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Mitochondrial Short-Chain Enoyl-CoA Hydratase 1 Deficiency

Synonyms: ECHS1D, ECHS1 Deficiency, Mitochondrial Short-Chain Enoyl-CoA Hydratase Deficiency, SCEH Deficiency

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Summary

Clinical characteristics

Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D) represents a clinical spectrum in which several phenotypes have been described:

- The most common phenotype presents in the neonatal period with severe encephalopathy and lactic acidosis and later manifests Leigh-like signs and symptoms. Those with presentation in the neonatal period typically have severe hypotonia, encephalopathy, or neonatal seizures within the first few days of life. Signs and symptoms typically progress quickly and the affected individual ultimately succumbs to central apnea or arrhythmia.
- A second group of affected individuals present in infancy with developmental regression resulting in severe developmental delay.
- A third group of affected individuals have normal development with isolated paroxysmal dystonia that may be exacerbated by illness or exertion.

Across all three groups, T_2 hyperintensity in the basal ganglia is very common, and may affect any part of the basal ganglia.

Diagnosis/testing

The diagnosis of ECHS1D is established in a proband by the identification of biallelic pathogenic variants in *ECHS1* on molecular genetic testing or low short-chain enoyl-CoA hydratase (SCEH) activity using cultured skin fibroblasts.

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Management

Treatment of manifestations: Treatment of severe metabolic acidosis with bicarbonate therapy; hyperammonemia (which may be related to severe acidosis or low ATP from impaired aerobic oxidation) may be addressed by treatment of the metabolic acidosis and/or consideration of hemodialysis. Inadequate nutrition may require feeding therapy; placement of a feeding tube may be considered. Paroxysmal dystonia may respond to benzodiazepines, whereas chronic dystonia may require botulinum toxin injections. Treatment of dystonia with levodopa may also be considered. Standard treatment for seizures, cardiomyopathy, pulmonary hypertension, optic atrophy, sensorineural hearing loss, and developmental delay.

Surveillance: At least annual echocardiogram, dilated eye examination, and audiologic evaluation. Routine monitoring for neurologic symptoms and developmental issues. Assessment of acid/base status and blood lactate level with all illnesses or metabolic stressors.

Agents/circumstances to avoid: Mitochondrial toxins (i.e., valproic acid, prolonged propofol infusions); ketogenic diet.

Genetic counseling

ECHS1 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% change of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if the *ECHS1* pathogenic variants in the family are known.

Diagnosis

No consensus clinical diagnostic criteria for ECHS1 deficiency (ECHS1D) have been published.

Suggestive Findings

Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D) **should be suspected** in individuals with clinical features of Leigh syndrome and/or exercise-induced dystonia who have supportive brain MRI and biochemical findings, including early-onset lactic acidosis.

Clinical features

- **Neurologic**
  - Developmental delay, often severe [Sakai et al 2015, Tetreault et al 2015, Huffnagel et al 2018, Aretini et al 2018]
  - Infantile encephalopathy (may be epileptic), hypotonia, and/or spasticity [Ferdinandusse et al 2015, Haack et al 2015, Bedoyan et al 2017, Aretini et al 2018]
  - Dystonia (exercise induced) and/or choreoathetotic movements [Korenke et al 2016, Olgiati et al 2016, Mahajan et al 2017]
- **Growth.** Failure to thrive, which may present prenatally as intrauterine growth restriction and/or oligohydramnios in the most severe cases [Ganetzky et al 2016, Bedoyan et al 2017]
- **Cardiorespiratory**
  - Hypertrophic or dilated cardiomyopathy [Haack et al 2015, Ganetzky et al 2016, Nair et al 2016, Nouguès et al 2017]
  - Pulmonary hypertension [Ferdinandusse et al 2015]
- **Ophthalmologic**
  - Optic atrophy [Haack et al 2015, Aretini et al 2018]

- Nystagmus [Tetreault et al 2015]
- Glaucoma [Ferdinandusse et al 2015]
- Strabismus [Aretini et al 2018]
- Corneal clouding [Ganetzky et al 2016]

- **Other**
  - Sensorineural hearing loss [Haack et al 2015, Tetreault et al 2015]
  - Nonspecific dysmorphic features or structural abnormalities (no consistent pattern has emerged) [Haack et al 2015, Ganetzky et al 2016]

