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# *SUCLG1*-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria

Synonyms: SUCLG1 Deficiency, *SUCLG1*-Related Succinyl-CoA Ligase Deficiency

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## Summary

### Clinical characteristics

*SUCLG1*-related mitochondrial DNA (mtDNA) depletion syndrome, encephalomyopathic form with methylmalonic aciduria is characterized in the majority of affected newborns by hypotonia, muscle atrophy, feeding difficulties, and lactic acidosis. Affected infants commonly manifest developmental delay / cognitive impairment, growth retardation / failure to thrive, hepatopathy, sensorineural hearing impairment, dystonia, and hypertonia. Notable findings in some affected individuals include hypertrophic cardiomyopathy, epilepsy, myoclonus, microcephaly, sleep disturbance, rhabdomyolysis, contractures, hypothermia, and/or hypoglycemia. Life span is shortened, with median survival of 20 months.

### Diagnosis/testing

The diagnosis of *SUCLG1*-related mtDNA depletion syndrome is established in a proband by the identification of biallelic pathogenic variants in *SUCLG1* on molecular genetic testing.

### Management

*Treatment of manifestations:* Management is supportive and is best provided by a multidisciplinary team. Treatment may include physical therapy to help maintain muscle function and prevent joint contractures, nutritional support by a dietitian, use of a nasogastric tube or gastrostomy tube feedings, chest physiotherapy, and aggressive antibiotic treatment of chest infections. When present, seizures are treated using standard anti-seizure medication.

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*Surveillance:* The suggested evaluations (with frequency varying according to the needs of the child) can include developmental and neurologic assessment, nutritional and growth assessment, echocardiogram, liver function tests, hearing evaluation, and ophthalmologic examination.

## Genetic counseling

*SUCLG1*-related mtDNA depletion syndrome 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 *SUCLG1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

# Diagnosis

## Suggestive Findings

*SUCLG1*-related mitochondrial DNA (mtDNA) depletion syndrome, encephalomyopathic form with methylmalonic aciduria (MMA) typically manifests at birth or during early infancy and **should be suspected** in individuals with a combination of the following supportive clinical, brain MRI, laboratory, and muscle biopsy findings.

**Clinical features**

Present in >50%:

- Developmental delay and cognitive impairment
- Hypotonia
- Muscle atrophy
- Feeding difficulties

Present in 20%-50%:

- Growth retardation / failure to thrive
- Hepatopathy
- Sensorineural hearing impairment
- Dystonia
- Hypertonia

Present in <20%:

- Hypertrophic cardiomyopathy
- Recurrent respiratory infections, respiratory distress, and apnea
- Recurrent vomiting and gastroesophageal reflux disease
- Ptosis and strabismus
- Epilepsy, myoclonus, and microcephaly
- Hyperhidrosis
- Sleep disturbance
- Rhabdomyolysis
- Contractures
- Hypothermia

**Brain MRI findings** [Carrozzo et al 2016]

- Basal ganglia hyperintensities (80%)

- Cerebral atrophy (30%)
- Leukoencephalopathy (20%)

**Supportive laboratory findings**

- **Urine organic acid analysis**
  - Elevation of urinary methylmalonic acid (MMA) in all affected children. Urinary MMA ranges from 10 to 500 mmol/mol creatinine (normal <3 mmol/mol creatinine).

    Note: In classic methylmalonic aciduria urinary MMA is ~1,000-10,000 mmol/mol creatinine, and in defects of cobalamin metabolism urinary MMA is ~100s mmol/mol creatinine (see Differential Diagnosis).
  - Several other metabolites that may be elevated in urine include methylcitrate, 3-methylglutaconic acid, 3-hydroxyisovaleric acid, and Krebs cycle intermediates (e.g., succinate, fumarate, 2-ketoglutarate).
- **Plasma MMA level** is elevated in all affected children and ranges from 1 to10 mmol/L (normal <0.3 mmol/L). Note: In classic methylmalonic aciduria plasma MMA is ~100-1,000 mmol/L, and in defects of cobalamin metabolism plasma MMA is ~10s mmol/L (see Differential Diagnosis).
- **Acylcarnitine profile** can show elevated C3; thus, this condition can potentially be detected by newborn screening.
- **Plasma and CSF lactate levels** are elevated in most affected individuals.
- **Hypoglycemia** can occasionally occur [Carrozzo et al 2016].

