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

NLM Citation: Almannai M, Faqeih E, El-Hattab AW, et al. FARS2 Deficiency. 2019 Mar 14. 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/

FARS2 Deficiency

Mohammed Almannai, MD, FAAP, FACMG,[1] Eissa Faqeih, MD,[1] Ayman W El-Hattab, MD, FAAP, FACMG,[2] and Lee-Jun C Wong, PhD, FACMG[3]

Created: March 14, 2019.

Summary

Clinical characteristics

The spectrum of FARS2 deficiency ranges from the infantile-onset phenotype, characterized by epileptic encephalopathy with lactic acidosis and poor prognosis (70% of affected individuals), to the later-onset phenotype, characterized by spastic paraplegia, less severe neurologic manifestations, and longer survival (30% of affected individuals). To date FARS2 deficiency has been reported in 37 individuals from 25 families.

- *Infantile-onset phenotype.* Seizures are difficult to control and may progress quickly at an early age to intractable seizures with frequent status epilepticus; some children have hypsarrhythmia on EEG. All have developmental delay; most are nonverbal and unable to walk. Feeding difficulties are common. More than half of affected children die in early childhood.
- *Later-onset phenotype.* All affected individuals have spastic paraplegia manifested by weakness, spasticity, and exaggerated reflexes of the lower extremities associated with walking difficulties; some have developmental delay/intellectual disability; some have brief seizures that resolve over time.

Diagnosis/testing

The diagnosis of FARS2 deficiency is established in a proband with suggestive findings and biallelic pathogenic variants in *FARS2* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic and best provided by a multidisciplinary team comprising neurodevelopmental pediatricians, neurologists, physiatrists, occupational and physical therapists, feeding specialists, speech and language therapists, and social workers to assure adequate family support.

Author Affiliations: 1 Medical Genetics and Metabolic Consultant, Section of Medical Genetics, King Fahad Medical City, Riyadh, Saudi Arabia; Email: malmannai@kfmc.med.sa; Email: efaqeih@kfmc.med.sa. 2 Associate Professor, Department of Clinical Sciences, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates; Email: elhattabaw@yahoo.com. 3 Professor, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas; Email: ljwong@bcm.edu.

Surveillance: For those with infantile onset: routine monitoring of feeding and nutrition, seizure control, developmental progress, OT/PT needs, and family social support.

For those with later onset: routine monitoring of OT/PT needs (e.g., mobility and activities of daily living), orthopedic complications (contractures, scoliosis, foot deformities), seizure control, speech and language development, and educational and social needs.

Agents/circumstances to avoid: While valproic acid can induce liver failure in persons with mitochondrial diseases, some individuals with FARS2 deficiency received valproic acid with no evidence of liver dysfunction or worsening of existing liver disease. Given the limited number of affected individuals reported to date, no general recommendation can be made.

Genetic counseling

FARS2 deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has 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 *FARS2* pathogenic variants have been identified in an affected family member, carrier testing of at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

FARS2 Deficiency: Included Phenotypes [1]
• *FARS2*-related infantile-onset epileptic mitochondrial encephalopathy • *FARS2*-related later-onset spastic paraplegia

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

FARS2 deficiency comprises a spectrum of disease severity that ranges between two phenotypes: infantile-onset epileptic mitochondrial encephalopathy and less severe, later-onset spastic paraplegia.

Formal diagnostic criteria for FARS2 deficiency have not been established.

Suggestive Findings

The two phenotypes known to date to be associated with FARS2 deficiency are infantile-onset epileptic mitochondrial encephalopathy and later-onset spastic paraplegia.

***FARS2*-related infantile-onset epileptic mitochondrial encephalopathy should be considered** in children from birth to age six months with the following clinical, laboratory, and imaging findings.