Brain MRI findings

- T_2 hyperintense signal in the basal ganglia (especially putamen and globus pallidus) [Ferdinandusse et al 2015, Haack et al 2015, Tetreault et al 2015, Korenke et al 2016]
- Cerebral atrophy [Ferdinandusse et al 2015, Huffnagel et al 2018]
- Agenesis or thinning of the corpus callosum [Ferdinandusse et al 2015, Haack et al 2015, Ganetzky et al 2016]
- High lactate with normal lactate to pyruvate ratio peak on MR-spectroscopy [Peters et al 2014, Haack et al 2015, Tetreault et al 2015]

Biochemical features

- Lactic acidosis. Pyruvate may be mildly elevated, elevated proportionally to the lactate, or normal [Ferdinandusse et al 2015, Sakai et al 2015, Ganetzky et al 2016, Bedoyan et al 2017].
- Abnormal urine organic acids, including elevations of:
  - 2-methyl-2,3-dihydoxybutyrate [Ferdinandusse et al 2015, Haack et al 2015, Bedoyan et al 2017]
  - Branched-chain ketoacids [Bedoyan et al 2017]
  - 3-hydroxyisovalerate [Huffnagel et al 2018]
  - 3-methylglutaconic acid, ketones, and lactate [Bedoyan et al 2017]
- Elevations of urine acryloyl-cysteamine, acryloyl-l-cysteamine, N-acetyl-acryloyl-cysteine, methacryl-cysteamine, methacryl-cysteamine, or N-acetyl-methacryl-l-cysteamine [Peters et al 2014, Peters et al 2015, Yamada et al 2015, Huffnagel et al 2018]
- While plasma acylcarnitine profile is often normal, slight elevations of C4 acylcarnitines may be seen [Ganetzky et al 2016, Nair et al 2016, Bedoyan et al 2017].
- If performed, muscle or fibroblast electron transport chain function (ETC) is typically normal, although mild decreases in complex I, III, IV, or multiple complexes, with residual activity above 30% of control function, can be seen [Haack et al 2015, Sakai et al 2015, Tetreault et al 2015, Bedoyan et al 2017, Aretini et al 2018, Fitzsimons et al 2018].

Note: Muscle biopsy is not required to make a diagnosis of ECHS1D.

Establishing the Diagnosis

The diagnosis of ECHS1D **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *ECHS1* on 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.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of ECHS1D is broad, individuals with the distinctive biochemical findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with lactic acidosis, Leigh syndrome, and/or dystonia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of ECHS1D, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ECHS1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A mitochondrial disease, Leigh syndrome, or lactic acidosis multigene panel** that includes *ECHS1* 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 phenotype is indistinguishable from many other inherited disorders characterized by early epileptic encephalopathy, Leigh Syndrome, or lactic acidosis, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic (particularly if only one pathogenic variant has been identified), an **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 ECHS1 Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
ECHS1	Sequence analysis [3]	30/31
	Gene-targeted deletion/duplication analysis [4]	1/31 [5]

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. 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.
4. 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.
5. One affected individual had a larger deletion that included *ECHS1* and adjacent genes [Aretini et al 2018].

Clinical Characteristics

Clinical Description

Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D) has been reported in 40 individuals representing 31 families [Peters et al 2014, Ferdinandusse et al 2015, Haack et al 2015, Sakai et al 2015, Yamada et al 2015, Ganetzky et al 2016, Nair et al 2016, Olgiati et al 2016, Al Mutairi et al 2017, Balasubramaniam et al 2017, Bedoyan et al 2017, Mahajan et al 2017, Fitzsimons et al 2018]. ECHS1D represents a clinical spectrum in which several phenotypes have been described. The most common phenotype is presentation in the neonatal period with severe encephalopathy and lactic acidosis and later-onset Leigh-like signs and symptoms. A small number of affected individuals have normal development, exercise-induced dystonia, and basal ganglia abnormalities on MRI [Olgiati et al 2016, Mahajan et al 2017].

Age of onset is soon after birth in a majority of reported individuals (median age of onset: 1 day; range 1 day – 8 years, n=40); only five reported individuals have presented after the first year of life. In five affected individuals, prenatal signs (intrauterine growth restriction and/or oligohydramnios) were identified; two of those individuals were born prematurely [Ganetzky et al 2016, Nair et al 2016, Fitzsimons et al 2018].

