U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Chmiela T, Wszolek ZK. *AARS2*-Related Disorder. 2024 Oct 31. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

AARS2-Related Disorder

Tomasz Chmiela, MD[1,2] and Zbigniew K Wszolek, MD[1]

Created: October 31, 2024.

Summary

Clinical characteristics

AARS2-related disorder includes two distinct phenotypes, infantile-onset cardiomyopathy and neurodegeneration with or without leukoencephalopathy. *AARS2*-related infantile-onset cardiomyopathy is characterized by hypertrophic cardiomyopathy, hypotonia, skeletal myopathy, and often lung hypoplasia. Some individuals have nonimmune hydrops and/or seizures. *AARS2*-related neurodegeneration with or without leukoencephalopathy is characterized by movement disorders, cognitive decline, ovarian failure in females, and psychiatric manifestations. Additional neurologic manifestations (seizures, developmental delay, neuropathy, and/or myopathy) and ocular manifestations can also be present.

Diagnosis/testing

The diagnosis of *AARS2*-related disorder is established in a proband with suggestive findings and biallelic pathogenic variants in *AARS2* identified by molecular genetic testing.

Management

Treatment of manifestations: In *AARS2*-related infantile-onset cardiomyopathy, standard treatment for hypertrophic cardiomyopathy, respiratory failure, and seizures; feeding therapy with tube feedings as required.

In *AARS2*-related neurodegeneration with or without leukoencephalopathy, levodopa or other dopaminergic therapies for parkinsonism; botulinum toxin for spasticity; additional management of motor dysfunction per orthopedist, physical medicine and rehabilitation specialist, physical therapist, and occupational therapist; cognitive behavioral therapy; psychoeducational interventions; treatment of hypogonadism in females per endocrinologist and/or gynecologist; psychotherapy and neuropsychological rehabilitation for neuropsychiatric manifestations; standard treatments for ocular manifestations and seizures.

Author Affiliations: 1 Department of Neurology, Mayo Clinic, Jacksonville, Florida; Email: chmiela.tomasz@mayo.edu; Email: wszolek.zbigniew@mayo.edu. 2 Department of Neurology, Faculty of Medical Sciences, Medical University of Silesia, Katowice, Poland; Email: chmiela.tomasz@mayo.edu.

Surveillance: In *AARS2*-related infantile-onset cardiomyopathy, cardiology evaluation including EKG and echocardiogram with frequency per cardiologist; assessment of growth and feeding at each visit; assessment of respiratory function as needed; neurologic evaluation, brain MRI, and EEG as needed.

In *AARS2*-related neurodegeneration with or without leukoencephalopathy, neurologic assessment for movement disorders, changes in tone, and seizures every six months or as needed; assessment of mobility and self-help skills at each visit; assessment of cognitive function every six to 12 months; assessment for features of premature ovarian failure with frequency per endocrinologist and/or gynecologist; psychiatric assessment every six to 12 months; ophthalmology evaluation with frequency per ophthalmologist.

Agents/circumstances to avoid: Sedatives, antipsychotics, and other medications that may decrease alertness and increase the risk of falling should be used cautiously.

Genetic counseling

AARS2-related disorder is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *AARS2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *AARS2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

AARS2-Related Disorder: Included Phenotypes [1]
• Infantile-onset cardiomyopathy • Neurodegeneration with or without leukoencephalopathy

1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

Formal diagnostic criteria for *AARS2*-related disorder have not been established. *AARS2*-related disorder includes two distinct phenotypes: (1) infantile-onset cardiomyopathy and (2) neurodegeneration with or without leukoencephalopathy.

Suggestive Findings

AARS2-related disorder **should be suspected** in probands with the following clinical, laboratory, histopathology, imaging, and family history findings.

AARS2-Related Infantile-Onset Cardiomyopathy

Clinical findings

- Hypertrophic cardiomyopathy
- Hypotonia
- Muscle weakness
- Lung hypoplasia
- Nonimmune hydrops fetalis

Laboratory findings. Lactic acidosis [Pickup et al 2024]

Histopathology findings. Muscle biopsy shows combined respiratory chain complex deficiencies in complexes I, III, and IV, mitochondrial proliferation, a deficiency of cytochrome *c* oxidase (COX) activity, and mitochondrial ultrastructural cytopathy [Tang et al 2019, Pickup et al 2024].

AARS2-Related Neurodegeneration with or without Leukoencephalopathy

Clinical findings

- Motor disorders, including ataxia, dystonia, chorea, parkinsonism, tremor spasticity, and/or hyperreflexia
- Cognitive decline
- Endocrine manifestations (in females) such as hypogonadism and premature ovarian failure
- Psychiatric manifestations, including depression, psychosis, anxiety, and/or behavioral changes
- Ocular manifestations such as nystagmus and ophthalmoplegia

Imaging findings [Dallabona et al 2014, Parikh et al 2015, Lakshmanan et al 2017, Lynch et al 2019, De Cocker & Castillo 2021]

- Progressive bilateral white matter lesions, hyperintense in T_2, predominantly affecting the periventricular and deep white matter. Lesions involving pyramidal tract and basal ganglia are also common.
- Linear or punctate lesions on diffusion-weighted imaging. Partly confluent lesions are typically present. Lesions may be found in the corona radiata and centrum semiovale.
- Brain atrophy and thinning of corpus callosum
- Absence of white matter calcifications
- White matter demonstrates rarefaction with suppression on fluid-attenuated inversion recovery MRI sequences.