Clinical findings

- Seizures
- Developmental delay
- Truncal hypotonia

Laboratory findings

- Elevated plasma lactate levels; seen in all affected individuals [Almannai et al 2018]
- Elevated cerebrospinal fluid lactate

- Electron transport chain enzyme activity; ranges from normal to low complex I activity, low complex IV activity, or combined deficiency of both
- Elevated liver enzymes (ALT, AST) and gamma-glutamyl transferase in some affected individuals

Neuroimaging findings

- **MRI.** Nonspecific diffuse cortical and subcortical cerebral atrophy particularly later in the disease course; thinning of the corpus callosum (reflecting reduced cerebral white matter volume)

  Occasional findings:

  - Evidence of deep cerebellar white matter involvement and hyperintensity of the hila of the dentate nuclei [Raviglione et al 2016, Almannai et al 2018]
  - Abnormalities in basal ganglia signal intensity [Elo et al 2012, Shamseldin et al 2012, Walker et al 2016]
  - Cystic degeneration with diffuse and symmetric swelling and abnormal signal intensity of the cerebral subcortical white matter, which was completely suppressed on fluid-attenuated inversion recovery (FLAIR) sequence

- **MR spectroscopy (MRS).** High lactate peak

***FARS2*-related later-onset spastic paraplegia should be considered** in individuals age six months and older with the following clinical and laboratory findings.

Clinical findings

- Spastic paraplegia, seen in all individuals with this phenotype, characterized by lower-extremity weakness, spasticity, and exaggerated reflexes associated with walking difficulties
- Spastic paraplegia can be pure or can be complicated by other less common neurologic findings including the following:
  - Developmental delay / intellectual disability
  - Brief seizures that resolve over time

Laboratory findings. Elevated plasma lactate

Establishing the Diagnosis

The diagnosis of FARS2 deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *FARS2* identified by molecular genetic testing (see Table 1).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Because the phenotype of FARS2 deficiency is indistinguishable from many other inherited disorders presenting with infantile epileptic encephalopathy or spastic paraplegia, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *FARS2*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A multigene panel** that includes *FARS2* 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*. Of note, given the rarity of FARS2 deficiency, some panels for infantile epileptic encephalopathy and/or spastic paraplegia may not include *FARS2*. (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 FARS2 deficiency a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

  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 FARS2 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method [3]
FARS2	Sequence analysis [4]	~95%-98%
	Gene-targeted deletion/duplication analysis [5]	3 reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Elo et al [2012], Shamseldin et al [2012], Almalki et al [2014], Vernon et al [2015], de Kovel et al [2016], Raviglione et al [2016], Walker et al [2016], Yang et al [2016], Cho et al [2017], Vantroys et al [2017], Almannai et al [2018], Sahai et al [2018]
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Almalki et al [2014]) may not be detected by these methods.

Clinical Characteristics

Clinical Description

The spectrum of FARS2 deficiency ranges between two phenotypes: infantile-onset disease characterized by epileptic encephalopathy with lactic acidosis and poor prognosis (70% of affected individuals) and later-onset spastic paraplegia (30% of affected individuals) associated with less severe neurologic manifestations and longer survival.

The findings in the 37 individuals with FARS2 deficiency reported to date are summarized in Table 2 [Elo et al 2012, Shamseldin et al 2012, Almalki et al 2014, Vernon et al 2015, de Kovel et al 2016, Raviglione et al 2016, Walker et al 2016, Yang et al 2016, Cho et al 2017, Vantroys et al 2017, Almannai et al 2018, Sahai et al 2018].

Table 2. Clinical, Neuroimaging, and Metabolic Findings in FARS2 Deficiency

		Infantile Onset	Later Onset
Number of families		19	6
Number of individuals		26	11
Age at presentation		Birth-6 mos (median 35 days; mean 62 days)	6 mos-5 yrs (median 2 yrs; mean 2.1 yrs)
Outcome	Alive	8/23 (age range: 4 mos-3.5 yrs; median 1.6 yrs; mean 1.8 yrs)	11/11 (age range: 5.5-41 yrs; median 17 yrs; mean 20 yrs) [1]
	Deceased	15/23 (age range 2 days-15 yrs; median 4 mos; mean 20 mos)	0/11
Neurologic manifestations	DD/ID	24/24	6/11
	Truncal hypotonia	16/19	2/9
	Spasticity	11/19	10/10 (spastic paraplegia)
	Seizures	24/25	3/11
Neuroimaging	MRI: brain atrophy	15/19	2/11
	MRI: thin corpus callosum	12/19	0/11
	MRI: hyperintensity of dentate nuclei	4/19	1/11
	MRS: ↑ lactate peak	8/11	NA
Liver	Enlarged	5/19	0/11
	↑ transaminases	14/19	0/11
	↑ GGT [2]	8/8	NA
Growth	Failure to thrive	9/17	0/8
	Microcephaly	14/18	0/7
Metabolic	Lactic acidosis	21/22	3/10
	↑ CSF lactate	7/7	2/3
	↑ plasma alanine	13/17	4/6
ETC enzyme activity	Low complex I activity	3/7	1/2
	Low complex IV activity	4/7	1/2
	Normal activity	2/7	0/2

