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SUCLA2-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria

Synonym: SUCLA2 Deficiency

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Summary

Clinical characteristics

SUCLA2-related mitochondrial DNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria (*SUCLA2*-related mtDNA depletion syndrome) is characterized by onset of the following features in infancy: developmental delay, hypotonia, dystonia, muscular atrophy, sensorineural hearing impairment, growth failure, and feeding difficulties. Other less frequent features include choreoathetosis, muscle weakness, recurrent vomiting, ptosis, and kyphoscoliosis. The median survival is age 20 years; approximately 30% of affected individuals succumb during childhood.

Diagnosis/testing

The diagnosis of *SUCLA2*-related mtDNA depletion syndrome is established in a proband with suggestive findings and biallelic pathogenic variants in *SUCLA2* identified by molecular genetic testing.

Management

Treatment of manifestations: Appropriate early developmental support; physical therapy to maintain muscle function and prevent joint contractures; antiseizure medication for epileptic seizures; hearing aids / cochlear implantation for sensorineural hearing loss; gastrostomy tube placement as needed to assure adequate caloric intake; blepharoplasty for significant ptosis; low vision services as needed; chest physiotherapy, aggressive antibiotic treatment of chest infections, and consideration of respiratory aids; bracing to treat scoliosis or kyphosis.

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Surveillance: Routine monitoring of development, growth, and hearing; periodic ophthalmologic evaluations; routine skeletal evaluations for kyphoscoliosis and joint contractures.

Genetic counseling

SUCLA2-related mtDNA depletion syndrome is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *SUCLA2* 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 *SUCLA2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing for *SUCLA2*-related mtDNA depletion syndrome are possible.

Diagnosis

No consensus clinical diagnostic criteria for *SUCLA2*-related mitochondrial DNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria (*SUCLA2*-related mtDNA depletion syndrome) have been published.

Suggestive Findings

SUCLA2-related mtDNA depletion syndrome typically manifests during early infancy and **should be suspected** in a proband with a combination of the following clinical, brain MRI, and supportive laboratory findings and family history.

Clinical findings

- **Developmental delay (DD) / intellectual disability (ID).** Mild-to-profound developmental delay and intellectual disability
- **Neuromuscular features**
  - Hypotonia, axial or generalized
  - Dystonia
  - Muscle atrophy
- **Sensorineural hearing impairment**
- **Feeding and growth issues**
  - Feeding difficulties
  - Growth deficiency affecting both weight gain and linear growth

Brain MRI findings

- Basal ganglia hyperintensities
- Cerebral atrophy
- Leukoencephalopathy

Supportive laboratory findings

- **Urine organic acid analysis** [Carrozzo et al 2016]
  - Elevation of methylmalonic acid (MMA) in most affected children. However, the MMA level is considerably less pronounced than in classic methylmalonic aciduria and can be only marginally elevated or even normal on rare occasions.
  - Other metabolites that may be elevated in urine include methylcitrate, 3-methylglutaconic acid, 3-hydroxyisovaleric acid, and Krebs cycle intermediates such as succinate, fumarate, and 2-ketoglutarate.

- **Plasma MMA level** is more sensitive than organic acid analysis. Elevated plasma MMA has been reported even in those with marginally elevated urine MMA level [Carrozzo et al 2016].
- **Plasma acylcarnitine profile.** Elevated C3
- **Plasma and cerebrospinal fluid lactate levels.** Elevated in most affected individuals

Muscle biopsy findings. In most cases muscle biopsy is not needed; however, muscle biopsy can be considered when molecular testing reveals variants of uncertain significance and further evidence is needed to confirm the diagnosis (see Molecular Pathogenesis, **Specific laboratory technical considerations**).

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 *SUCLA2*-related mtDNA depletion syndrome **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *SUCLA2* 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 section is understood to include likely pathogenic variants. (2) Identification of biallelic *SUCLA2* variants of uncertain significance (or of one known *SUCLA2* pathogenic variant and one *SUCLA2 v*ariant 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) depending on the phenotype. 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

When the phenotypic and laboratory findings suggest the diagnosis of *SUCLA2*-related mtDNA depletion syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *SUCLA2* 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.