**Muscle biopsy**, typically performed during the evaluation of individuals with mitochondrial diseases, can show variable abnormalities or can occasionally be normal. The following findings can suggest the diagnosis:

- Increased fiber size variability, atrophic fibers, intracellular lipid accumulation, ragged-red fibers (RRF), and COX-deficient fibers
- Structurally altered mitochondria with abnormal cristae on electron microscopy
- Abnormal electron transport chain activity. The most common abnormalities are combined complex I and IV deficiencies, combined complex I, III, and IV deficiencies, and isolated complex IV deficiency.
- Reduced mtDNA content; typically 15%-50% of tissue- and age-matched controls [Ostergaard et al 2007, Valayannopoulos et al 2010, Randolph et al 2011, Landsverk et al 2014]

## Establishing the Diagnosis

The diagnosis of *SUCLG1*-related mtDNA depletion syndrome **is established** in a proband by the identification of biallelic pathogenic (or likely pathogenic) variants in *SUCLG1* on 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 *SUCLG1* variants of uncertain significance (or of one known *SUCLG1* pathogenic variant and one *SUCLG1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **genomic testing** (comprehensive 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 *SUCLG1*-related mtDNA depletion syndrome is broad, children with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from other inherited mitochondrial disorders are more likely to be diagnosed using genomic testing (see Option 2).

## Option 1

The phenotypes of *SUCLG1*-related mtDNA depletion syndrome and *SUCLA2*-related mtDNA depletion syndrome are difficult to distinguish and both are associated with elevated MMA. Therefore, when the phenotypic and laboratory findings suggest the diagnosis of *SUCLG1*-related mtDNA depletion syndrome, molecular genetic testing approaches can include ***SUCLG1* and *SUCLA2* testing** or use of a **multigene panel**:

- ***SUCLG1* and *SUCLA2* testing.** Sequence analysis of *SUCLG1* and *SUCLA2* is performed first. If only one pathogenic variant is found, gene-targeted deletion/duplication analysis of that gene could be considered; however, to date no exon or whole-gene deletions of either gene have been reported.
- **A multigene panel** that includes *SUCLG1*, *SUCLA2*, and other genes related to **mtDNA depletion syndromes** (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. Of note, given the rarity of *SUCLG1*-related mtDNA depletion syndrome, some panels for mtDNA depletion syndromes may not include this gene. (3) 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 mitochondrial disorders**, molecular genetic testing approaches can include **genomic testing** (comprehensive genome sequencing) and/or **gene-targeted testing** (multigene panel):

- **Comprehensive genome sequencing** (when clinically available) includes exome sequencing and genome sequencing.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.
- **A multigene panel** for **inherited mitochondrial disorders** may also be considered.

**Table 1.** Molecular Genetic Testing Used in *SUCLG1*-Related mtDNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria

| Gene [1] | Method | Proportion of Probands with Pathogenic Variants [2] Detectable by Method |
|---|---|---|
| *SUCLG1* | Sequence analysis [3] | 21/21 [4] |
| | Gene-targeted deletion/duplication analysis [5] | None reported to date [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.* Carrozzo et al [2016]
*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.

# Clinical Characteristics

## Clinical Description

To date 29 individuals with *SUCLG1*-related mitochondrial DNA (mtDNA) depletion syndrome, encephalomyopathic form with methylmalonic aciduria (MMA) have been reported [Ostergaard et al 2007, Ostergaard et al 2010, Rivera et al 2010, Rouzier et al 2010, Valayannopoulos et al 2010, Van Hove et al 2010, Randolph et al 2011, Sakamoto et al 2011, Honzik et al 2012, Navarro-Sastre et al 2012, Landsverk et al 2014, Carrozzo et al 2016, Chu et al 2016, Donti et al 2016, Liu et al 2016, Pupavac et al 2016].

The clinical description here is based on the findings reported in these 29 individuals. The common clinical manifestations are summarized in Table 2 [Carrozzo et al 2016].