CSF = cerebrospinal fluid; DD = developmental delay; ETC = electron transport chain; GGT = gamma-glutamyl transferase; ID = intellectual disability; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy

1. One individual who had hypoxic-ischemic encephalopathy was not included in age-of-onset calculations. For another individual (who had seizures with a normal EEG following vaccination at age 2 months), age of onset was considered to be 3 years (the age at which he was evaluated for developmental delay [Vernon et al 2015].

2. Elevations up to 1,700 U/L were observed.

Infantile-Onset Epileptic Mitochondrial Encephalopathy

Seizures. Seizures were the most common presenting manifestation. Of note, the only infant who did not have seizures was a premature infant who died at age two days.

Seizures tend to be focal with associated facial or eye twitching and myoclonic jerks of the extremities. Other types of seizures include generalized tonic-clonic, infantile spasms, and epilepsia partialis continua. Seizures are difficult to control and may progress quickly at an early age to intractable seizures with frequent status epilepticus. EEG usually shows multifocal epileptic discharges. A few children had hypsarrhythmia.

Developmental delay. All children had developmental delays affecting all domains. Most did not develop expressive language and were not able to walk. Regression was noted in a few individuals after the onset of seizures.

Variable degree of truncal hypotonia, observed early in the course of the disease, is usually associated with appendicular hypertonia and long tract signs.

Several children with the infantile-onset phenotype developed central visual impairment, usually with normal fundoscopic examination (i.e., without optic atrophy or retinal changes). One child was reported to have coarse retinal pigmentation [Elo et al 2012].

Growth. Failure to thrive reflects the often observed feeding and swallowing difficulties. Microcephaly, which is of postnatal onset, results from diffuse cerebral atrophy that develops later in the disease course.

Liver disease. There was no significant elevation in total and direct bilirubin to suggest cholestasis. Liver involvement of unknown cause manifested as enlarged liver in some individuals. In one child, liver biopsy showed enlarged hepatocytes and increased amounts of glycogen and lysosomal iron and copper. The neuropathologic brain findings of this child met diagnostic criteria for Alpers-Huttenlocher disease [Elo et al 2012] (see also *POLG*-Related Disorders).

Of note: Although some children were treated with valproic acid (which can induce liver failure in persons with mitochondrial disorders) [Krähenbühl et al 2000], none had evidence of liver dysfunction or worsening of existing liver disease [Elo et al 2012, Walker et al 2016, Cho et al 2017].

Less frequently reported manifestations include the following:

- Strabismus [Raviglione et al 2016]
- Nystagmus [Raviglione et al 2016]
- Non-epileptic myoclonus [Almalki et al 2014, Walker et al 2016]

Prognosis. More than half of the reported children with the infantile-onset phenotype died early. Causes of death included uncontrolled seizures and secondary infections. Several children with profound developmental delay and uncontrolled seizures died shortly after the decision was made to provide palliative care only.

FARS2-Related Later-Onset Spastic Paraplegia

All individuals with the later-onset phenotype had spastic paraplegia, manifest as weakness, spasticity, and exaggerated reflexes of the lower extremities associated with walking difficulties. Spastic paraplegia could be pure or complicated by other less common neurologic findings including the following:

- Developmental delay / intellectual disability that is less severe than the DD/ID seen in the infantile-onset phenotype (e.g., 5/6 affected individuals developed expressive language)
- Brief seizures that resolved over time [Vernon et al 2015, Vantroys et al 2017]

Less frequently reported neurologic findings:

- Startle myoclonus [Vantroys et al 2017]
- Inattention tremor [Vernon et al 2015, Vantroys et al 2017]
- Bradykinesia [Vantroys et al 2017]
- Dystonia [Vantroys et al 2017]

- Dysarthria [Vernon et al 2015, Vantroys et al 2017]

Less frequently reported manifestations:

- Strabismus [Vernon et al 2015]
- Scoliosis [Vernon et al 2015, Vantroys et al 2017]

Prognosis. All 11 individuals with the later-onset phenotype were alive at the time of reporting. Three were able to walk independently; the remainder depended on a walker or wheelchair for mobility. Five of the 11 individuals had normal speech, five had dysarthric speech, and one was nonverbal. Five of the 11 had normal cognition; the remainder had variable, mostly mild intellectual disability.