Common clinical manifestations are summarized in Table 2 and discussed below.

Table 2. Common Clinical Manifestations of ECHS1 Deficiency

	Clinical Manifestation	Frequency
Neurologic [1]	Signal abnormalities in the basal ganglia	28/32 (88%)
	Developmental delay	27/32 (84%)
	Hypotonia	21/30 (70%)
	Dystonia	15/29 (52%)
	Seizures	12/23 (52%)
	Encephalopathy	12/31 (39%)
	Ataxia/choreoathetosis	5/25 (20%)
Growth	Failure to thrive	20/32 (62%)
	Microcephaly	7/30 (23%)
	Intrauterine growth restriction	5/27 (18%)

Table 2. continued from previous page.

	Clinical Manifestation	Frequency
Cardiovascular	Cardiomyopathy	9/15 (60%)
	Pulmonary hypertension	3/14 (21%)
Ophthalmologic	Nystagmus	10/31 (32%)
	Optic atrophy	8/27 (30%)
	Corneal clouding	1/27 (4%)
Other	Sensorineural hearing loss	13/27 (48%)
	Apnea	7/37 (19%)
	Liver steatosis &/or hepatomegaly	5/6 (83%)
Biochemical/ Enzymatic	Lactic acidemia	27/36 (75%)
	Low PDC activity (in cultured fibroblasts)	5/12 (42%)

1. Neurologic manifestations were seen in all 40 individuals reported [Ganetzky et al 2016, Nair et al 2016, Fitzsimons et al 2018].

Neurologic. Most affected individuals reported have presented with severe hypotonia, encephalopathy, or neonatal seizures within the first few days of life. In this scenario, signs and symptoms typically progress quickly and the affected individual ultimately succumbs to central apnea or arrhythmia [Haack et al 2015, Ganetzky et al 2016, Nair et al 2016, Bedoyan et al 2017]. Affected individuals who survive the neonatal period typically have continued truncal hypotonia but develop limb spasticity. They tend to have severe static developmental delay.

A second group of affected individuals present in infancy (after the neonatal period up to age 24 months) with developmental regression [Tetreault et al 2015, Yamada et al 2015, Fitzsimons et al 2018], typically leading to severe developmental delay.

There have been two reports of individuals with isolated paroxysmal dystonia and otherwise normal development. In one report, two of three affected individuals were sibs, one of whom had learning disabilities [Olgiati et al 2016]. The other (unrelated) reported individual had attention deficit with hyperactivity disorder [Mahajan et al 2017].

Dystonia, or less commonly choreoathetosis and/or ataxia, is usually chronically present, but is exacerbated by illness or exertion [Tetreault et al 2015, Olgiati et al 2016].

Across all three phenotypes, T_2 hyperintensity in the basal ganglia is very common (88%) and may affect any part of the basal ganglia. This is seen even in those whose clinical presentation is limited to paroxysmal exercise-induced dystonia [Olgiati et al 2016, Mahajan et al 2017].

Growth. Most children with ECHS1 deficiency require enteral feeding tubes because of severe developmental delay and hypotonia. Dysphagia has been reported in three individuals, one of whom suffered aspiration events [Ferdinandusse et al 2015, Yamada et al 2015].

Cardiac. Cardiomyopathy may be dilated or hypertrophic. In two affected individuals, cardiac hypertrophy was transient [Ferdinandusse et al 2015, Fitzsimons et al 2018]. Three individuals with pulmonary hypertension have been reported [Ferdinandusse et al 2015, Nair et al 2016]. Two other individuals have had terminal bradycardiac arrhythmias in the setting of lactic acidosis. It is unclear whether this was as a result of a predisposition to arrhythmia or secondary to overwhelming metabolic acidosis [Ganetzky et al 2016, Al Mutairi et al 2017].

Sensorineural hearing loss. Hearing loss may be found incidentally by audiologic screening. Hearing loss may be mild and is often stable. Two affected individuals required hearing aids for severe hearing loss [Tetreault et al 2015, Aretini et al 2018].

Liver dysfunction. Hepatomegaly or hepatosplenomegaly has been seen in multiple infantile cases. Liver steatosis is often present in those who have had postmortem examinations. However, no individuals with clinically significant liver dysfunction have been reported [Ferdinandusse et al 2015, Ganetzky et al 2016, Bedoyan et al 2017, Fitzsimons et al 2018].

