous count = 0	C=0.000004 (1/251398) homozygous count = 0	NE

CADD = Combined Annotation Dependent Depletion (https://cadd.gs.washington.edu/snv); ESP = Exome Sequencing Project database (http://evs.gs.washington.edu/EVS/); jMorp: https://jmorp.megabank.tohoku.ac.jp/; ExAC = Exome Aggregation Consortium database (http://exac.broadinstitute.org/); HGVD = The Human Genetic Variation Database; MAF = minor allele frequency; NE = not exist; PROVEAN = Protein Variation Effect Analyzer; SIFT = Sorting Intolerant from Tolerant;

Supplementary table 3: Electrophysiological findings of patients carrying biallelic variants in *COA7* in current and previous reports)

Patient No.			This study			Our past cases[1)]				Case by Anabel et al[2)]	Case by Ban et al[3)]	Case by Ouchi et al[4)]
			Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age at examination			8	76	39	62	15	26	23	n.a	n.a	60
Nerve	Median	DL	2.5	3.6	n.a	3.9	3.1	3.8	3.6	n.a	n.a	Normal in both limbs
		MCV	50.9	54.7	58.2	50.5	50.0	49.6	50.5	n.a	n.a	
		dCMAP	17.1	5.1	1.8	8.0	4	4.7	14.0	n.a	n.a	
		SCV	ND	45.8	ND	ND	ND	ND	ND	n.a	n.a	
		SNAP	ND	2.0	ND	ND	ND	ND	ND	n.a	n.a	
	Ulnar	DL	NE	2.8	n.a	3.0	NA	2.9	n.a	n.a	n.a	
		MCV	NE	66.7	n.a	61.8	56.5	52.8	n.a	n.a	n.a	
		dCMAP	NE	4.4	n.a	7.4	NA	9.0	n.a	n.a	n.a	
		SCV	NE	59.1	ND	ND	NA	ND	ND	n.a	n.a	
		SNAP	NE	0.6	ND	ND	NA	ND	ND	n.a	n.a	
	Tibial	DL	4.1	ND	ND	ND	ND	ND	n.a	n.a	n.a	n.a
		MCV	45.8	ND	ND	ND	ND	ND	n.a	n.a	n.a	33.9
		dCMAP	9.86	ND	ND	ND	ND	ND	1.5	n.a	n.a	0.26
	Peroneal	DL	NE	NE	n.a	NE	ND	n.a	n.a	n.a	n.a	ND
		MCV	NE	NE	n.a	NE	ND	n.a	n.a	n.a	n.a	ND
		dCMAP	NE	NE	n.a	NE	ND	n.a	n.a	n.a	n.a	ND
	Sural	SCV	ND	ND	ND	ND	ND	ND	ND	n.a	n.a	ND
		SNAP	ND	ND	ND	ND	ND	ND	ND	n.a	n.a	ND

DL: distal latency (ms); MCV: motor conduction velocity (m/s); dCMAP: distal compound muscle action potential (mV); SCV: sensory conduction velocity (m/s); SNAP: sensory nerve action potential (μV); n.a: not available; ND: not detected (evoked); NE: not examined

1) Higuchi Y, Okunushi R, Hara T, Hashiguchi A, Yuan J, Yoshimura A, et al. Mutations in COA7 cause spinocerebellar ataxia with axonal neuropathy. Brain. 2018;141:1622-36.
2) Martinez Lyons A, Ardissone A, Reyes A, Robinson AJ, Moroni I, Ghezzi D, et al. COA7 (C1orf163/RESA1) mutations associated with mitochondrial leukoencephalopathy and cytochrome c oxidase deficiency. J Med Genet. 2016.
3) Ban R, Liu Z, Shimura M, Tong X, Wang J, Yang L, et al. Biallelic COA7-Variants Leading to Developmental Regression With Progressive Spasticity and Brain Atrophy in a Chinese Patient. Front Genet. 2021;12:685035.
4) Ouchi S, Ishii K, Kosaki K, Suzuki H, Yamada M, Takenouchi T, et al. Parkinsonism in spinocerebellar ataxia with axonal neuropathy caused by adult-onset COA7 variants: a case report. BMC Neurol. 2023;23:211.

Supplementary table 4: Mitochondrial and nuclear genes associated with dystonia and parkinsonism