**Table 2.** Clinical Manifestations of *SUCLG1*-Related mtDNA Depletion Syndrome

| Frequency | Manifestations |
|---|---|
| >50% | • Developmental delay & cognitive impairment<br>• Hypotonia<br>• Muscle atrophy<br>• Feeding difficulties<br>• Lactic acidosis |
| 20%-50% | • Growth retardation / failure to thrive<br>• Hepatopathy<br>• Sensorineural hearing impairment<br>• Dystonia<br>• Hypertonia |

*Table 2. continued from previous page.*

| Frequency | Manifestations |
|---|---|
| <20% | • Hypertrophic cardiomyopathy<br>• Recurrent respiratory infections<br>• Respiratory distress<br>• Apnea<br>• Recurrent vomiting<br>• Gastroesophageal reflux disease<br>• Ptosis<br>• Strabismus<br>• Epilepsy<br>• Myoclonus<br>• Microcephaly<br>• Choreoathetosis<br>• Hyperhidrosis<br>• Sleep disturbance<br>• Rhabdomyolysis<br>• Contractures<br>• Hypothermia<br>• Hypoglycemia |

**Age of onset and phenotypic spectrum.** Although *SUCLG1*-related mtDNA depletion syndrome can present from the prenatal period to age one year, the majority of affected infants present at birth [Carrozzo et al 2016].

The majority have an uncomplicated pregnancy and normal birth weight; however, five neonates had intrauterine growth restriction (IUGR) or were small for gestational age (SGA) [Ostergaard et al 2007, Randolph et al 2011, Carrozzo et al 2016]. Rare prenatal manifestations may include oligohydramnios and abnormal fetal heart rate [Carrozzo et al 2016].

The majority of affected infants present with early-onset encephalomyopathy and neurocognitive problems as well as hepatopathy, feeding and growth problems, and cardiorespiratory complications.

Death from severe metabolic acidosis during the neonatal period (fatal infantile lactic acidosis) has been reported in five infants [Ostergaard et al 2007, Rivera et al 2010].

**Neurocognitive.** The majority of affected children demonstrate developmental delay, cognitive impairment, hypotonia, and muscle atrophy. Other, less frequent, neurologic manifestations include: sensorineural hearing impairment, dystonia, hypertonia, epilepsy, myoclonus, microcephaly, choreoathetosis, ptosis, and strabismus.

**Hepatopathy.** Approximately 40% of affected individuals have liver involvement manifesting as hepatomegaly, steatosis, and elevated liver enzymes. One affected infant developed intermittent episodes of liver failure [Van Hove et al 2010].

**Feeding and growth.** Failure to thrive, growth retardation, and feeding difficulties, often necessitating tube feeding, occur commonly. Recurrent vomiting and gastroesophageal reflux disease (GERD) occasionally occur. The feeding difficulties, recurrent vomiting, and GERD can cause or contribute to growth failure.

**Cardiac.** Hypertrophic cardiomyopathy was reported in 15% of affected children. Ventricular hypertrophy is typically mild and appears in the neonatal period or infancy [Carrozzo et al 2016].

**Respiratory.** Recurrent respiratory infections are reported in some. Respiratory distress due to muscle weakness, apnea, and abnormal breathing has been reported.

**Congenital malformations.** One affected infant had multiple congenital anomalies including cleft lip and palate, aortic coarctation, patent ductus arteriosus, patent foramen ovale, shortening of the left femur and both humeri, dilatation of the left renal collecting system, and accessory left kidney [Landsverk et al 2014].

Other congenital anomalies reported in single infants each are interrupted aortic arch, polydactyly, and hypospadias [Ostergaard et al 2007, Rivera et al 2010].

**Metabolic derangements.** In addition to elevated MMA, the majority of affected children develop lactic acidosis that can be severe and life threatening. Hypoglycemia was occasionally reported.

**Others.** Other, less frequent, manifestations include hyperhidrosis, hypothermia, sleeping disturbance, rhabdomyolysis, and joint contractures.

**Prognosis.** Life span is shortened, with median survival of 20 months. Two thirds (14/21) of affected children died during childhood – five in the neonatal period and nine during infancy and early childhood [Carrozzo et al 2016].

### Genotype-Phenotype Correlations

Pathogenic *SUCLG1* missense variants can result in some residual enzyme activity, and hence a milder phenotype. Survival in children with biallelic pathogenic missense variants was longer (median age: 18 months) than in children with biallelic loss-of-function variants (splice site, frameshift, and nonsense variants) (median age: birth) [Carrozzo et al 2016].

### Nomenclature

Succinyl-CoA ligase deficiency can result from either biallelic pathogenic variants in *SUCLG1* (*SUCLG1*-related mtDNA depletion syndrome) or biallelic pathogenic variants in *SUCLA2* (*SUCLA2*-related mtDNA depletion syndrome).

