Supplementary Table 2. Diseases caused by recessive mutations in mitochondrial ARSs and associated animal studies. Some mouse ARS knockout models were generated and phenotyped by the International Mouse Phenotyping Consortium (IMPC), with data available at www.mousephenotype.org. Note that in *C. elegans*, the genes corresponding to the mitochondrial alanyl- and valyl-tRNA synthetase genes are *aars-1* and *vars-1*. Other *C. elegans* genes follow the standard pattern of nomenclature, where cytosolic and bifunctional ARS genes are assigned the suffix *-1* and mitochondrial genes are assigned the suffix *-2*.

Human ARS gene	Clinical presentation(s)	Animal studies and disease models
AARS2	• Combined oxidative phosphorylation deficiency 8 [OMIM #614096]; (Gotz et al., 2011; Taylor et al., 2014; Mazurova et al., 2017; Sommerville et al., 2019; Nielsen et al., 2020; van Helden et al., 2021) • Progressive leukoencephalopathy with ovarian failure [OMIM #615889] (Dallabona et al., 2014; Zhou et al., 2019; Fan et al., 2022) • Leukodystrophy without ovarian failure (Sun et al., 2017; Srivastava et al., 2019; Wang et al., 2019; Axelsen et al., 2021) • Early-onset epileptic encephalopathy with hypomyelination (Simons et al., 2015; Nakayama et al., 2017) • Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia *(prev. known as hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) or pigmentary orthochromatic leukodystrophy (POLD))* (Lynch et al., 2016; Taglia et al., 2018) • Primary pulmonary hypoplasia (Kiraly-Borri et al., 2019) • Ataxia without leukoencephalopathy (Srivastava et al., 2019; Kuo et al., 2020; Okamoto et al., 2022) • Retinopathy and optic atrophy (Peragallo et al., 2018)	***C. elegans*** • RNAi *aars-1* knockdown (Zheng et al., 2022a) **Mouse (*Mus musculus*)** • Introduction of editing defective *Aars2* variants (Hilander et al., 2018) • *Aars2* knockout (IMPC data) (Dickinson et al., 2016)
CARS2	• Combined oxidative phosphorylation deficiency 27 [OMIM #616672] (Hallmann et al., 2014; Coughlin et al., 2015; Samanta et al., 2018; Kapoor et al., 2021; Li et al., 2021b)	***C. elegans*** • RNAi bifunctional *cars-1* knockdown (Zheng et al., 2022a) **Zebrafish (*Danio rerio*)** • Morpholino *cars2* knockdown (Wang et al., 2015) **Mouse (*Mus musculus*)** • Homozygous and heterozygous *Cars2* knockout (Akaike et al., 2017)
DARS2	• Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation; LBSL [OMIM #611105] (van der Knaap et al., 2003; Petzold et al., 2006; Scheper et al., 2007; Uluc et al., 2008; Isohanni et al., 2010; Lin et al., 2010; Labauge et al., 2011; Mierzewska et al., 2011; Miyake et al., 2011; Orcesi et al., 2011; Sharma et al., 2011; Steenweg et al., 2011; Synofzik et al., 2011; Steenweg et al., 2012b; Tzoulis et al., 2012; Cheng et al., 2013; Martikainen et al.,	***C. elegans*** • RNAi *dars-2* knockdown (Zheng et al., 2022a) **Mouse (*Mus musculus*)** • Conditional *Dars2* knockout in neurons (Aradjanski et al., 2017; Nemeth et al., 2020; Rumyantseva et al., 2020) • Conditional *Dars2* knockout in oligodendrocytes (Aradjanski et al., 2017)

	2013; Yamashita et al., 2013; Tylki-Szymanska et al., 2014; van Berge et al., 2014; Köhler et al., 2015; Lan et al., 2017; Çavuşoğlu et al., 2018; Yahia et al., 2018; Lin et al., 2019; Yelam et al., 2019; Al Balushi et al., 2020; Felhi et al., 2020; Yazici Gencdal et al., 2020; Axelsen et al., 2021; Li et al., 2021c; Ngo et al., 2021; Roux et al., 2021; Stellingwerff et al., 2021; Wongkittichote et al., 2022)	• Conditional *Dars2* knockout in heart and skeletal muscle (Dogan et al., 2014) • Heterozygous and homozygous *Dars2* knockout (Dickinson et al., 2016; Aradjanski et al., 2017)