Genotype-Phenotype Correlations

It is difficult to establish a genotype-phenotype correlation in FARS2 deficiency given the limited number of affected individuals and the complication of compound heterozygosity in such studies.

All 14 individuals homozygous for the most commonly reported variant, p.Tyr144Cys, had the infantile-onset phenotype (see Table 9).

Although the number of affected individuals reported to date is small, the infantile-onset and later-onset phenotypes have not shared the same genotypes.

Nomenclature

FARS2-related infantile-onset epileptic mitochondrial encephalopathy may also be referred to as combined oxidative phosphorylation deficiency 14 or phenylalanyl aminoacyl tRNA synthetase deficiency.

FARS2-related later-onset spastic paraplegia may also be referred to as autosomal recessive spastic paraplegia 77 (SPG77).

Prevalence

FARS2 deficiency is rare; the exact prevalence is unknown. To date, 37 affected individuals from 25 families have been reported.

The 25 families belong to different ethnic groups.

- Eleven families (all with children with the infantile-onset phenotype) were Arabs, ten from Saudi Arabia and one from Iraq. In all but two families, the parents were consanguineous.
- Other affected populations include Asian, European, North American, Ashkenazi Jewish, and Hispanic.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic germline pathogenic variants in *FARS2*.

Differential Diagnosis

Phenotypic features associated with *FARS2* pathogenic variants are not sufficient to diagnose FARS2 deficiency.

For children with a phenotype consistent with **infantile-onset epileptic mitochondrial encephalopathy**, all genes known to be associated with early-infantile epileptic encephalopathy (>65 have been identified; see OMIM Phenotypic Series) should be included in the differential diagnosis.

For individuals with **later-onset spastic paraplegia**, all genes known to be associated with complicated spastic paraplegia (see Hereditary Spastic Paraplegia Overview) should be included in the differential diagnosis. Because some of the individuals with the later-onset phenotype were diagnosed initially to have cerebral palsy (CP), this diagnosis should be considered in individuals with a diagnosis of CP, especially when it progresses over time or the family history is positive.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with FARS2 deficiency, the evaluations summarized in Table 3 and Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with FARS2 Deficiency: Infantile-Onset Epileptic Encephalopathy

System/Concern	Evaluation	Comment
Constitutional	Assess height, weight, head circumference.	FTT is a significant issue for all patients.
Neurologic	Assess for seizures.	Seizures are usually focal but other forms are possible. EEG usually shows multifocal epileptic discharges.
	Assess for myoclonus.	Eye & facial twitching; myoclonic jerks of extremities
	Assess for hypotonia.	Axial hypotonia could be assoc w/appendicular hypertonia.
Development	Developmental assessment	Incl assessment of age-appropriate motor, speech/language, cognitive skills
Ophthalmologic	Assess visual acuity.	Central visual impairment (i.e., w/o retinal or optic nerve changes) is common.
Musculoskeletal	Physical medicine & rehab / PT & OT eval	Assess tone & spasticity.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	Assess swallowing, feeding, & nutritional status to determine safety of oral vs gastrostomy feeding.
	Assess for evidence of hepatic involvement.	Liver enzymes & hepatic ultrasound exam
Respiratory	Assess airway, pulmonary function, & secretion mgmt.	Sleep study to assess for apnea
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

FTT = failure to thrive; OT = occupational therapy; PT = physical therapy

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with FARS2 Deficiency: Later-Onset Spastic Paraplegia

System/Concern	Evaluation	Comment
Neurologic	Assess for seizures.	Seizures are uncommon & usually brief & self-limited.
	Assess for truncal hypotonia &/or spastic paraplegia.	Lower-limb spasticity w/weakness, hyperreflexia, & abnormal gait
	Assess for myoclonus, tremor, bradykinesia, dystonia, dysarthria.	Findings that are occasionally seen
Musculoskeletal	Orthopedic, physical medicine & rehab, & PT/OT eval	Assess tone, spasticity, range of motion, gait, & need for assistive devices.
Development	Developmental assessment	Incl assessment of age-appropriate motor, speech/ language, cognitive, vocational skills

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Speech	Assessment by a speech pathologist	For those w/dysarthria
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Treatment is symptomatic and best provided by a multidisciplinary team comprising neurodevelopmental pediatricians, neurologists, physiatrists, occupational and physical therapists, feeding specialists, speech and language therapists, and social workers to assure adequate family support.