Biochemical and enzymatic features

- Lactate levels may be extremely high, causing metabolic acidosis as the primary clinical finding [Haack et al 2015, Ganetzky et al 2016, Nair et al 2016, Al Mutairi et al 2017, Bedoyan et al 2017]. However, in cases with onset after the neonatal period, lactic academia may be intermittent [Huffnagel et al 2018].
- Two affected individuals have had moderate hyperammonemia in the setting of profound neonatal metabolic stress, potentially related to their severe metabolic acidosis and/or low ATP secondary to impaired aerobic oxidation. Levels have been reported ranging from 150 to 800 µmol/L in cases with a concommittent pH < 7.1 [Ferdinandusse et al 2015, Nair et al 2016].
- Elevated creatine kinase (CK) levels (hyperCKemia) to about 3,000 IU/L in a critically ill newborn [Ferdinandusse et al 2015] and transient mild hypoglycemia [Olgiati et al 2016] have also been reported.
- In affected individuals, low pyruvate dehydrogenase complex (PDC) activity in cultured fibroblasts is noted in about 40% of cases [Bedoyan et al 2017]. Low PDC activity has also been noted in lymphocytes as well as liver and skeletal muscle [Ferdinandusse et al 2015, Bedoyan et al 2017].

Other manifestations. Variable dysmorphic facial features and structural anomalies have each been reported in a few affected individuals.

- Facial features are variable, but may include a long philtrum, similar to what is seen in individuals with pyruvate dehydrogenase deficiency [Ganetzky et al 2016, Balasubramaniam et al 2017].
- The only recurrent structural abnormality is thinning or absence of the corpus callosum [Ganetzky et al 2016, Bedoyan et al 2017, Fitzsimons et al 2018].
- The following have each been described in one affected individual:
  - Hypospadias [Ganetzky et al 2016]
  - Gastroschisis [Haack et al 2015]
  - Cutis laxa [Balasubramaniam et al 2017]
  - Hypertrichosis [Fitzsimons et al 2018]
  - Abnormal lung septation, multiple splenules, and a preauricular tag [Ganetzky et al 2016]

Prognosis. The prognosis of neonatal-onset ECHS1 deficiency is poor. Of the 18 reported neonatal cases, 16 (89%) are deceased, mostly within days to weeks of birth from overwhelming lactic acidosis, apnea, hypotension, or bradycardia. Of the 13 later-onset cases, five are deceased (38%), all in early childhood.

In contrast, those with the paroxysmal dystonia phenotype have been mildly affected with no reported deaths and relatively normal cognitive development. There is likely a broad spectrum between the infantile phenotype and the paroxysmal dystonia phenotype, as individuals with paroxysmal dystonia have been diagnosed after metabolic decompensation [Olgiati et al 2016] or stroke-like episodes [Authors, unpublished observation], but this is not yet clear.

Genotype-Phenotype Correlations

All affected individuals with the paroxysmal dystonia phenotype have been compound heterozygous for the pathogenic c.518C>T variant and a second pathogenic variant [Korenke et al 2016, Olgiati et al 2016, Mahajan et al 2017]. The c.518C>T variant, however, has not been identified in affected individuals with other, more severe clinical phenotypes [Bedoyan et al 2017].

Prevalence

ECHS1 deficiency is rare; the exact prevalence and incidence are unknown.

To date, 40 affected individuals representing 31 families from different ethnic backgrounds / geographic locations – including European, East Asian, French Canadian, and Middle Eastern – have been reported [Nair et al 2016]. No affected individuals of African heritage have yet been reported.

Additional data are required to determine if the c.538A>G (p.Thr180Ala) variant is a French Canadian founder variant [Sharpe & McKenzie 2018].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ECHS1*.