EARS2	• Leukoencephalopathy With Thalamus and Brainstem Involvement and High Lactate; LTBL [OMIM #614924] (Steenweg et al., 2012a; Biancheri et al., 2015; Danhauser et al., 2016; Güngör et al., 2016; Kevelam et al., 2016; Şahin et al., 2016; Taskin et al., 2016; Oliveira et al., 2017; Sellars et al., 2017; Al Balushi et al., 2020; Barbosa-Gouveia et al., 2020; Felhi et al., 2020; Ni et al., 2021; Roux et al., 2021; Sawada et al., 2021)	***C. elegans*** • RNAi *ears-2* knockdown (Zheng et al., 2022a) **Mouse (*Mus musculus*)** • *Ears2* knockout (IMPC data) (Dickinson et al., 2016)
FARS2	• Combined oxidative phosphorylation deficiency 14 [OMIM #613658]; mitochondrial encephalopathy (Elo et al., 2012; Shamseldin et al., 2012; Almalki et al., 2014; Vernon et al., 2015; Walker et al., 2016; Almannai et al., 2018; Ville et al., 2020; Barcia et al., 2021b; Guerrero and Bhatia, 2021; Li et al., 2021b; Roux et al., 2021) • Juvenile onset refractory epilepsy (Hotait et al., 2020) • Autosomal recessive spastic paraplegia 77 [OMIM #617046] (Raviglione et al., 2016; Yang et al., 2016; Vantroys et al., 2017; Almannai et al., 2018; Forman et al., 2019; Meszarosova et al., 2020)	***C. elegans*** • RNAi *fars-2* knockdown (Zheng et al., 2022a) ***Drosophila melanogaster*** • *PheRS-m* knockout using CRISPR/Cas9 (Fan et al., 2021) • RNAi *PheRS-m* knockdown (Fan et al., 2021) • Introduction of loss-of-function missense mutations into *PheRS-m* (Mo et al., 2023) **Zebrafish (*Danio rerio*)** • Morpholino *fars2* knockdown (Li et al., 2021a; Chen et al., 2022) **Mouse (*Mus musculus*)** • *Fars2* knockout (IMPC data) (Dickinson et al., 2016) • Introduction of human patient mutation into *Fars2* (Chen et al., 2022) • *Fars2 knockout using CRISPR/Cas9* (Chen et al., 2022) • Conditional *Fars2* knockout in neurons (Chen et al., 2022)
HARS2	• Perrault Syndrome 2 [OMIM #614926] (Pierce et al., 2011; Lerat et al., 2016; Demain et al., 2020; Yu et al., 2020; Zou et al., 2020; Souissi et al., 2021)	***C. elegans*** • RNAi bifunctional *hars-1* knockdown (Pierce et al., 2011; Zheng et al., 2022a) **Zebrafish (*Danio rerio*)** • Morpholino knockdown of bifunctional *hars1* (Waldron et al., 2019) • *hars1* variants identified in mutagenesis screen for genes important for early development (Amsterdam et al., 2004) **Mouse (*Mus musculus*)** • Conditional *Hars2* knockout in hair cells (Xu et al., 2021) • *Hars2* knockout (IMPC data) (Dickinson et al., 2016)

IARS2	• Cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysplasia; CAGSSS [OMIM #616007] (Liberfarb et al., 1993; Schwartzentruber et al., 2014; Jabbour and Harissi-Dagher, 2016; Moosa et al., 2017; Vona et al., 2018; Lee et al., 2020) • Leigh syndrome, West syndrome & CAGSSS (Takezawa et al., 2018) • Infantile spasms, Leigh disease and Wolff-Parkinson White pattern (Upadia et al., 2022) • Sideroblastic anemia (Barcia et al., 2021a; Gong et al., 2022), with hypoparathyroidism (Gong et al., 2022)	***C. elegans*** • RNAi *iars-2* knockdown (Zheng et al., 2022a) **Mouse (*Mus musculus*)** • *Iars2* knockout (IMPC data) (Dickinson et al., 2016)