Table 5. Treatment of Manifestations in Individuals with FARS2 Deficiency: Infantile-Onset Epileptic Encephalopathy

Manifestation/ Concern	Treatment	Considerations/Other
Central visual impairment	No specific treatment; early intervention to help stimulate visual development	
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Respiratory insufficiency	Standard treatment per respiratory review	
Seizures	Treatment by experienced neurologist	Most common ASMs (e.g., levetriacetam, phenobarbital, clobazam, lacosamide) are not successful in controlling seizures. [1, 2]
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

ASM = anti-seizure medication

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

2. One child remained seizure-free for 23 months on vigabatrin 50 mg/kg/day. He had also received adrenocorticotropic hormone (ACTH), which was tapered off over eight weeks [Raviglione et al 2016]. Another child developed infantile spasms at age 6 months that resolved with prednisolone; however, refractory seizures occurred six months later [Almalki et al 2014].

Table 6. Treatment of Manifestations in Individuals with FARS2 Deficiency: Later-Onset Spastic Paraplegia

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
	• Anti-spasticity medications (e.g., oral or intrathecal baclofen) • Botulinum toxin injections • Surgical interventions to ↓ spasticity	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Seizures	Treatment by experienced neurologist	• Standard treatment w/ASM by experienced neurologist • See footnote 1.

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

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states and provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; however, for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life. Some issues to consider:

- IEP services for those who require specially designed instruction/related services
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP services to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - Services are reviewed annually to determine if any changes are needed.
  - As a child enters teen years, a transition plan should be discussed and incorporated into the IEP. For those receiving IEP services, the public school district is required to provide services until age 21 years.
- A 504 (Section 504: a federal statute that prohibits discrimination based on disability) plan can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

- **Gross motor dysfunction**
  - Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
  - Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
  - For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.
- **Communication issues.** Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech (e.g., picture exchange communication) to high-tech (e.g., voice-generating devices). Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.
- **Oral-motor dysfunction** should be reassessed at each visit, and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Feeding therapy can be helpful to improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled to provide more safety, but when severe feeding dysfunction is present, an NG-tube or a G-tube may be necessary.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Individuals with FARS2 deficiency should be evaluated periodically by an interdisciplinary team that includes a neurologist, clinical geneticist, physiatrist, and developmental specialist to assess disease progression (Table 7 and Table 8), to maximize ambulation and communication skills, and to reduce other manifestations (Table 8).

Table 7. Recommended Surveillance for Individuals with FARS2 Deficiency: Infantile-Onset Epileptic Encephalopathy

System/Concern	Evaluation	Frequency
Feeding	Assess nutritional status & feeding w/attention to poor weight gain, choking/gagging during feeds, feeding refusal not otherwise explained.	At each visit
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Neurologic	Monitor those w/seizures as clinically indicated.	
Development	Monitor developmental progress & educational needs.	
Musculoskeletal	• PT/OT eval for contractures, scoliosis, & foot deformities • Consider need for positioning devices.	
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy

Table 8. Recommended Surveillance for Individuals with FARS2 Deficiency: Later-Onset Spastic Paraplegia

System/Concern	Evaluation	Frequency
Musculoskeletal	PT/OT eval; assessment for contractures, scoliosis, & foot deformities; consider need for positioning &/or mobility devices.	Each visit
Neurologic	Monitor those w/seizures as clinically indicated.	If concerns for new seizure activity or progression of seizures; seizures are usually brief & resolve over time
	Assess for new manifestations such as myoclonus, tremor, bradykinesia, dystonia, dysarthria.	Each visit
Development	Monitor developmental progress & educational needs.	If concern for developmental delay / learning difficulties

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Valproic acid can induce liver failure in persons with mitochondrial diseases [Krähenbühl et al 2000]. Some individuals with FARS2 deficiency received valproic acid and showed no evidence of liver dysfunction or worsening of existing liver disease [Elo et al 2012, Walker et al 2016, Cho et al 2017]. Given the limited number of affected individuals reported to date, no general recommendation can be made.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs of an individual with the later-onset spastic paraplegia phenotype in order to identify as early as possible those who would benefit from prompt initiation of intervention for developmental and/or neurologic problems (e.g., spasticity).