Note: In *AARS2*-related neurodegeneration without leukoencephalopathy, brain MRI is normal [Kuo et al 2020].

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *AARS2*-related disorder **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *AARS2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *AARS2* variants of uncertain significance (or of one known *AARS2* pathogenic variant and one *AARS2* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *AARS2* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected

by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A leukodystrophy or leukoencephalopathy multigene panel that includes *AARS2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of *AARS2*-related disorder has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *AARS2* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *AARS2*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
AARS2	Sequence analysis [3]	~98% [4]
	Gene-targeted deletion/duplication analysis [5]	~2% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Kiraly-Borri et al [2019], Srivastava et al [2019], Parra et al [2021], Zhang et al [2023], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

AARS2-related disorder includes two distinct phenotypes, infantile-onset cardiomyopathy and neurodegeneration with or without leukoencephalopathy. To date, about 60 individuals have been identified with biallelic pathogenic variants in *AARS2* [Kiraly-Borri et al 2019, Srivastava et al 2019, Axelsen et al 2021,

Parra et al 2021, Zhang et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

AARS2-Related Infantile-Onset Cardiomyopathy

Table 2. *AARS2*-Related Infantile-Onset Cardiomyopathy: Frequency of Select Features

Feature	% of Persons w/Feature [1]	Comment
Hypertrophic cardiomyopathy	83%	A few instances of lethal primary pulmonary hypoplasia w/o cardiomyopathy have been reported; some authors suggest that this might represent a separate phenotype. [1]
Hypotonia	72%	
Pulmonary hypoplasia	44%	
Nonimmune hydrops	11%	
Lactic acidosis	83%	Of those persons tested

1. Percentages are based on 18 individuals with *AARS2*-related infantile-onset cardiomyopathy [Kiraly-Borri et al 2019].

Hypertrophic cardiomyopathy. Cardiac involvement is present in almost all reported infants. Cardiac dysfunction is present before or shortly after birth. Significant cardiac hypertrophy can lead to secondary lung hypoplasia [Götz et al 2011, Kiraly-Borri et al 2019].

Hypotonia and myopathy. Hypotonia, with or without evidence of muscular mitochondriopathy on histopathology, is present in most infants. All affected individuals required early intensive care due to hypotonia and poor feeding [Kiraly-Borri et al 2019].

Lung hypoplasia is often secondary to cardiomyopathy, although there are reported infants with primary lung hypoplasia without signs of cardiac involvement [Götz et al 2011, Kiraly-Borri et al 2019].

Nonimmune hydrops was reported in some infants. Severe fetal hydrops with pleural effusion may lead to secondary pulmonary hypoplasia [Bruwer et al 2018].

Seizures. Generalized tonic-clonic or myoclonic seizures were reported in some individuals [Wu et al 2020].

Prognosis. The prognosis is poor. Cardiac and respiratory failure result in death shortly after birth (mean age of death is 2.1 months). The oldest survivor died at age 11 months [Kiraly-Borri et al 2019]. Death in utero has also been reported [Götz et al 2011, Calvo et al 2012, Taylor et al 2014, Euro et al 2015].

AARS2-Related Neurodegeneration with or without Leukoencephalopathy

Table 3. *AARS2*-Related Neurodegeneration with or without Leukoencephalopathy: Frequency of Select Features

Feature	% of Persons w/Feature [1]	Comment
Movement disorder	71%	Ataxia, dystonia, chorea, parkinsonism, & tremor
Cognitive impairment/decline	67%	
Spasticity & hyperreflexia	64%	
Premature ovarian failure	84% of females	
Psychiatric manifestations	46%	Depression, psychosis, anxiety, & behavioral changes
Ocular manifestations	38%	Nystagmus, ophthalmoplegia

1. Percentages are based on 48 individuals with *AARS2*-related neurodegeneration with or without leukoencephalopathy [Parra et al 2021].

Onset. The age of onset of *AARS2*-related neurodegeneration with or without leukoencephalopathy can range from childhood to adulthood.

Movement disorder. The most common manifestations are ataxia, dystonia, chorea, parkinsonism, and tremor [Peragallo et al 2018, Parra et al 2021, Zhang et al 2023, Green et al 2024].

Cognitive decline is documented in most individuals. The onset of cognitive decline is often with disease onset. Cognitive deficits include difficulties with sustained attention, loss of inhibition, frontal dysfunction, severe memory impairment, and impaired calculation and language [Axelsen et al 2021, Parra et al 2021, Zhang et al 2023].