LARS2	• Hydrops, lactic acidosis, and sideroblastic anemia; HLASA [OMIM #617021] (Riley et al., 2016; Riley et al., 2020) • Perrault syndrome 4 [OMIM #615300] (Pierce et al., 2013; Lerat et al., 2016; Soldà et al., 2016; Demain et al., 2017; Kosaki et al., 2018; Al-Jaroudi et al., 2019; van der Knaap et al., 2019; Carminho-Rodrigues et al., 2020; Pan et al., 2020; Riley et al., 2020; Tucker et al., 2020; Buonfiglio et al., 2022; Sun et al., 2022) • Premature ovarian insufficiency without hearing loss (Neyroud et al., 2022) • Reversible mitochondrial myopathy, lactic acidosis and developmental delay (Riley et al., 2020)	***C. elegans*** • Expression of protein-truncating *lars-2* variant (Pierce et al., 2013) • *lars-2* variant identified in genetic screen for genes affecting *C. elegans* lifespan (Lee et al., 2003) • RNAi *lars-2* knockdown (Zheng et al., 2022a)
MARS2	• Combined oxidative phosphorylation deficiency 25 [OMIM #616430] (Webb et al., 2015) • Autosomal recessive spastic ataxia with leukoencephalopathy; ARSAL [OMIM #611390] (Thiffault et al., 2006; Bayat et al., 2012)	***C. elegans*** • RNAi bifunctional *mars-1* knockdown (Zheng et al., 2022a) ***Drosophila melanogaster*** • *MetRS-m* variant identified in a forward genetic screen causing photoreceptor neuron degeneration (Bayat et al., 2012) **Mouse (*Mus musculus*)** • *Mars2* knockout (Dickinson et al., 2016; Cheong et al., 2020)
NARS2	• Autosomal recessive deafness 94; DFNB94 [OMIM #618434] (Simon et al., 2015; Al-Sharif et al., 2022) • Combined oxidative phosphorylation deficiency 24 [OMIM #616239], Alpers syndrome, Leigh syndrome (Simon et al., 2015; Sofou et al., 2015; Vanlander et al., 2015; Mizuguchi et al., 2017; Seaver et al., 2018; Lee et al., 2020; Li et al., 2021b; Sofou et al., 2021; Štěrbová et al., 2021; Ait-El-Mkadem Saadi et al., 2022; Cokyaman et al., 2022; Hu et al., 2022; Tanaka et al., 2022; Vafaee-Shahi et al., 2022; Yang et al., 2022b; Kistol et al., 2023)	***C. elegans*** • RNAi *nars-2* knockdown (Zheng et al., 2022a) **Mouse (*Mus musculus*)** • *Nars2* knockout (Dickinson et al., 2016; Cheong et al., 2020)

	• Developmental delay, epilepsy, and neonatal diabetes (Yagasaki et al., 2022)	
PARS2	• Developmental and epileptic encephalopathy 75; DEE75 [OMIM #618437], Alpers syndrome (Sofou et al., 2012; Sofou et al., 2015; Mizuguchi et al., 2017; Ciara et al., 2018; Yin et al., 2018; Al Balushi et al., 2020; M et al., 2020; Li et al., 2021b; Okamoto et al., 2022)	***C. elegans*** • RNAi *pars-2* knockdown (Zheng et al., 2022a)
RARS2	• Fatal infantile encephalopathy with mitochondrial respiratory chain defects (Pontocerebellar Hypoplasia, Type 6 (PCH6)) [OMIM #611523] (Edvardson et al., 2007; Rankin et al., 2010; Namavar et al., 2011; Glamuzina et al., 2012; Cassandrini et al., 2013; Joseph et al., 2014; Li et al., 2015; Alkhateeb et al., 2016; Ngoh et al., 2016; Al Balushi et al., 2020; Nevanlinna et al., 2020; Roux et al., 2021; de Valles-Ibáñez et al., 2022; Nuovo et al., 2022; Zhang et al., 2022) • Epileptic encephalopathy without pontocerebellar hypoplasia (atypical PCH6) (Kastrissianakis et al., 2013; Lühl et al., 2016; Nishri et al., 2016; van Dijk et al., 2017; Mathew et al., 2018; Zhang et al., 2018; Minardi et al., 2020; Xu et al., 2020) • PCH6 with cardiomyopathy, hydrops and pulmonary hypoplasia (Lax et al., 2015) • PCH6 with liver involvement (Sevinç et al., 2022)	***C. elegans*** • RNAi *rars-2* knockdown (Zheng et al., 2022a) **Zebrafish (*Danio rerio)*** • Morpholino *rars2* knockdown (Kasher et al., 2011) **Mouse (*Mus musculus*)** • *Rars2* knockout (IMPC data) (Dickinson et al., 2016)