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

FARS2 deficiency is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *FARS2* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has 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

- Unless an affected individual's reproductive partner also has *FARS2*-related later-onset spastic paraplegia or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *FARS2*.
- To date, individuals with *FARS2*-related infantile-onset epileptic mitochondrial encephalopathy are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *FARS2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FARS2* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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 *FARS2* 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 testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

No specific resources for FARS2 Deficiency have been identified by *GeneReviews* staff.

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. FARS2 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
FARS2	6p25.1	Phenylalanine--tRNA ligase, mitochondrial	FARS2	FARS2

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 FARS2 Deficiency (View All in OMIM)

611592	PHENYLALANYL-tRNA SYNTHETASE 2, MITOCHONDRIAL; FARS2
614946	COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 14; COXPD14
617046	SPASTIC PARAPLEGIA 77, AUTOSOMAL RECESSIVE; SPG77

Molecular Pathogenesis

FARS2 encodes mitochondrial phenylalanine-tRNA ligase (phenylalanyl-tRNA synthetase [mtPheRS]), which transfers phenylalanine (Phe) to its cognate tRNA in mitochondria [Bullard et al 1999]. Human mtPheRS includes four domains: the N-terminal region (residues 37-83), the catalytic (aminoacylation) domain (residues 84-325), the linker region (residues 326-358), and the anticodon binding domain (residues 359–451) [Klipcan et al 2008]. MtPheRS has two functional conformations. In its open "active" form, it binds tRNA and catalyzes the attachment of Phe to its cognate tRNA in the aminoacylation domain. In the closed "inactive" form, the anticodon binding domain rotates back close to the aminoacylation domain, thereby failing to exhibit an electrostatic complementarity to cognate tRNA [Klipcan et al 2008].

Mechanism of disease causation. Different types of *FARS2* pathogenic variants result in structural and kinetic changes in MtPheRS that in turn affect one or more steps in the process of transferring Phe to its cognate tRNA in the mitochondria – thus affecting mitochondrial protein synthesis [Kartvelishvili et al 2017]. All large deletions, splice site variants, and nonsense variants are *in trans* with a missense variant. This suggests that complete loss of function may be incompatible with life.

Table 9. Notable *FARS2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_006567.4	c.431A>G	p.Tyr144Cys	Arab founder variant [Shamseldin et al 2012, Almannai et al 2018]
	c.424G>T	p.Asp142Tyr	Reported in homozygous state in later-onset phenotype [Yang et al 2016]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Revision History

- 14 March 2019 (bp) Review posted live
- 9 November 2018 (ljw) Original submission

References

Literature Cited

Almalki A, Alston CL, Parker A, Simonic I, Mehta SG, He L, Reza M, Oliveira JMA, Lightowlers RN, McFarland R, Taylor RW, Chrzanowska-Lightowlers ZMA. Mutation of the human mitochondrial phenylalanine-tRNA synthetase causes infantile-onset epilepsy and cytochrome c oxidase deficiency. Biochim Biophys Acta. 2014;1842:56–64. PubMed PMID: 24161539.

Almannai M, Wang J, Dai H, El-Hattab AW, Faqeih EA, Saleh MA, Al Asmari A, Alwadei AH, Aljadhai YI, AlHashem A, Tabarki B, Lines MA, Grange DK, Benini R, Alsaman AS, Mahmoud A, Katsonis P, Lichtarge O, Wong L-JC. FARS2 deficiency; new cases, review of clinical, biochemical, and molecular spectra, and variants interpretation based on structural, functional, and evolutionary significance. Mol Genet Metab. 2018;125:281–91. PubMed PMID: 30177229.

Bullard JM, Cai Y-C, Demeler B, Spremulli LL. Expression and characterization of a human mitochondrial phenylalanyl-tRNA synthetase. J Mol Biol. 1999;288:567–77. PubMed PMID: 10329163.