Other neurologic manifestations. Seizures are observed in around 6% of individuals [Parra et al 2021]. Preexisting developmental delay or motor problems in childhood have been described in some individuals [Peragallo et al 2018, Parra et al 2021]. Neuropathy or clinically evident myopathy are less common manifestations [Peragallo et al 2018, Parra et al 2021].

Endocrine manifestations. The majority of affected females have premature ovarian failure. Ovarian failure occurs most commonly in the 3rd and 4th decade of life; primary and secondary amenorrhea have been reported [Dallabona et al 2014, Sun et al 2017, França & Mendonca 2022].

Psychiatric manifestations. Common manifestations include depression, psychosis, anxiety, and behavioral changes [Kim et al 2018, Axelsen et al 2021, Parra et al 2021, Kazakova et al 2023].

Ocular manifestations. Nystagmus and ophthalmoplegia have been noted in 28% of individuals. Less common ocular manifestations include progressive optic atrophy and retinopathy [Parra et al 2021].

Prognosis is poor; to date, there are no disease-modifying treatments. Most affected individuals experience progressive motor and cognitive decline. Typically, individuals progress to severe disability with no or very limited interaction with their environment within five to ten years of diagnosis. Death is due to late complications of disability [Fine et al 2019].

Genotype-Phenotype Correlations

AARS2-related infantile congenital cardiomyopathy has been associated with the recurrent homozygous or compound heterozygous pathogenic variant p.Arg592Trp (c.1774C>T) located in the editing domain for deacylating mischarged tRNAs of AARS2 [Euro et al 2015, Axelsen et al 2021].

Pathogenic variants affecting the aminoacylation domain (residues 24-477) have been shown to cause leukoencephalopathy and premature ovarian failure in women [Podmanicky et al 2024].

No other genotype-phenotype correlations have been identified.

Prevalence

AARS2-related disorder is an ultrarare disorder with fewer than 70 affected individuals reported to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *AARS2*.

Differential Diagnosis

AARS2-Related Infantile-Onset Cardiomyopathy

Table 4. Genes of Interest in the Differential Diagnosis of *AARS2*-Related Infantile-Onset Cardiomyopathy

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/*AARS2*-related infantile-onset CM	Distinguishing from *AARS2*-related infantile-onset CM
GAA	Pompe disease	AR	• Hypertrophic CM • Muscle weakness • Respiratory deficiency	• Macroglossia • Less severe manifestations
GLA	Fabry disease	XL	Hypertrophic CM	• Angiokeratomas • Hypohidrosis • Proteinuria • Kidney disease
LAMP2	Danon disease	XL	• Hypertrophic CM • Skeletal muscle weakness	Less severe manifestations w/later age of onset (teenage years)
MT-TI	*MT-TI*-related Leigh syndrome spectrum (See Mitochondrial DNA-Associated Leigh Syndrome Spectrum.)	Mat	• Fatal early-onset CM • Lactic acidosis	
PRKAG2	Glycogen storage disease of the heart, lethal congenital (OMIM 261740)	AD	Hypertrophic CM	• Neonatal hypoglycemia • Dysmorphic facies
SCO2	*SCO2*-related Leigh syndrome spectrum (See Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview.)	AR	Early-onset CM	• Phenotype of spinal muscular atrophy • Less severe manifestations
TAFAZZIN (*TAZ*)	Barth syndrome	XL	Infantile-onset CM, often fatal in childhood	Less severely affected persons can live to teenage years or early adulthood
TMEM70	Mitochondrial complex V deficiency (OMIM 614052)	AR	• Hypertrophic CM • Hypotonia	• Hyperammonemia • Characteristic pattern of facial features

AD = autosomal dominant; AR = autosomal recessive; CM = cardiomyopathy; Mat = maternal; MOI = mode of inheritance; XL = X-linked

See also Hypertrophic Cardiomyopathy Overview.

AARS2-Related Neurodegeneration with or without Leukoencephalopathy

Genetic disorders. As leukoencephalopathy and neurodegeneration (without leukoencephalopathy) can be seen in many genetic disorders with variable and overlapping manifestations (see Table 3), *AARS2*-related neurodegeneration with or without leukoencephalopathy can be difficult to diagnose based on clinical manifestations or neuroimaging only. Accurate diagnosis requires molecular genetic testing.