  Note: Targeted analysis for the c.534+1G>A pathogenic founder variant can be performed first in probands of Faroese ancestry (see Table 7).

- **A mitochondrial disease multigene panel** that includes *SUCLA2* 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

Exome sequencing is most commonly used; **genome sequencing** is also possible. To date, the majority of *SUCLA2* 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 *SUCLA2*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SUCLA2	Sequence analysis [3]	90% [4]
	Gene-targeted deletion/duplication analysis [5]	10% [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 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020], Carrozzo et al [2016], Maas et al [2016], Fang et al [2017], Garone et al [2017], Huang et al [2017], Kang et al [2020], Alkhater et al [2021], and Hiramatsu et al [2022]
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

SUCLA2-related mitochondrial DNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria (*SUCLA2*-related mtDNA depletion syndrome) is characterized by onset of the following features in infancy: developmental delay, hypotonia, dystonia, muscular atrophy, sensorineural hearing impairment, growth failure, and feeding difficulties. Other less frequent features include choreoathetosis, muscle weakness, recurrent vomiting, ptosis, and kyphoscoliosis. The median survival is age 20 years; approximately 30% of affected individuals succumb during childhood.

To date, 61individuals have been identified with biallelic pathogenic variants in *SUCLA2*, including 50 cases reviewed by Carrozzo et al [2016], Maas et al [2016], Fang et al [2017], Garone et al [2017], Huang et al [2017], Kang et al [2020], Alkhater et al [2021], Hiramatsu et al [2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *SUCLA2*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria: Frequency of Select Features

Feature		% of Persons w/Feature
Development	Developmental delay / intellectual disability	95%
	Regression	10%
Neuromuscular	Hypotonia	90%
	Dystonia	80%
	Muscle atrophy	40%
	Choreoathetosis	30%
	Muscle weakness	20%
	Hypertonia	10%
	Epilepsy	10%
	Myoclonus	10%
	Neuropathy	10%
Sensorineural hearing impairment		90%
Feeding/gastrointestinal	Feeding difficulties	50%
	Recurrent vomiting	20%
	Gastroesophageal reflux disease	10%
Growth deficiency		90%
Vision/ophthalmologic	Ptosis	20%
	Ophthalmoplegia	10%
	Strabismus	10%
Respiratory	Respiratory distress	10%
	Recurrent respiratory infections	10%
Skeletal	Kyphoscoliosis	20%
	Joint contractures	10%
Other	Hypoglycemia	10%
	Hyperhidrosis	10%

Children with *SUCLA2*-related mtDNA depletion syndrome typically have an uncomplicated prenatal course and birth, and present during infancy with delayed development and hypotonia.

Developmental delay (DD) and intellectual disability (ID). Global developmental delay and intellectual disabilities occur in most affected children and vary from mild to severe.

Neuromuscular. Hypotonia, first manifesting in infancy, is a presenting sign in most cases. Hypotonia can be axial or generalized. Dystonia and muscle atrophy also occur commonly. Other, less frequent neurologic manifestations include choreoathetosis, muscle weakness, hypertonia, epilepsy (including infantile spasms and generalized convulsions), myoclonus, and axonal peripheral neuropathy [Carrozzo et al 2016, Maas et al 2016, Fang et al 2017, Garone et al 2017, Huang et al 2017, Kang et al 2020, Alkhater et al 2021, Hiramatsu et al 2022].

Brain MRI typically shows basal ganglia hyperintensities (70%), cerebral atrophy (70%), and leukoencephalopathy (15%) [Carrozzo et al 2016].

Hearing. Most affected children develop sensorineural hearing impairment; some benefit from a cochlear implant. Hearing impairment can be congenital or appear during early childhood [Huang et al 2017, Alkhater et al 2021].

Vision/ophthalmologic. Ptosis, ophthalmoplegia, and strabismus are present in some individuals [Carrozzo et al 2016].

Feeding/gastrointestinal. Feeding difficulties, often necessitating gastrostomy tube placement, occur commonly. Recurrent vomiting and gastroesophageal reflux disease occur occasionally.