Cho JS, Kim SH, Kim HY, Chung T, Kim D, Jang S, Lee SB, Yoo SK, Shin J, Kim J-I, Kim H, Hwang H, Chae J-H, Choi J, Kim KJ, Lim BC. FARS2 mutation and epilepsy: possible link with early-onset epileptic encephalopathy. Epilepsy Res. 2017;129:118–24. PubMed PMID: 28043061.

de Kovel CGF, Brilstra EH, van Kempen MJA, Van't Slot R, Nijman IJ, Afawi Z, De Jonghe P, Djémié T, Guerrini R, Hardies K, Helbig I, Hendrickx R, Kanaan M, Kramer U, Lehesjoki A-EE, Lemke JR, Marini C, Mei D, Møller RS, Pendziwiat M, Stamberger H, Suls A, Weckhuysen S, Koeleman BPC, et al. Targeted sequencing of 351 candidate genes for epileptic encephalopathy in a large cohort of patients. Mol Genet Genomic Med. 2016;4:568–80. PubMed PMID: 27652284.

Elo JM, Yadavalli SS, Euro L, Isohanni P, Götz A, Carroll CJ, Valanne L, Alkuraya FS, Uusimaa J, Paetau A, Caruso EM, Pihko H, Ibba M, Tyynismaa H, Suomalainen A. Mitochondrial phenylalanyl-tRNA synthetase mutations underlie fatal infantile Alpers encephalopathy. Hum Mol Genet. 2012;21:4521–9. PubMed PMID: 22833457.

Kartvelishvili E, Tworowski D, Vernon H, Moor N, Wang J, Wong L, Chrzanowska-Lightowlers Z, Safro M. Kinetic and structural changes in H smt PheRS, induced by pathogenic mutations in human FARS 2. Protein Sci. 2017;26:1505–16. PubMed PMID: 28419689.

Klipcan L, Levin I, Kessler N, Moor N, Finarov I, Safro M. The tRNA-induced conformational activation of human mitochondrial phenylalanyl-tRNA synthetase. Structure. 2008;16:1095–1104. PubMed PMID: 18611382.

Krähenbühl S, Brandner S, Kleinle S, Liechti S, Straumann D. Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure. Liver. 2000;20:346–8. PubMed PMID: 10959815.

Raviglione F, Conte G, Ghezzi D, Parazzini C, Righini A, Vergaro R, Legati A, Spaccini L, Gasperini S, Garavaglia B, Mastrangelo M. Clinical findings in a patient with FARS2 mutations and early-infantile-encephalopathy with epilepsy. Am J Med Genet A. 2016;170:3004–7. PubMed PMID: 27549011.

Sahai SK, Steiner RE, Au MG, Graham JM, Salamon N, Ibba M, Pierson TM. FARS2 mutations presenting with pure spastic paraplegia and lesions of the dentate nuclei. Ann Clin Transl Neurol. 2018;5:1128–33. PubMed PMID: 30250868.

Shamseldin HE, Alshammari M, Al-Sheddi T, Salih MA, Alkhalidi H, Kentab A, Repetto GM, Hashem M, Alkuraya FS. Genomic analysis of mitochondrial diseases in a consanguineous population reveals novel candidate disease genes. J Med Genet. 2012;49:234–41. PubMed PMID: 22499341.

Vantroys E, Larson A, Friederich M, Knight K, Swanson MA, Powell CA, Smet J, Vergult S, De Paepe B, Seneca S, Roeyers H, Menten B, Minczuk M, Vanlander A, Van Hove J, Van Coster R. New insights into the phenotype of FARS2 deficiency. Mol Genet Metab. 2017;122:172–81. PubMed PMID: 29126765.

Vernon HJ, McClellan R, Batista DAS, Naidu S. Mutations in FARS2 and non-fatal mitochondrial dysfunction in two siblings. Am J Med Genet A. 2015;167A:1147–51. PubMed PMID: 25851414.

Walker MA, Mohler KP, Hopkins KW, Oakley DH, Sweetser DA, Ibba M, Frosch MP, Thibert RL. Novel compound heterozygous mutations expand the recognized phenotypes of FARS2-linked disease. J Child Neurol. 2016;31:1127–37. PubMed PMID: 27095821.

Yang Y, Liu W, Fang Z, Shi J, Che F, He C, Yao L, Wang E, Wu Y. A newly identified missense mutation in FARS2 causes autosomal-recessive spastic paraplegia. Hum Mutat. 2016;37:165–9. PubMed PMID: 26553276.

License