Table 5. Genetic Disorders in the Differential Diagnosis of *AARS2*-Related Neurodegeneration with or without Leukoencephalopathy

Gene(s)	Disorder	MOI	Key Features of Disorder	
			Overlapping w/*AARS2*-related neurodegeneration w/ or w/o leukoencephalopathy	Distinguishing from *AARS2*-related neurodegeneration w/ or w/o leukoencephalopathy
AARS1	*AARS1*-related leukoencephalopathy (Swedish hereditary diffuse leukoencephalopathy with spheroids) (OMIM 619661)	AD	Similar clinical phenotype (leukoencephalopathy & neurodegeneration)	Different neuroimaging pattern, w/ centrifugally expanding rim of decreased diffusion
CSF1R	Late-onset *CSF1R*-related disorder	AD (AR)	Similar clinical phenotype [1] (leukoencephalopathy & neurodegeneration)	• Older age of onset • No premature ovarian failure in females • White matter calcification on brain MRI
EIF2B1 *EIF2B2* *EIF2B3* *EIF2B4* *EIF2B5*	Childhood ataxia w/central nervous system hypomyelination / vanishing white matter	AR	• Cognitive decline • Behavioral changes • Presence of ovarian failure in females	Corpus callosum & long descending tracks are not affected.
APP *PSEN1* *PSEN2*	Early-onset Alzheimer disease	AD	• Cognitive decline • Executive dysfunction	Episodic memory loss & WML are less pronounced.
LMNB1	Adult-onset *LMNB1*-related autosomal dominant leukodystrophy	AD	• Cognitive impairment (late manifestation) • Ataxia • Pyramidal signs	• Early autonomic dysfunction • Periventricular rims of lateral ventricles normal or mildly affected on brain MRI
GFAP	Alexander disease, adult form	AD	• Neurodegeneration • Ataxia • Pyramidal signs	• Normal cognitive function in adults • Palatal myoclonus
ARSA	Adult metachromatic leukodystrophy (See Arylsulfatase A Deficiency.)	AR	• Cognitive decline • Pyramidal signs • Seizures • Psychiatric features	• Peripheral neuropathy • No WML in cerebellum
CLN3 *CLN5* *CLN6* *CLN8* *CTSD* *CTSF* *DNAJC5* *GRN* *KCTD7* *MFSD8* *PPT1* *TPP1*	Neuronal ceroid lipofuscinoses (OMIM PS256730)	AR AD [2]	Neurodegeneration	Retinal degeneration
GALC	Krabbe disease	AR	Pyramidal signs	• Peripheral neuropathy • MRI changes predominantly in posterior white matter • Demyelination in brain stem & cerebellum

Table 5. continued from previous page.

Gene(s)	Disorder	MOI	Key Features of Disorder	
			Overlapping w/*AARS2*-related neurodegeneration w/ or w/o leukoencephalopathy	Distinguishing from *AARS2*-related neurodegeneration w/ or w/o leukoencephalopathy
ABCD1	X-linked adrenoleukodystrophy	XL	• Cognitive decline • Pyramidal signs	• Neuropathy • WML are contrast enhancing.
ADAR *IFIH1* *RNASEH2A* *RNASEH2B* *RNASEH2C* *SAMHD1* *TREX1*	Aicardi-Goutières syndrome	AR (AD) [3]	Neurodegeneration	Chilblain skin lesions
AQP4 *GPRC5B* *HEPACAM* *MLC1*	Megalencephalic leukoencephalopathy w/ subcortical cysts	AD AR	Neurodegeneration	Subcortical cysts on neuroimaging
C9orf72	*C9orf72* frontotemporal dementia &/or amyotrophic lateral sclerosis	AD	Neurodegeneration	• Frontal & temporal atrophy • Fewer WML • Motor neuron disease
GLA	Fabry disease	XL	WML	Grey matter pathology [4]
GLB1 *GM2A*	GM1 & GM2 gangliosidoses (See *GLB1*-Related Disorders & GM2 Activator Deficiency.)	AR	Neurodegeneration	• Skin changes, hepatosplenomegaly (GM1) • Early-childhood onset, cherry-red spots of macula (GM2)
GRN	*GRN* frontotemporal dementia	AD	Neurodegeneration	• Frontal & temporal atrophy • Fewer WMLs
NOTCH3	CADASIL	AD	WML	• Stroke-like clinical signs • Multiple clinical infarcts
POLR1C *POLR3A* *POLR3B*	POLR3-related leukodystrophy	AR	• Neurologic dysfunction • Ataxia • Tremor • Delayed or arrested puberty	• Growth hormone deficiency • Hypogonadotropic hypogonadism
TREM2 *TYROBP*	Polycystic lipomembranous osteodysplasia w/sclerosing leukoencephalopathy (OMIM PS221770)	AR	• Clinical decline • Psychiatric & neurologic features	• Polycystic osseous lesions • Pathologic fractures

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; WML = white matter lesions; XL = X-linked

1. Kinoshita et al [2024]

2. Neuronal ceroid lipofuscinosis (NCL) is inherited in an autosomal recessive manner with the exception of *DNAJC5*-related NCL, which is inherited in an autosomal dominant manner.

3. Aicardi-Goutières syndrome is most frequently inherited in an autosomal recessive manner; in a few instances the disease can result from specific *de novo* or inherited autosomal dominant pathogenic variants in *ADAR* or *TREX1*, and a variety of heterozygous autosomal dominant pathogenic variants in *IFIH1*.