Growth deficiency / poor weight gain and linear growth deficiency. Birth weight and length are typically within the normal range. Feeding and gastrointestinal difficulties can contribute to subsequent growth deficiency. Ongoing postnatal growth restriction with low weight and length/height is common [Carrozzo et al 2016].

Respiratory. Recurrent respiratory infections occur occasionally. Respiratory distress due to muscle weakness, obstructive sleep apnea, and tracheomalacia has also been reported [Carrozzo et al 2016].

Skeletal. Progressive kyphoscoliosis has been reported occasionally and may require treatment. Joint contractures can develop in the extremities secondary to decreased movement.

Other

- Hyperhidrosis [Carrozzo et al 2016]
- Neonatal hypoglycemia [Carrozzo et al 2016]

Prognosis. Life span is shortened, with median survival of age 20 years. Approximately 30% of affected individuals die during childhood [Carrozzo et al 2016].

Genotype-Phenotype Correlations

Biallelic *SUCLA2* pathogenic missense variants can result in some residual enzyme activity and hence are associated with a milder phenotype and a longer median survival (age 21 years), whereas biallelic loss-of-function *SUCLA2* variants (deletion, frameshift, and nonsense) are associated with a more severe phenotype and a shorter median survival (age 15 years) [Carrozzo et al 2016].

Prevalence

SUCLA2-related mtDNA depletion syndrome is rare; the exact prevalence is unknown. To date, 61 individuals of different ethnic origins have been reported (see Clinical Description).

A founder pathogenic variant in families of Faroese ancestry has been identified (see Table 7); the disorder has a high incidence (1:1,700) and a carrier frequency of 1:33 in the Faroe Islands [Ostergaard et al 2007].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SUCLA2*.

A contiguous gene deletion involving *SUCLA2* and *RB1* occurring in *trans* with a *SUCLA2* pathogenic variant was reported in an individual with both *SUCLA2*-related mtDNA depletion syndrome and retinoblastoma [Matilainen et al 2015].

Differential Diagnosis

SUCLA2-related mitochondrial DNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria (*SUCLA2*-related mtDNA depletion syndrome) needs to be differentiated from other mtDNA depletion syndromes, a genetically and clinically heterogeneous group of primarily autosomal recessive disorders that are characterized by a severe reduction in mtDNA content leading to impaired energy production in affected tissues and organs (see Table 3).

Mitochondrial DNA depletion syndromes occur as a result of defects in mtDNA maintenance caused by pathogenic variants in nuclear genes that function in either mitochondrial nucleotide synthesis (*TK2*, *SUCLA2*, *SUCLG1*, *RRM2B*, *DGUOK*, and *TYMP*) or mtDNA replication (*POLG*, *TWNK*, *TFAM*, *RNASEH1*, *MGME1*) and are phenotypically classified into hepatocerebral, encephalomyopathic, encephaloneuropathic, neurogastrointestinal, and myopathic forms [El-Hattab & Scaglia 2013]. See also the Mitochondrial DNA Maintenance Defects Overview.

The phenotype of *SUCLG1*-related mtDNA depletion syndrome may be difficult to distinguish from *SUCLA2*-related mtDNA depletion syndrome. *SUCLG1*-related mtDNA depletion syndrome is characterized by developmental delay, intellectual disability, hypotonia, muscle atrophy, feeding difficulties, growth restriction, dystonia, hearing loss, lactic acidosis, elevated urine and plasma methylmalonic acid, and mtDNA depletion. However, hepatopathy and cardiomyopathy occur in *SUCLG1*-related mtDNA depletion only.