Gene Symbol	Gene/Locus MIM number	Phenotype MIM number	Phenotype	Function
C19orf12	614297	614298	Neurodegeneration with brain iron accumulation 4	mitochondrial iron metabolism
CARS2	612800	616672	Combined oxidative phosphorylation deficiency 27	Aminoacyl-tRNA synthetase
CHCHD2	616244	616710	Parkinson disease 22	destabilization of cytochrome c
CLPB	616254	619813	Neutropenia, severe congenital, 9, autosomal dominant	cellular stress and heat shock responses, chaperone
COA7	615623	618387	Spinocerebellar ataxia, autosomal recessive, with axonal neuropathy	assembly of mitochondrial complex IV, heme-binding protein with disulfide reductase activity
COASY	609855	615643	Neurodegeneration with Brain Iron Accumulation 6 (NBIA6)	biosynthesis of coenzyme A
COX20	614698	619054	Mitochondrial complex IV deficiency, nuclear type 11	assembly of mitochondrial complex IV
COXFA4	603833	619065	Mitochondrial complex IV deficiency, nuclear type 21?	subunit of complex IV (COX)
DNAJC30	618202	619382	Leber hereditary optic neuropathy, autosomal recessive	regulator of mitochondrial respiration, ATP synthase complex, chaperone protein, turnover of the subunits of mitochondrial complex I N-module.
ECHS1D	602292	616277	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency, Leigh-like, dystonia	Mitochondrial short-chain enoyl-CoA hydratase 1
FTL	134790	606159	Neurodegeneration with brain iron accumulation 3	mitochondrial iron metabolism
HTRA2	606441	610297	Parkinson disease 13, Encephalopathy + Dystonia	serine protease、apotosis
LIPT1	610284	616299	Lipoyltransferase 1 deficiency	lipid transfer between the cell membrane and mitochondria, fatty acid metabolism
LIPT2	617659	617668	Encephalopathy, neonatal severe, with lactic acidosis and brain abnormalities	lipid metabolism, transfer of phospholipids between the ER and mitochondria,
LRPPRC	607544	220111	Mitochondrial complex IV deficiency, nuclear type 5	cytoskeletal organization, vesicular transport, transcriptional regulation of both nuclear and mitochondrial genes.
LRRK2	609007	607060	Parkinson syndrome 8	serine/threonine-protein kinase, phosphorylation
MECR	608205	617282	Dystonia, childhood-onset, with optic atrophy and basal ganglia abnormalities	mitochondrial fatty acid synthesis
MT-ND1	516000	-	Alzheimer's/Parkinsonism, Leber hereditary optic neuropathy	mitochondrial complex I subunit
MT-ND4	516003	-	Spastic dystonia, Leber hereditary optic neuropathy	subunit of complex I

MT-ND6	516006	-	Leigh with Complex I deficiency, Dystonia, deafness	subunit of complex I
MT-TK	590060	-	Parkinson syndrome, Neuropathy & Myopathy	mitochondrial tRNA for Lysine
MT-TP	590075	545000	Myopathy, MERRF, parkinsonism	mitochondrial tRNA for Proline
MT-TT	590090	-	Occasional sporadic Parkinsonism	mitochondrial tRNA for Threonine
NDUFA12	614530	618244	Mitochondrial complex I deficiency, nuclear type 23	subunit of complex I
NDUFA2	602137	618235	Mitochondrial complex I deficiency, nuclear type 13	subunit of complex I
NDUFA9	603834	618247	Mitochondrial complex I deficiency, nuclear type 26	subunit of complex I, assembly of complex IV
NDUFAF6	612392	618239	Mitochondrial complex I deficiency, nuclear type 17	assembly and maturation of complex I
NDUFS1	157655	618226	Mitochondrial complex I deficiency, nuclear type 5	subunit of complex I
NDUFS3	603846	618230	Mitochondrial complex I deficiency, nuclear type 8	subunit of complex I
NDUFS6	603848	618232	Mitochondrial complex I deficiency, nuclear type 9	mitochondrial complex I subunit
PANK2	606157	234200	Neurodegeneration with brain iron accumulation 1	coenzyme A biosynthesis
PARK7	602533	606324	Parkinson disease 7	cell protection against oxidative stress and cell death acting as oxidative stress sensor and redox-sensitive chaperone and protease
PINK1	608309	605909	Parkinson syndrome 6 (Recessive; Early onset)	serine/threonine-protein kinase, mitochondrial quality control
PNPT1	610316	614932	Combined oxidative phosphorylation deficiency 13	mitochondrial DNA replication
PRKN	602544	600116	Parkinson disease, juvenile, type 2	component of a multiprotein E3 ubiquitin ligase complex, mitochondrial quality control
SCO2	604272	604377	Mitochondrial complex IV deficiency, nuclear type 2	assembly of mitochondrial complex IV, synthesis and maturation of cytochrome c oxidase subunit II
SERAC1	614725	614739	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome	regulation of mitochondrial phospholipid metabolism and the maintenance of mitochondrial membrane structure and function.
SUCLG1	611224	245400	Mitochondrial DNA depletion syndrome 9	subunit of succinyl CoA synthetase, TCA cycle
SURF1	185620	220110	Mitochondrial complex IV deficiency, nuclear type 1	cytochrome c assembly factor
TACO1	612958	619052	Mitochondrial complex IV deficiency, nuclear type 8	mitochondrial translational activator.
TIMM8A	300356	304700	Deafness-Dystonia-Dementia syndromes, Mohr-Tranebjaerg syndrome	metabolite transporters from cytoplasm to mitochondrial inner membrane
TWNK	606075	609286	Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant 3	mtDNA Helicase, mtDNA maintenance
TXN2	609063	616811	?Combined oxidative phosphorylation deficiency 29	maintaining the proper folding and function of many mitochondrial proteins by reducing disulfide bonds
WARS2	604733	619738	Parkinsonism-dystonia 3, childhood-onset	Aminoacyl-tRNA synthetase