**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](http://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 cytoplasmic 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., 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)
 | ***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)
* 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)
* Developmental delay, epilepsy, and neonatal diabetes (Yagasaki et al., 2022)
 | ***C. elegans**** RNAi *nars-2* knockdown (Zheng et al., 2022a)

**Mouse (*Mus musculus*)*** *Nars2* knockout (Dickinson et al., 2016; Cheong et al., 2020)
 |
| *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)
* Epilepsy, mental retardation, short stature, growth hormone deficiency and hypogonadism (Alsemari et al., 2017)
 | ***C. elegans**** RNAi *vars-1* knockdown (Zheng et al., 2022a)

**Zebrafish (*Danio rerio*)*** Morpholino *vars2* knockdown (Kayvanpour et al., 2022)

**Mouse (*Mus musculus*)*** *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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