Table 3. Mitochondrial DNA Depletion Syndromes

Phenotype [1]	Gene	Disorder/Phenotype	Additional Common Manifestations [2]
Hepatocerebral (Encephalohepatopathic)	*DGUOK*	DGUOK deficiency	DD, hypotonia, nystagmus, lactic acidosis
	POLG	Alpers-Huttenlocher syndrome	DD, psychomotor regression, epilepsy, hearing impairment
	MPV17	MPV17 deficiency	DD, hypotonia, poor weight gain, hearing impairment, lactic acidosis
	TWNK	Encephalohepatopathy (OMIM 271245)	DD, hypotonia, lactic acidosis
	TFAM	Encephalohepatopathy (OMIM 617156)	IUGR, hypoglycemia
Encephalomyopathic	*FBXL4*	FBXL4 deficiency	DD, hypotonia, epilepsy, hearing impairment, lactic acidosis
	SUCLG1	SUCLG1 deficiency	DD, hypotonia, hearing impairment, ↑ MMA
	RRM2B	*RRM2B* encephalomyopathic MDMD	DD, hypotonia, GI dysmotility, renal tubulopathy
	OPA1	Encephalomyopathy (OMIM 616896)	DD, HCM, optic atrophy
	ABAT	Encephalomyopathy w/↑ GABA (OMIM 613163)	DD, hypotonia, epilepsy, ↑ GABA in plasma, urine, & CSF
	RNASEH1	Encephalomyopathy (OMIM 616479)	Ophthalmoplegia, ptosis, ataxia
Neurogastrointestinal encephalopathic	*TYMP*	MNGIE type 1	GI dysmotility, cachexia, peripheral neuropathy, ophthalmoplegia, muscle weakness, leukoencephalopathy [3]
	POLG	MNGIE type 4B	
	RRM2B	MNGIE type 8B	

Table 3. continued from previous page.

Phenotype [1]	Gene	Disorder/Phenotype	Additional Common Manifestations [2]
Myopathic	*TK2*	TK2 deficiency	Hypotonia, loss of acquired motor skills
	AGK	Sengers syndrome (OMIM 212350)	Hypotonia, HCM, cataracts
	MGME1	Myopathy (OMIM 615084)	Ptosis, ophthalmoplegia
	SLC25A4	Cardiomyopathy (OMIM 617184)	Hypotonia, HCM (Mitochondrial DNA depletion phenotype is assoc w/autosomal dominant inheritance.)
Encephaloneuropathic	*TWNK*	Infantile-onset spinocerebellar ataxia	Hypotonia, hearing impairment

CSF = cerebrospinal fluid; DD = developmental delay; GABA = gamma-aminobutyric acid; GI = gastrointestinal; HCM = hypertrophic cardiomyopathy; IUGR = intrauterine growth restriction; MDMD = mitochondrial DNA maintenance defect; MMA = methylmalonic acid; MNGIE = mitochondrial neurogastrointestinal encephalopathy

1. Within each phenotypic category, mitochondrial DNA depletion syndromes are ordered by relative prevalence.

2. Common manifestations seen in addition to the primary phenotype (i.e., in addition to encephalohepatopathy, encephalomyopathy, etc.)

3. Leukoencephalopathy is not present in *POLG*-related neurogastrointestinal encephalopathy.

Management

No clinical practice guidelines for *SUCLA2*-related mitochondrial DNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria (*SUCLA2*-related mtDNA depletion syndrome) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SUCLA2*-related mtDNA depletion syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *SUCLA2*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neuromuscular	Neurologic eval	• To incl assessment for hypotonia, dystonia, hypertonia, muscle weakness, muscle atrophy, movement disorders, & clinical signs of seizures • Brain MRI • Consider EMG to assess myopathy. • Consider EEG if seizures are a concern.
	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hearing	Audiologic eval	To assess for sensorineural hearing loss

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Feeding/ Gastrointestinal	Gastroenterology / nutrition / feeding team eval	• To incl eval of swallowing function / aspiration risk, nutritional status, & GERD • Consider eval for gastrostomy tube placement in affected persons w/dysphagia &/or aspiration risk.
Growth	Measure weight, length/height, & head circumference; review growth charts.	To assess for growth deficiency / failure to thrive
Vision/Ophthalmologic	Ophthalmologic eval	To assess for reduced vision, ophthalmoplegia, ptosis, & strabismus that may require referral for subspecialty care &/or low vision services
Respiratory	Pulmonary eval	To assess for sleep apnea
Skeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Joint contractures & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SUCLA2*-related mtDNA depletion syndrome to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; mtDNA = mitochondrial DNA; OT = occupational therapy; PT = physical therapy

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

Treatment of Manifestations

There is no cure for *SUCLA2*-related mitochondrial mtDNA depletion syndrome.

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 5).