Differential Diagnosis

Table 3. Disorders to Consider in the Differential Diagnosis of ECHS1 Deficiency (ECHS1D)

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/ECHS1D	Distinguishing from ECHS1D
Primary pyruvate dehydrogenase complex deficiency (PDCD)	*DLAT* *DLD* *PDHA1* *PDHB* *PDHX* *PDK3* *PDP1*	AR XL	• Pyruvate dehydrogenase complex deficiency • Lactic acidosis • ↑ pyruvate • Nl lactate to pyruvate ratio • Long philtrum • Corpus callosum hypoplasia	• May be a complete phenocopy [1] • Persons w/ECHS1D may have abnl acylcarnitine profile or urine organic acids not typically seen in primary PDCD.
3-hydroxyisobutyryl-CoA hydrolase deficiency (HIBCHD) (OMIM 250620)	*HIBCH*	AR	• Lactic acidosis • Basal gangliar lesions • ↑ 2-methyl-2,3-dihydroxybutyrate	Organic acid abnormalities typically more pronounced in HIBCH
FBXL4-related encephalomyopathic mitochondrial DNA depletion syndrome	*FBXL4*	AR	• Neonatal/primary lactic acidosis • Variable cardiomyopathy	• FBXL4 deficiency typically has more striking hyperammonemia. • ATP synthase deficiency typically has more prominent 3-methylglutaconic aciduria. • ECHS1D may be suspected (rather than FBXL4 or TMEM70 deficiency) if 2-methyl-2,3-dihydroxybutyrate is present or lactate-to-pyruvate ratio is nl.
Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2 (OMIM 614052)	*TMEM70*			
Mitochondrial complex I deficiency due to ACAD9 deficiency (OMIM 611126)	*ACAD9*			
Other Leigh syndromes (See Nuclear Gene-Encoded Leigh Syndrome Overview & Mitochondrial DNA-Associated Leigh Syndrome and NARP.)	>60 genes	AR mt XL	• T_2 hyperintensity of the basal ganglia • Dystonia • Developmental regression • Lactic acidosis	ECHS1D may be clinically indistinguishable from other Leigh syndromes.

Table 3. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/ECHS1D	Distinguishing from ECHS1D
Paroxysmal exercise-induced dyskinesia & epilepsy (See Glucose Transporter Type 1 Deficiency Syndrome.)	*SLC2A1*	AD AR [2]	Paroxysmal exercise-induced dystonia	Nl brain MRI
Paroxysmal kinesogenic dyskinesia (See *PRRT2*-Associated Paroxysmal Movement Disorders.)	*PRRT2*	AD AR [2]	Paroxysmal dystonia (may be exercise induced)	Nl brain MRI
Familial paroxysmal nonkinesigenic dyskinesia	*PNKD*	AD		
Pyruvate carboxylase deficiency	*PC*	AR	↑ lactate, pyruvate, & ammonia	• More striking hyperammonemia • Ketonuria • Nl organic acids

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance; mt = mitochondrial; nl = normal; XL = X-linked

1. Bedoyan et al [2017], Nouguès et al [2017]

2. Autosomal recessive inheritance is rare.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D), the evaluations summarized in Table 4 (if they have not already been completed) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with ECHS1 Deficiency

System/Concern	Evaluation	Comment
Neurologic	Brain MRI/MRS to evaluate for basal ganglia involvement & structural brain anomalies	
	Electroencephalogram to evaluate for epileptic encephalopathy	In those w/neonatal or infantile form
Growth/ Gastrointestinal	• Nutritional eval • Swallowing assessment • Liver ultrasound to evaluate for hepatosplenomegaly	Nutritional & swallowing evals should be performed in all affected persons, but liver ultrasound is only necessary in neonates.
Cardiovascular	Echocardiogram to evaluate for cardiomyopathy in those w/ neonatal form	Measurement of pulmonary artery pressure is important to evaluate for pulmonary hypertension.
Ophthalmologic	Dilated eye exam to evaluate for optic atrophy & other findings	In all affected persons
Audiologic	Audiologic eval for sensorineural hearing loss	In all affected persons
Biochemical	Lactate & blood gas to evaluate acid/base status	In all affected persons
	• Blood glucose level • Urine organic acids	For those presenting w/neonatal or infantile form
	• Blood ammonia level • Creatine kinase level	For those who present in neonatal period

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Other	Developmental eval	In all affected persons
	Physical exam & consideration of imaging for possible structural anomalies	For those presenting w/neonatal or infantile form
	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Management is best provided by a multidisciplinary team including specialists in clinical genetics / metabolism, neurology, nutrition, and developmental pediatrics. Other specialists, such as a cardiologist and an ophthalmologist, may be involved based on the associated complications. In those presenting in the neonatal period, involvement of a palliative care team is also essential to determine goals of care given the poor prognosis for this group. This should be especially considered for neonates with major structural abnormalities in whom surgical management is being considered.