4. Underhill et al [2015], Ginsberg et al [2006]

Acquired, potentially treatable causes of white matter disease in the differential diagnosis of *AARS2*-related neurodegeneration with or without leukoencephalopathy include the following [Lynch et al 2019]:

- Infectious disease (e.g., HIV, syphilis, hepatitis B and C, and tuberculosis)
- Drug use (e.g., heroin and methanol)

- Inflammatory disease (e.g., systemic lupus erythematosus)
- Progressive multifocal leukoencephalopathy associated with JC virus in immunosuppressed individuals
- Primary central nervous system lymphoma and gliomatosis and treatment with chemo- or radiotherapy
- Small vessel disease (typically associated with an older age of onset and significant cardiovascular risk factors)

Management

No clinical practice guidelines for *AARS2*-related disorder have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *AARS2*-related infantile-onset cardiomyopathy, the evaluations summarized in Table 6a (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6a. *AARS2*-Related Infantile-Onset Cardiomyopathy: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Cardiac	Eval by pediatric cardiologist for cardiomyopathy incl EKG & echocardiogram	
Growth/Nutrition	• Assessment of weight, length, & head circumference • Feeding assessment	
Respiratory	Assessment of respiratory function to determine need for respiratory support (e.g., mechanical ventilation)	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *AARS2*-related disorder to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

To establish the extent of disease and needs in an individual diagnosed with *AARS2*-related neurodegeneration with or without leukoencephalopathy, the evaluations summarized in Table 6b (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6b. *AARS2*-Related Neurodegeneration with or without Leukoencephalopathy: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Complete neurologic assessment	Incl assessment for movement disorder, motor impairment, gait abnormalities, bradykinesia, & spasticity
	Assessment of cognitive function	To incl executive function, language processing, visuospatial/visuoconstructional skills
	Consider EEG if seizures are a concern.	
Hypogonadism (in females)	Gynecologic & endocrinologic eval	
Neurobehavioral/ psychiatric manifestations	• Assessment for anxiety, depression, apathy, indifference, abulia, disinhibition, distraction, & other behavioral or personality changes • Referral to psychologist &/or neuropsychologist as needed	
Ocular manifestations	Detailed ophthalmologic eval	Incl assessment of visual acuity, visual fields, & intraocular pressure
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *AARS2*-related disorder to facilitate medical & personal decision making
Family/caregiver support & resources	By clinicians, wider care team, & family support organizations	Assessment of family/caregiver & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement • Home nursing referral

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 7a and Table 7b).

Table 7a. *AARS2*-Related Infantile-Onset Cardiomyopathy: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Hypertrophic cardiomyopathy	Standard treatment per pediatric cardiologist & neonatologist	
Feeding issues	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Respiratory failure	Standard treatment per pulmonologist & neonatologist (typically requiring mechanical ventilation)	

Table 7a. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]

ASM = anti-seizure medication
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Table 7b. *AARS2*-Related Neurodegeneration with or without Leukoencephalopathy: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Motor dysfunction	• Levodopa or other dopaminergic therapies for parkinsonism • Botulinum toxin for spasticity	To date, there is no data on benefits of these treatments in persons w/*AARS2*-related disorder.
	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Cognitive decline / Dementia	• Cognitive behavioral therapy • Psychoeducational interventions	
Hypogonadism (in females)	Treatment per endocrinologist & gynecologist	
Neuropsychiatric manifestations	Psychotherapy / neuropsychological rehab	• There are no data on long-term efficacy of psychiatric treatments for depression, suicidal tendencies, anxiety, & psychosis. • The use of antipsychotic drugs should be discussed w/individual &/or family due to potential risk of extrapyramidal symptoms. They may be considered in persons w/ aggression.
Ocular manifestations	Standard treatments per ophthalmologist &/or ophthalmic subspecialist for more complex findings (e.g., optic nerve atrophy, retinopathy)	
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Family/Community	Education re social issues & ↑ risk of depression	Social issues (e.g., unemployment, divorce, financial challenges, & substance abuse) & suicidal tendencies may be assoc w/disease progression.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 8a and Table 8b are recommended.

Table 8a. *AARS2*-Related Infantile-Onset Cardiomyopathy: Surveillance

System/Concern	Evaluation	Frequency
Cardiac	• Cardiology eval to assess cardiac function • EKG & echocardiogram per cardiologist	As recommended by cardiologist
Feeding/Nutrition	• Assessment of growth parameters • Feeding assessment	At each visit
Respiratory	Assessment of respiratory function	As needed
Neurologic	• Neurologic eval • Brain MRI • EEG	

Table 8b. *AARS2*-Related Neurodegeneration with or without Leukoencephalopathy: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Assess for ↑ severity or new manifestations incl movement disorders, changes in tone, & seizures	Every 6 mos or as needed
	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
	Assessment of cognitive function to incl executive function, language processing, visuospatial/visuoconstruction skills	Every 6-12 mos
Hypogonadism (in females)	Assessment by endocrinologist &/or gynecologist for features of premature ovarian failure	Per endocrinologist or gynecologist
Neuropsychiatric	Psychiatric assessment for depression, psychosis, anxiety, & behavioral changes	Every 6-12 mos
Ocular manifestations	Assessment by ophthalmologist	Per ophthalmologist