Table 5. *SUCLA2*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Dystonia	Standardized treatment for dystonia by experienced neurologist	
Hypertonia/Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	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]
Sensorineural hearing impairment	Hearing aids &/or cochlear implantation may be helpful per otolaryngologist & audiologist.	Community hearing services through early intervention or school district
Feeding difficulties / GERD / Growth deficiency / Failure to thrive	• Nutritional support by dietitian • 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 • Intervention for GERD/vomiting as indicated
Vision/Ophthalmologic	Ophthalmologist	Strabismus, ptosis, ophthalmoplegia
	Ophthalmic subspecialist	Blepharoplasty for significant ptosis
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Respiratory	• Chest physiotherapy • Aggressive antibiotic treatment of chest infections	Artificial ventilation (incl assisted nasal ventilation or intubation & use of tracheostomy & ventilator) for respiratory insufficiency (See **Ethics consultation** in this table.)
Skeletal	• PT to help maintain muscle function & prevent joint contractures • Bracing or surgery for kyphoscoliosis per orthopedist	
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 • Consider involvement in adaptive sports or Special Olympics.
Ethics consultation	Clinical ethics services	• Assess health care decisions in the context of the best interest of the child & values & preferences of the family. • For difficult life-prolonging decisions or for clarification of treatment options, consider further consultation w/independent clinical teams. [2]

ASM = antiseizure medication; GERD = gastroesophageal reflux disease; 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.
2. Linney et al [2019]

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 that 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; 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 (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - 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 child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP 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.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) 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.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *SUCLA2*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Neuromuscular	Monitor those w/dystonia, hypertonia, muscle atrophy, muscle weakness, choreoathetosis, or seizures as clinically indicated.	Per treating neurologist
	Assess for new manifestations such as changes in muscle tone, emergence of movement disorders, or signs of seizures.	At each visit
Hearing	Monitor hearing status.	Per treating otolaryngologist & audiologist
Feeding/Gastrointestinal	• Eval of safety of oral intake • Monitor for GERD/vomiting.	At each visit
Growth	• Measurement of growth parameters • Eval of nutritional status	
Vision/Ophthalmologic	Monitor vision, ocular alignment/movement, & ptosis.	Per treating ophthalmologist(s)
	Low vision services	Per treating clinicians
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	At each visit
Skeletal	Monitor those w/scoliosis or joint contractures for progression.	Per treating orthopedist
	• Monitor for new development of kyphoscoliosis or joint contractures. • Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

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

SUCLA2-related mitochondrial DNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria (*SUCLA2*-related mtDNA depletion syndrome) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *SUCLA2* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *SUCLA2* 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, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant 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 a *SUCLA2* 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. To date, individuals with *SUCLA2*-related mtDNA depletion syndrome 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 *SUCLA2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SUCLA2* 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 carriers or are at risk of being carriers.
- Carrier testing for the reproductive partners of known carriers should be considered, particularly if both partners are of the same ethnic background. A founder pathogenic variant in families of Faroese origin has been identified; the disorder has a high incidence (1:1,700) and a carrier frequency of 1:33 in the Faroe Islands (see Table 7).

Prenatal Testing and Preimplantation Genetic Testing

Once the *SUCLA2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for *SUCLA2*-related mtDNA depletion syndrome 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.

- **The Charlie Gard Foundation**
  United Kingdom
  Email: hello@thecharliegardfoundation.org
  www.thecharliegardfoundation.org
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **Human Disease Gene Website Series - Registry**
  SUCLA2
- **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. SUCLA2-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SUCLA2	13q14.2	Succinate--CoA ligase [ADP-forming] subunit beta, mitochondrial	SUCLA2 database	SUCLA2	SUCLA2

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 SUCLA2-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria (View All in OMIM)

603921	SUCCINATE-CoA LIGASE, ADP-FORMING, BETA SUBUNIT; SUCLA2
612073	MITOCHONDRIAL DNA DEPLETION SYNDROME 5 (ENCEPHALOMYOPATHIC WITH OR WITHOUT METHYLMALONIC ACIDURIA); MTDPS5