SARS2	• Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis (HUPRA syndrome) [OMIM #613845] (Belostotsky et al., 2011; Rivera et al., 2013; Zhou et al., 2021; Göknar et al., 2022; Yang et al., 2022a) • Progressive spastic paresis (Linnankivi et al., 2016) • HUPRA and progressive spastic paresis with seizures (Yu et al., 2022) • Congenital sideroblastic anemia (Colin et al., 2021)	***C. elegans*** • RNAi *sars-2* knockdown (Zheng et al., 2022a) ***Drosophila melanogaster*** • RNAi *SerRS-m* knockdown (Guitart et al., 2013) **Mouse (*Mus musculus*)** • *Sars2* expression and localization data (Gibbons et al., 2004) • Introduction of human patient variants into *Sars2* (Yu et al., 2022)
TARS2	• Combined oxidative phosphorylation deficiency 21 [OMIM #615918] (Diodato et al., 2014; Li et al., 2020; Gao et al., 2022; Zheng et al., 2022b; He et al., 2023)	***C. elegans*** • RNAi bifunctional *tars-1* knockdown (Zheng et al., 2022a) **Mouse (*Mus musculus*)** • *Tars2* knockout (IMPC data) (Dickinson et al., 2016)
VARS2	• Combined oxidative phosphorylation deficiency 20 [OMIM #615917] (Diodato et al., 2014; Taylor et al., 2014; Baertling et al., 2017; Bruni et al., 2018; Ma et al., 2018; Pereira et al., 2018; Begliuomini et al., 2019; Chin et al., 2019; Ruzman et al., 2019; Kušíková et al., 2021; Wu et al., 2022)	***C. elegans*** • RNAi *vars-1* knockdown (Zheng et al., 2022a) **Zebrafish (*Danio rerio*)** • Morpholino *vars2* knockdown (Kayvanpour et al., 2022) **Mouse (*Mus musculus*)**

	• Epilepsy, mental retardation, short stature, growth hormone deficiency and hypogonadism (Alsemari et al., 2017)	• *Vars2* knockout (IMPC data) (Dickinson et al., 2016)
WARS2	• Mitochondrial neurodevelopmental disorder, with abnormal movements and lactic acidosis, with or without seizures; NEMMLAS [OMIM #617710] (Theisen et al., 2017; Wortmann et al., 2017; Vantroys et al., 2018; Maffezzini et al., 2019; Virdee et al., 2019; Ilinca et al., 2022) • Childhood-onset Parkinsonism-dystonia 3; PKDYS3 [OMIM #619738] (Burke et al., 2018; Martinelli et al., 2020; Ilinca et al., 2022; Skorvanek et al., 2022) • Hyperkinetic movement disorder (Hübers et al., 2020) • Intellectual disability, ataxia and athetosis (Musante et al., 2017)	***C. elegans*** • RNAi *wars-2* knockdown (Zheng et al., 2022a) ***Drosophila melanogaster*** • RNAi *TrpRS-m* silencing (Maffezzini et al., 2019) **Zebrafish (*Danio rerio*)** • Morpholino *wars2* knockdown (Wang et al., 2016) **Rat (*Rattus norvegicus*)** • Heterozygous and homozygous *Wars2* knockout with zinc finger nuclease (Wang et al., 2016) • *Wars2* variant (p.L53F) identified through linkage analysis with effects on metabolism and coronary blood flow (Wang et al., 2016; Pravenec et al., 2017) **Mouse (*Mus musculus*)** • *Wars2* knockout (IMPC data) (Dickinson et al., 2016) • *Wars2* variant identified in a mutagenesis screen causing age-related hearing loss (Potter et al., 2016) • *Wars2* variant identified in mutagenesis screen causing hearing loss and metabolic changes (Agnew et al., 2018; Mušo et al., 2022)
YARS2	• Myopathy, lactic acidosis, and sideroblastic anemia 2; MLASA2 [OMIM #613561] (Riley et al., 2010; Sasarman et al., 2012; Riley et al., 2013; Shahni et al., 2013; Nakajima et al., 2014; Ardissone et al., 2015; Sommerville et al., 2017; Riley et al., 2018; Smith et al., 2018; Carreño-Gago et al., 2021; Roux et al., 2021; Rudaks et al., 2022)	***C. elegans*** • RNAi *yars-2* knockdown (Zheng et al., 2022a) ***Drosophila melanogaster*** • Interaction between *TyrRS-m* mutation and a mutation in mtDNA-encoded tyrosine tRNA (Meiklejohn et al., 2013; Holmbeck et al., 2015) **Zebrafish (*Danio rerio*)** • *yars2* knockout using CRISPR/Cas9 (Jin et al., 2021) **Dog (*Canis lupus familiaris*)** • Identification of missense *Yars2* variant causing cardiomyopathy and juvenile mortality (Gurtner et al., 2020)

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