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Many individuals with *AARS2*-related disorder have gait and cognitive decline. Sedatives, antipsychotics, and other medications that may decrease alertness and increase the risk of falling should be used cautiously.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

AARS2-related disorder is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an *AARS2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *AARS2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *AARS2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *AARS2*-related disorder are obligate heterozygotes (carriers) for a pathogenic variant in *AARS2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *AARS2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *AARS2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *AARS2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider decisions regarding prenatal and preimplantation genetic testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Compassionate Friends**
  Supporting Family After a Child Dies
  Phone: 877-969-0010
  compassionatefriends.org
- **RESOLVE: The National Infertility Association**
  Phone: 703-556-7172
  Email: info@resolve.org
  resolve.org
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  ulf.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. AARS2-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
AARS2	6p21.1	Alanine--tRNA ligase, mitochondrial	AARS2	AARS2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for AARS2-Related Disorder (View All in OMIM)

612035	ALANYL-tRNA SYNTHETASE 2; AARS2
614096	COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 8; COXPD8
615889	LEUKOENCEPHALOPATHY, PROGRESSIVE, WITH OVARIAN FAILURE; LKENP

Molecular Pathogenesis

AARS2 (mitochondrial alanyl-tRNA synthetase 2) is a nuclear gene that encodes mitochondrial alanine-tRNA ligase, which is responsible for transferring the amino acid alanine to the accepting mitochondrial tRNA in the mitochondrial matrix. *AARS2* pathogenic variants cause impaired OXPHOS, lactic acid deregulation, and loss of muscle function, with underlying mechanisms undefined. The underlying mechanism of heart disease remains unknown; however, mitochondrial alanine-tRNA ligase is a critical regulator of heart development [Lu et al 2023].

Mechanism of disease causation. The mechanisms of disease causation are not fully understood and likely differ depending on the *AARS2* pathogenic variant(s) and interaction with other genetic and non-genetic factors.

Chapter Notes

Author Notes

Dr Chmiela (chmiela.tomasz@mayo.edu; tchmiela@sum.edu.pl) and Dr Wszolek (wszolek.zbigniew@mayo.edu) are actively involved in clinical research regarding individuals with hereditary leukoencephalopathies. They would be happy to communicate with persons who have any questions regarding diagnosis of *AARS2*-related disorder or other considerations.

Dr Chmiela and Dr Wszolek are also interested in hearing from clinicians treating families affected by hereditary leukoencephalopathies in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Chmiela and Dr Wszolek and to inquire about review of *AARS2* variants of uncertain significance.

Dr Wszolek serves as PI or Co-PI on Biohaven Pharmaceuticals, Inc. (BHV4157-206), Vigil Neuroscience, Inc (VGL101-01.002, VGL101-01.201, PET tracer development protocol, Csf1r biomarker and repository project, and ultra-high field MRI in the diagnosis and management of CSF1R-related adult-onset leukoencephalopathy with axonal spheroids and pigmented glia), ONO-2808-03, and Amylyx AMX0035-009 projects/grants. He serves as Co-PI of the Mayo Clinic APDA Center for Advanced Research and as an external advisory board member for the Vigil Neuroscience, Inc, and as a consultant for Eli Lilly & Company and for NovoGlia, Inc

Acknowledgments

Dr Wszolek is partially supported by the NIH/NIA and NIH/NINDS (1U19AG063911, FAIN: U19AG063911), the Haworth Family Professorship in Neurodegenerative Diseases fund, the Albertson Parkinson's Research Foundation, PPND Family Foundation, and the Margaret N and John Wilchek Family.

Revision History

- 31 October 2024 (sw) Review posted live
- 25 July 2024 (zw) Original submission

References

Literature Cited

Axelsen TM, Vammen TL, Bak M, Pourhadi N, Stenør CM, Grønborg S. Case report: AARS2 leukodystrophy. Mol Genet Metab Rep. 2021;28:100782. PubMed PMID: 34285876.

Bruwer Z, Al Riyami N, Al Dughaishi T, Al Murshedi F, Al Sayegh A, Al Kindy A, Meftah D, Al Kharusi K, Al Foori A, Al Yarubi N, Scott P, Al-Thihli K. Inborn errors of metabolism in a cohort of pregnancies with non-immune hydrops fetalis: a single center experience. J Perinat Med. 2018;46:968-74. PubMed PMID: 28822227.

Calvo SE, Compton AG, Hershman SG, Lim SC, Lieber DS, Tucker EJ, Laskowski A, Garone C, Liu S, Jaffe DB, Christodoulou J, Fletcher JM, Bruno DL, Goldblatt J, Dimauro S, Thorburn DR, Mootha VK. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. Sci Transl Med. 2012;4:118ra10. PubMed PMID: 22277967.