Molecular Pathogenesis

SUCLA2 encodes a subunit of succinyl-CoA ligase (SUCL). SUCL has two important metabolic functions. First, it is a mitochondrial tricarboxylic acid (Krebs) cycle enzyme that catalyzes the reversible conversion of succinyl-CoA and either ADP or GDP to succinate and either ATP or GTP. SUCL is composed of an alpha subunit, encoded by *SUCLG1*, and a beta subunit, encoded by either *SUCLA2* or *SUCLG2*. The alpha subunit forms a heterodimer with either of its beta subunits, resulting in an ADP-forming SUCL and a GDP-forming SUCL, respectively. Second, SUCL forms a complex with the mitochondrial nucleoside diphosphate kinase, which is

involved in the synthesis of mitochondrial nucleotides. These nucleotides are then used to synthesize mitochondrial DNA.

The pathogenic variants lead to dysfunctional SUCL protein. As SUCL forms a complex with the mitochondrial nucleoside diphosphate kinase, the lack of this complex formation in SUCL deficiency can disturb the kinase function, resulting in decreased mitochondrial nucleotide synthesis and therefore decreased mitochondrial DNA (mtDNA) synthesis leading to mtDNA depletion [El-Hattab et al 2017].

Mechanism of disease causation. Loss of protein function

Specific laboratory technical considerations. For *SUCLA2* variants of uncertain significance, findings on muscle biopsy that help confirm the diagnosis of *SUCLA2*-related mitochondrial DNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria include:

- Electron microscopic findings of increased fiber size variability, atrophic fibers, intracellular lipid accumulation, COX-deficient fibers, and structurally altered mitochondria with abnormal cristae.
- Deficiencies in electron transport chain activity in combined complex I and IV; in combined complex I, III, and IV; and in isolated complex IV.
- Mitochondrial DNA content in affected muscle tissue typically reduced to 20%-60% of that in tissue- and age-matched controls.

Table 7. *SUCLA2* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003850.2 NP_003841.1	c.534+1G>A	--	Founder variant in Faroe Islands [Carrozzo et al 2007, Ostergaard et al 2007, Morava et al 2009]

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

Author Notes

Dr Ayman El-Hattab (elhattabaw@yahoo.com) is actively involved in clinical research regarding individuals with mitochondrial disorders. He would be happy to communicate with persons who have any questions regarding diagnosis of mitochondrial disorders or other considerations.

Dr El-Hattab is also interested in hearing from clinicians treating families affected by mitochondrial disorders 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 El-Hattab to inquire about review of *SUCLA2* variants of uncertain significance.

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References

Literature Cited

Alkhater RA, Ahonen S, Minassian BA. SUCLA2 Arg407Trp mutation can cause a nonprogressive movement disorder - deafness syndrome. Ann Clin Transl Neurol. 2021;8:252-8. PubMed PMID: 33231368.

Carrozzo R, Dionisi-Vici C, Steuerwald U, Lucioli S, Deodato F, Di Giandomenico S, Bertini E, Franke B, Kluijtmans LA, Meschini MC, Rizzo C, Piemonte F, Rodenburg R, Santer R, Santorelli FM, van Rooij A, Vermunt-de Koning D, Morava E, Wevers RA. SUCLA2 mutations are associated with mild methylmalonic aciduria, Leigh-like encephalomyopathy, dystonia and deafness. Brain. 2007;130:862-74. PubMed PMID: 17301081.

Carrozzo R, Verrigni D, Rasmussen M, de Coo R, Amartino H, Bianchi M, Buhas D, Mesli S, Naess K, Born AP, Woldseth B, Prontera P, Batbayli M, Ravn K, Joensen F, Cordelli DM, Santorelli FM, Tulinius M, Darin N, Duno M, Jouvencel P, Burlina A, Stangoni G, Bertini E, Redonnet-Vernhet I, Wibrand F, Dionisi-Vici C, Uusimaa J, Vieira P, Osorio AN, McFarland R, Taylor RW, Holme E, Ostergaard E. Succinate-CoA ligase deficiency due to mutations in SUCLA2 and SUCLG1: phenotype and genotype correlations in 71 patients. J Inherit Metab Dis. 2016;39:243-52. PubMed PMID: 26475597.