### Prevalence

*SUCLG1*-related mtDNA depletion syndrome is rare; the exact prevalence is unknown. To date 29 individuals with *SUCLG1*-related mtDNA depletion have been reported in families of different ethnic origins [Ostergaard et al 2007, Ostergaard et al 2010, Rivera et al 2010, Rouzier et al 2010, Valayannopoulos et al 2010, Van Hove et al 2010, Randolph et al 2011, Sakamoto et al 2011, Honzik et al 2012, Navarro-Sastre et al 2012, Landsverk et al 2014, Carrozzo et al 2016, Chu et al 2016, Donti et al 2016, Liu et al 2016, Pupavac et al 2016].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SUCLG1*.

## Differential Diagnosis

*SUCLG1*-related mtDNA depletion syndrome needs to be differentiated from other mtDNA depletion syndromes, a genetically and clinically heterogeneous group of autosomal recessive disorders that are characterized by a severe reduction in mtDNA content leading to impaired energy production in affected tissues and organs. Table 3 includes the currently known mtDNA depletion syndromes.

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 (e.g., *TK2*,

*SUCLA2*, *SUCLG1*, *RRM2B*, *DGUOK*, and *TYMP*) or mtDNA replication (e.g., *POLG* and *TWNK* [*C10orf2*]). The function of *FBXL4* is not yet known.

Mitochondrial DNA depletion syndromes are phenotypically classified into hepatocerebral, encephalomyopathic, neurogastrointestinal, and myopathic forms [El-Hattab & Scaglia 2013].

**Table 3.** Mitochondrial DNA Depletion Syndromes

| Phenotype [1] | Gene | Mitochondrial DNA Depletion Syndrome #, Type | Reference [2] |
|---|---|---|---|
| Hepato-cerebral | *DGUOK* | 3, hepatocerebral type | |
| | *POLG* | 4A, Alpers type | *POLG*-Related Disorders |
| | *MPV17* | 6, hepatocerebral type | *MPV17*-Related Hepatocerebral mtDNA Depletion Syndrome |
| | *TWNK* (*C10orf2*) | 7, hepatocerebral type | OMIM 271245 |
| | *TFAM* | 15, hepatocerebral type | OMIM 617156 |
| Encephalo-myopathic | *SUCLA2* | 5, encephalomyopathic type w/methylmalonic aciduria | *SUCLA2*-Related mtDNA Depletion Syndrome, Encephalomyopathic Form w/ Methylmalonic Aciduria |
| | *FBXL4* | 13, encephalomyopathic type | *FBXL4*-Related Encephalomyopathic mtDNA Depletion Syndrome |
| | *SUCLG1* | 9, encephalomyopathic type w/methylmalonic aciduria | *SUCLG1*-Related mtDNA Depletion Syndrome, Encephalomyopathic Form w/ Methylmalonic Aciduria |
| | *RRM2B* | 8A, encephalomyopathic type w/renal tubulopathy | *RRM2B*-Related Mitochondrial Disease |
| | *OPA1* | 14, encephalocardiomyopathic type | OMIM 616896 |
| | *ABAT* | Encephalomyopathic type | OMIM 613163 |
| Neurogastro-intestinal | *TYMP* | 1, MNGIE type | Mitochondrial Neurogastrointestinal Encephalopathy Disease |
| | *POLG* | 4B, MNGIE type | *POLG*-Related Disorders |
| | *RRM2B* | 8B, MNGIE type | *RRM2B*-Related Mitochondrial Disease |
| Myopathic | *TK2* | 2, myopathic type | *TK2*-Related mtDNA Depletion Syndrome, Myopathic Form |
| | *AGK* | 10, cardiomyopathic type (Sengers syndrome) | OMIM 212350 |
| | *MGME1* | 11, myopathic type | OMIM 615084 |
| | *SLC25A4* | 12B, cardiomyopathic type | OMIM 615418 |

*1.* Within each phenotypic category, mtDNA depletion syndromes are ordered by relative prevalence.
*2.* See hyperlinked *GeneReview* or OMIM phenotype entry for more information.

Among mtDNA depletion syndromes, methylmalonic acid (MMA) is elevated only in *SUCLG1*- and *SUCLA2*-related mtDNA depletion syndromes.

The phenotypes of *SUCLG1*-related mtDNA depletion syndrome and *SUCLA2*-related mtDNA depletion syndrome may be difficult to be differentiate (see Table 4).