No definite treatment is available to date; treatment is mainly supportive (see Table 5).

Table 5. Treatment of Manifestations in Individuals with ECHS1 Deficiency

Manifestation/Concern	Treatment	Comments
Dystonia (paroxysmal)	Benzodiazepines	Levodopa has been tried w/out success in 1 affected person; [1] nonetheless, trial of this low-risk, noninvasive therapy is probably reasonable.
Dystonia (chronic)	Botulinum toxin injections	
Seizures	Standard anti-seizure therapy	
Inadequate nutrition	Nasogastric tube or gastrostomy tube; feeding therapy w/speech therapist	
Cardiomyopathy or pulmonary hypertension	Standard treatment per cardiologist	
Optic atrophy	Low-vision support for educational settings	N-acetylcysteine & vitamin C use may be considered, but evidence for benefit is limited.
Sensorineural hearing loss	Hearing aids	See Hereditary Hearing Loss and Deafness Overview
Acidosis	Bicarbonate therapy for correction	Sodium citrate & acetate are unlikely to provide sufficient buffering capacity in these children w/ secondary impairment of the tricarboxylic acid cycle.
Hyperammonemia [2]	Correction of metabolic acidosis	High-concentration dextrose would result in ↑ lacticemia & should be used w/caution if at all.
	Consideration of hemodialysis	It is unknown if nitrogen scavengers would be of benefit.

1. Olgiati et al [2016]
2. The origin of the hyperammonemia is unclear. It may be secondary to metabolic acidosis, as it has only been observed in children with profound metabolic acidosis or as a result of low ATP secondary to impaired aerobic oxidation. Correction of acidosis is a reasonable first strategy.

Other treatment considerations

- Anecdotal reports of treatment with N-aceylcysteine to detoxify the reactive metabolites of methacrylyl-CoA and acroyacryl-CoA are mixed.
- Valine restriction would be a rational biochemical approach; it has never been attempted.

- Administration of cofactors and antioxidants, used in mitochondrial disorders with (generally) limited evidence of benefit, may be considered [Parikh et al 2009].

  In one affected individual with paroxysmal exercise-induced dystonia, this "cocktail" produced a subjective improvement [Mahajan et al 2017].

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. In the US, early intervention is a federally funded program available in all states.

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.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

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.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

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.

Surveillance

Table 6. Recommended Surveillance for Individuals with ECHS1 Deficiency

Evaluation	Recommended Interval	Comments
Comprehensive neurologic exam & developmental assessment	Depending on symptoms	Repeat MRI & EEG warranted only if symptoms concerning for new developments arise
Standard anthropometric monitoring	W/routine pediatric follow up	
Echocardiogram to monitor for cardiomyopathy	At least annually	Children w/cardiomyopathy noted on echocardiogram may need to be followed more closely.
Dilated eye exam to monitor for optic atrophy & other ophthalmologic findings	At ages 6 mos & 12 mos, then annually	Children w/ophthalmologic anomalies detected may need to be followed more closely.
Audiologic eval for sensorineural hearing loss	At least annually	Children w/abnormal hearing screens may need to be followed more closely.

Table 6. continued from previous page.

Evaluation	Recommended Interval	Comments
Sodium bicarbonate & lactate levels to monitor for acidosis	W/all illnesses or metabolic stressors	Children on chronic bicarbonate therapy also require routine monitoring of levels.

Agents/Circumstances to Avoid

Mitochondrial toxins, such as valproic acid and prolonged propofol infusions, should be avoided [Parikh et al 2009].

The ketogenic diet may be poorly tolerated because of partially impaired fatty acid oxidation [Haack et al 2015]; one preliminary report suggests rapid disease progression following initiation of the ketogenic diet [Nouguès et al 2017] and in two other affected individuals, subjects perished within days of starting a ketogenic diet [Ferdinandusse et al 2015, Bedoyan et al 2017]. Therefore, ketogenic diet may not be effective to control lactic acidosis and may be harmful or even lethal – and thus should be avoided.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic younger sibs of an individual affected by the paroxysmal exercise-induced dystonia phenotype by molecular genetic testing of the *ECHS1* pathogenic variants in the family in order to identify as early as possible those who would benefit from early initiation of exercise-guidance and dystonia-targeted therapies.