Dallabona C, Diodato D, Kevelam SH, Haack TB, Wong LJ, Salomons GS, Baruffini E, Melchionda L, Mariotti C, Strom TM, Meitinger T, Prokisch H, Chapman K, Colley A, Rocha H, Ounap K, Schiffmann R, Salsano E, Savoiardo M, Hamilton EM, Abbink TE, Wolf NI, Ferrero I, Lamperti C, Zeviani M, Vanderver A, Ghezzi D, van der Knaap MS. Novel (ovario) leukodystrophy related to AARS2 mutations. Neurology. 2014;82:2063-71. PubMed PMID: 24808023.

De Cocker LJL, Castillo M. Distinctive diffusion-weighted imaging features in late-onset genetic leukoencephalopathies. Neuroradiology. 2021;63:153-6. PubMed PMID: 32879996.

Euro L, Konovalova S, Asin-Cayuela J, Tulinius M, Griffin H, Horvath R, Taylor RW, Chinnery PF, Schara U, Thorburn DR, Suomalainen A, Chihade J, Tyynismaa H. Structural modeling of tissue-specific mitochondrial alanyl-tRNA synthetase (AARS2) defects predicts differential effects on aminoacylation. Front Genet. 2015;6:21. PubMed PMID: 25705216.

Fine AS, Nemeth CL, Kaufman ML, Fatemi A. Mitochondrial aminoacyl-tRNA synthetase disorders: an emerging group of developmental disorders of myelination. J Neurodev Disord. 2019;11:29. PubMed PMID: 31839000.

França MM, Mendonca BB. Genetics of ovarian insufficiency and defects of folliculogenesis. Best Pract Res Clin Endocrinol Metab. 2022;36:101594. PubMed PMID: 34794894.

Ginsberg L, Manara R, Valentine AR, Kendall B, Burlina AP. Magnetic resonance imaging changes in Fabry disease. Acta Paediatr Suppl. 2006;95:57-62. PubMed PMID: 16720467.

Götz A, Tyynismaa H, Euro L, Ellonen P, Hyötyläinen T, Ojala T, Hämäläinen RH, Tommiska J, Raivio T, Oresic M, Karikoski R, Tammela O, Simola KO, Paetau A, Tyni T, Suomalainen A. Exome sequencing identifies mitochondrial alanyl-tRNA synthetase mutations in infantile mitochondrial cardiomyopathy. Am J Hum Genet. 2011;88:635-42. PubMed PMID: 21549344.

Green K, MacIver CL, Ebden S, Rees DA, Peall KJ. Pearls & oysters: AARS2 leukodystrophy-tremor and tribulations. Neurology. 2024;102:e209296. PubMed PMID: 38507676.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Kazakova E, Téllez-Martínez JA, Flores-Lagunes L, Sosa-Ortiz AL, Carillo-Sánchez K, Molina-Garay C, González-Domínguez CA, Jimenez-Olivares M, Fernandez-Valverde F, Vargas-Cañas ES, Vázquez-Memije ME, Garcia-Latorre EA, Martínez-Duncker I, Alaez-Verson C. Uterus infantilis: a novel phenotype associated with AARS2 new genetic variants. A case report. Front Neurol. 2023;14:878446. PubMed PMID: 37456626.

Kim EJ, Kim YE, Jang JH, Cho EH, Na DL, Seo SW, Jung NY, Jeong JH, Kwon JC, Park KH, Park KW, Lee JH, Roh JH, Kim HJ, Yoon SJ, Choi SH, Jang JW, Ki CS, Kim SH. Analysis of frontotemporal dementia, amyotrophic lateral sclerosis, and other dementia-related genes in 107 Korean patients with frontotemporal dementia. Neurobiol Aging. 2018;72:186.e1-186.e7. PubMed PMID: 30054184.

Kinoshita M, Oyanagi K, Matsushima A, Kondo Y, Hirano S, Ishizawa K, Ishihara K, Terada S, Inoue T, Yazawa I, Washimi Y, Yamada M, Nakayama J, Mitsuyama Y, Ikeda SI, Sekijima Y. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP): estimation of pathological lesion stage from brain images. J Neurol Sci. 2024;461:123027. PubMed PMID: 38805875.

Kiraly-Borri C, Jevon G, Ji W, Jeffries L, Ricciardi JL, Konstantino M, Ackerman KG, Lakhani SA. Siblings with lethal primary pulmonary hypoplasia and compound heterozygous variants in the AARS2 gene: further delineation of the phenotypic spectrum. Cold Spring Harb Mol Case Stud. 2019;5:a003699. PubMed PMID: 30819764.

Kuo ME, Antonellis A, Shakkottai VG. Alanyl-tRNA synthetase 2 (AARS2)-related ataxia without leukoencephalopathy. Cerebellum. 2020;19:154-60. PubMed PMID: 31705293.