El-Hattab AW, Craigen WJ, Scaglia F. Mitochondrial DNA maintenance defects. Biochim Biophys Acta Mol Basis Dis. 2017;1863:1539-55. PubMed PMID: 28215579.

El-Hattab AW, Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. Neurotherapeutics. 2013;10:186-98. PubMed PMID: 23385875.

Fang F, Liu Z, Fang H, Wu J, Shen D, Sun S, Ding C, Han T, Wu Y, Lv J, Yang L, Li S, Lv J, Shen Y. The clinical and genetic characteristics in children with mitochondrial disease in China. Sci China Life Sci. 2017;60:746-57. PubMed PMID: 28639102.

Garone C, Gurgel-Giannetti J, Sanna-Cherchi S, Krishna S, Naini A, Quinzii CM, Hirano M. A novel SUCLA2 mutation presenting as a complex childhood movement disorder. J Child Neurol. 2017;32:246-50. PubMed PMID: 27651038.

Hiramatsu Y, Okamoto Y, Yoshimura A, Yuan JH, Ando M, Higuchi Y, Hashiguchi A, Matsuura E, Nozaki F, Kumada T, Murayama K, Suzuki M, Yamamoto Y, Matsui N, Miyazaki Y, Yamaguchi M, Suzuki Y, Mitsui J, Ishiura H, Tanaka M, Morishita S, Nishino I, Tsuji S, Takashima H. Complex hereditary peripheral neuropathies caused by novel variants in mitochondrial-related nuclear genes. J Neurol. 2022;269:4129-40. PubMed PMID: 35235001.

Huang X, Bedoyan JK, Demirbas D, Harris DJ, Miron A, Edelheit S, Grahame G, DeBrosse SD, Wong LJ, Hoppel CL, Kerr DS, Anselm I, Berry GT. Succinyl-CoA synthetase (SUCLA2) deficiency in two siblings with impaired activity of other mitochondrial oxidative enzymes in skeletal muscle without mitochondrial DNA depletion. Mol Genet Metab. 2017;120:213-22. PubMed PMID: 27913098.

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.

Kang L, Liu Y, Shen M, Liu Y, He R, Song J, Jin Y, Li M, Zhang Y, Dong H, Liu X, Yan H, Qin J, Zheng H, Chen Y, Li D, Wei H, Zhang H, Sun L, Zhu Z, Liang D, Yang Y. A study on a cohort of 301 Chinese patients with isolated methylmalonic acidemia. J Inherit Metab Dis. 2020;43:409-23. PubMed PMID: 31622506.

Linney M, Hain RDW, Wilkinson D, Fortune PM, Barclay S, Larcher V, Fitzgerald J, Arkell E. Achieving consensus advice for paediatricians and other health professionals: on prevention, recognition and management of conflict in paediatric practice. Arch Dis Child. 2019;104:413-6. PubMed PMID: 31000533.

Maas RR, Marina AD, de Brouwer AP, Wevers RA, Rodenburg RJ, Wortmann SB. SUCLA2 deficiency: a deafness-dystonia syndrome with distinctive metabolic findings (report of a new patient and review of the literature). JIMD Rep. 2016;27:27-32. PubMed PMID: 26409464.

Matilainen S, Isohanni P, Euro L, Lönnqvist T, Pihko H, Kivelä T, Knuutila S, Suomalainen A. Mitochondrial encephalomyopathy and retinoblastoma explained by compound heterozygosity of SUCLA2 point mutation and 13q14 deletion. Eur J Hum Genet. 2015;23:325-30. PubMed PMID: 24986829.

Morava E, Steuerwald U, Carrozzo R, Kluijtmans LA, Joensen F, Santer R, Dionisi-Vici C, Wevers RA. Dystonia and deafness due to SUCLA2 defect; Clinical course and biochemical markers in 16 children. Mitochondrion. 2009;9:438-42. PubMed PMID: 19666145.

Ostergaard E, Hansen FJ, Sorensen N, Duno M, Vissing J, Larsen PL, Faeroe O, Thorgrimsson S, Wibrand F, Christensen E, Schwartz M. Mitochondrial encephalomyopathy with elevated methylmalonic acid is caused by SUCLA2 mutations. Brain. 2007;130:853-61 PubMed PMID: 17287286.

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.

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.

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