In an at-risk newborn, it is crucial to ensure metabolic stability by evaluating a lactic acid level and a blood gas. Urine organic acids and acylcarnitine profile may also be used as biochemical screening testing while waiting for molecular genetic testing results; they can have high specificity, but sensitivity may be low.

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

Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D) is inherited in an autosomal recessive manner.

Parents of a proband

- In most instances, the parents of an affected child are heterozygotes (i.e., carriers of one *ECHS1* pathogenic variant).

- In rare cases, a proband has one *de novo* pathogenic variant and one pathogenic variant inherited from a carrier parent [Aretini et al 2018, Carlston et al 2019]; in these families, presumably only one parent is heterozygous for an *ECHS1* pathogenic variant.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are carriers, 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.
- If only one parent is a carrier (i.e., the proband is compound heterozygous for an inherited pathogenic variant and a *de novo* pathogenic variant), each sib of the proband has a 50% chance of being an asymptomatic carrier and a 50% chance of being unaffected and not a carrier.
- Sibs who inherit two pathogenic variants will be affected. Sibs who inherit one pathogenic variant (heterozygotes) are expected to be asymptomatic. A sib who is heterozygous for an inherited pathogenic variant could be affected if the sib also has another *de novo ECHS1* pathogenic variant on the other allele (i.e., *in trans*).

Offspring of a proband

- To date, individuals with the neonatal and infantile forms of ECHS1D are not known to reproduce.
- Each child of an individual with the paroxysmal dystonia form of ECHS1D has a 50% chance of inheriting the *ECHS1* pathogenic variant.

Other family members. In general, each sib of the proband's parents is at a 50% risk of being a carrier of an *ECHS1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ECHS1* 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 carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *ECHS1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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.

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

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. Mitochondrial Short-Chain Enoyl-CoA Hydratase 1 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ECHS1	10q26.3	Enoyl-CoA hydratase, mitochondrial	ECHS1	ECHS1

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 Mitochondrial Short-Chain Enoyl-CoA Hydratase 1 Deficiency (View All in OMIM)

602292	ENOYL-CoA HYDRATASE, SHORT-CHAIN, 1, MITOCHONDRIAL; ECHS1
616277	MITOCHONDRIAL SHORT-CHAIN ENOYL-CoA HYDRATASE 1 DEFICIENCY; ECHS1D

Molecular Pathogenesis

The mitochondrial short-chain enoyl-CoA hydratase (SCEH) has a primary function in the beta-oxidation of short-chain fats. However, the same enzyme also is involved in branched-chain amino acid metabolism, particularly valine metabolism [Peters et al 2014, Haack et al 2015]. The enoyl-CoA metabolites of valine catabolism that are the substrates of SCEH, methylacrylyl-CoA, and acryloyl-CoA are highly reactive intermediates [Haack et al 2015]. The most likely cause of the phenotype observed in this disorder is high concentrations of these toxic enoyl-CoA intermediates, which impair the function of pyruvate dehydrogenase complex (PDC) and the mitochondrial respiratory chain; however, the full mechanism(s) of this impairment are not yet fully elucidated [Ferdinandusse et al 2015, Bedoyan et al 2017]. Regardless of the exact mechanism, secondary deficiency of PDC is observed in about half of reported affected individuals. It is believed that PDC deficiency is an important contributor to the lactic acidosis [Bedoyan et al 2017].

Gene structure. *ECHS1* has eight exons.

Pathogenic variants. The majority of reported variants have been missense. A variety of other loss-of-function pathogenic variants have also been reported, including a splice site pathogenic variant [Peters et al 2014], abrogation of the start codon [Sakai et al 2015], impairment of the mitochondrial targeting sequence [Ganetzky et al 2016], amino acid duplication [Haack et al 2015], and a frameshift pathogenic variant [Haack et al 2015]. With the exception of the recurrent c.518C>T pathogenic variant, all pathogenic variants reported to date have been private [Nair et al 2016].

Table 7. Notable *ECHS1* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.518C>T	p.Ala173Val	NM_004092.3 NP_004083.3
c.538A>G	p.Thr180Ala	

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.

Normal gene product. SCEH has 290 amino acids. The first 27 amino acids are the mitochondrial targeting sequence.

Abnormal gene product. *ECHS1* pathogenic variants have loss of SCEH protein function [Bedoyan et al 2017].

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Chapter Notes

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