Lakshmanan R, Adams ME, Lynch DS, Kinsella JA, Phadke R, Schott JM, Murphy E, Rohrer JD, Chataway J, Houlden H, Fox NC, Davagnanam I. Redefining the phenotype of ALSP and AARS2 mutation-related leukodystrophy. Neurol Genet. 2017;3:e135. PubMed PMID: 28243630.

Lu YW, Liang Z, Guo H, Fernandes T, Espinoza-Lewis RA, Wang T, Li K, Li X, Singh GB, Wang Y, Cowan D, Mably JD, Philpott CC, Chen H, Wang DZ. PCBP1 regulates alternative splicing of AARS2 in congenital cardiomyopathy. bioRxiv [Preprint]. 2023:2023.05.18.540420.

Lynch DS, Wade C, Paiva ARB, John N, Kinsella JA, Merwick Á, Ahmed RM, Warren JD, Mummery CJ, Schott JM, Fox NC, Houlden H, Adams ME, Davagnanam I, Murphy E, Chataway J. Practical approach to the diagnosis of adult-onset leukodystrophies: an updated guide in the genomic era. J Neurol Neurosurg Psychiatry. 2019;90:543-54. PubMed PMID: 30467211.

Parikh S, Bernard G, Leventer RJ, van der Knaap MS, van Hove J, Pizzino A, McNeill NH, Helman G, Simons C, Schmidt JL, Rizzo WB, Patterson MC, Taft RJ, Vanderver A; GLIA Consortium. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephelopathies. Mol Genet Metab. 2015;114:501-15. PubMed PMID: 25655951.

Parra SP, Heckers SH, Wilcox WR, Mcknight CD, Jinnah HA. The emerging neurological spectrum of AARS2-associated disorders. Parkinsonism Relat Disord. 2021;93:50-4. PubMed PMID: 34784527.

Peragallo JH, Keller S, van der Knaap MS, Soares BP, Shankar SP. Retinopathy and optic atrophy: expanding the phenotypic spectrum of pathogenic variants in the AARS2 gene. Ophthalmic Genet. 2018;39:99-102. PubMed PMID: 28820624.

Pickup E, Moore SA, Suwannarat P, Grant C, Ah Mew N, Gropman A, Sen K. Expedited exome reanalysis following deep phenotyping and muscle biopsy in suspected mitochondrial disorder. Pediatr Neurol. 2024;156:178-81. PubMed PMID: 38788280.

Podmanicky O, Gao F, Munro B, Jennings MJ, Boczonadi V, Hathazi D, Mueller JS, Horvath R. Mitochondrial aminoacyl-tRNA synthetases trigger unique compensatory mechanisms in neurons. Hum Mol Genet. 2024;33:435-47. PubMed PMID: 37975900.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Srivastava S, Butala A, Mahida S, Richter J, Mu W, Poretti A, Vernon H, VanGerpen J, Atwal PS, Middlebrooks EH, Zee DS, Naidu S. Expansion of the clinical spectrum associated with AARS2-related disorders. Am J Med Genet A. 2019;179:1556-64. PubMed PMID: 31099476.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Sun J, Quan C, Luo SS, Zhou L, Zhao CB. Leukodystrophy without ovarian failure caused by compound heterozygous alanyl-tRNA synthetase 2 mutations. Chin Med J (Engl). 2017;130:3021-2. PubMed PMID: 29237946.

Tang Y, Qin Q, Xing Y, Guo D, Di L, Jia J. AARS2 leukoencephalopathy: a new variant of mitochondrial encephalomyopathy. Mol Genet Genomic Med. 2019;7:e00582. PubMed PMID: 30706699.

Taylor RW, Pyle A, Griffin H, Blakely EL, Duff J, He L, Smertenko T, Alston CL, Neeve VC, Best A, Yarham JW, Kirschner J, Schara U, Talim B, Topaloglu H, Baric I, Holinski-Feder E, Abicht A, Czermin B, Kleinle S, Morris AA, Vassallo G, Gorman GS, Ramesh V, Turnbull DM, Santibanez-Koref M, McFarland R, Horvath

R, Chinnery PF. Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. JAMA. 2014;312:68-77. PubMed PMID: 25058219.

Underhill HR, Golden-Grant K, Garrett LT, Uhrich S, Zielinski BA, Scott CR. Detecting the effects of Fabry disease in the adult human brain with diffusion tensor imaging and fast bound-pool fraction imaging. J Magn Reson Imaging. 2015;42:1611-22. PubMed PMID: 26018987.

Wu TH, Peng J, Zhang CL, Wu LW, Yang LF, Peng P, Pang N, Yin F, He F. [Mutations in aminoacyl-tRNA synthetase genes: an analysis of 10 cases]. Zhongguo Dang Dai Er Ke Za Zhi. 2020;22:595-601. PubMed PMID: 32571458.

Zhang X, Li J, Zhang Y, Gao M, Peng T, Tian T. AARS2-related leukodystrophy: a case report and literature review. Cerebellum. 2023;22:59-69. PubMed PMID: 35084689.

License