*SUCLA2*-related mtDNA depletion syndrome is characterized by onset of the following features in infancy or childhood: psychomotor retardation, hypotonia, dystonia, muscular atrophy, sensorineural hearing impairment, postnatal growth retardation, and feeding difficulties. Other, less frequent, features include distinctive facial features, contractures, kyphoscoliosis, gastroesophageal reflux, ptosis, choreoathetosis, ophthalmoplegia, and

epilepsy. Of note, hepatopathy and cardiomyopathy, which have been reported in *SUCLG1*-related mtDNA depletion syndrome, have not been described in *SUCLA2*-related mtDNA depletion syndrome [Carrozzo et al 2016].

**Table 4.** Comparison of the Phenotypes of *SUCLG1*-Related mtDNA Depletion Syndrome and *SUCLA2*-Related mtDNA Deletion Syndromes

| | | Mitochondrial DNA Depletion Syndrome | |
|---|---|---|---|
| Clinical Finding | | *SUCLG1*-Related | *SUCLA2*-Related |
| Age at onset | | Majority present at birth | Infancy or childhood |
| Median survival | | 20 months | 20 years |
| Developmental delay | | >50% | >75% |
| Hypotonia | | >50% | >75% |
| Muscular atrophy | | >50% | 25%-50% |
| Feeding problems | | Equally common | |
| Failure to thrive | | Equally common | |
| Liver involvement | | 40% | Not reported |
| Hearing impairment | | 20%-50% | >75% |
| Dystonia | | 25%-50% | >75% |
| Hypertonia | | 25%-50% | <20% |
| Hypertrophic cardiomyopathy | | 14% | Not reported |
| On brain MRI: | Basal ganglia hyperintensities | 80% | 70% |
| | Cerebral atrophy | 30% | 70% |
| | Leukoencephalopathy | 20% | 15% |

Carrozzo et al [2016]

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SUCLG1*-related mtDNA depletion syndrome the following evaluations are recommended:

- Comprehensive neurologic examination and developmental/cognitive assessment. The following diagnostic modalities can be considered to assess the degree of neurologic involvement:
  - Brain MRI (if not performed during the diagnostic evaluation) to establish the degree of central nervous system involvement
  - EEG if seizures are suspected
- Echocardiogram to assess for cardiomyopathy
- Liver function tests including transaminases, albumin, total and direct bilirubin, and coagulation profile
- Audiologic evaluation
- Ophthalmologic examination for evidence of ptosis and/or strabismus
- Nutritional evaluation and swallowing assessment for feeding difficulties and growth failure
- Consultation with a clinical geneticist and/or genetic counselor

## Treatment of Manifestations

Management is best provided by a multidisciplinary team including specialists in neurology, audiology, child development, gastroenterology, cardiology, nutrition, and clinical genetics. Treatments include the following:

- Physical therapy to help maintain muscle function and prevent joint contractures
- Standard treatment with anti-seizure medication for seizures
- Nutritional support by a dietitian and the use of a nasogastric tube or gastrostomy tube feedings to address feeding difficulties and failure to thrive
- Chest physiotherapy, aggressive antibiotic treatment of chest infections, and artificial ventilation (including assisted nasal ventilation or intubation and the use of a tracheostomy and ventilator) for respiratory insufficiency
- Hypertrophic cardiomyopathy and hepatopathy, when present, require standard management by cardiologists and hepatologists, respectively.

## Surveillance

No clinical guidelines for surveillance are available.

The following evaluations are suggested, with frequency varying according to the needs of the child:

- Developmental and neurologic assessment
- Nutritional and growth assessment
- Echocardiogram
- Liver function tests
- Hearing evaluation
- Ophthalmologic examination

## Evaluation of Relatives at Risk

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

## Therapies Under Investigation

A group of mtDNA depletion syndromes is caused by defects in genes encoding proteins involved in maintenance of the mitochondrial deoxyribonucleotide pool. Because in vitro experimental studies have demonstrated improved mtDNA content following deoxyribonucleotide supplementation, this could potentially be a treatment for some mtDNA depletion syndromes [Cámara et al 2014].

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.

# 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

*SUCLG1*-related mitochondrial DNA (mtDNA) depletion syndrome, encephalomyopathic form with methylmalonic aciduria is inherited in an autosomal recessive manner.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *SUCLG1* 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.** Individuals with *SUCLG1*-related mtDNA depletion syndrome are not reported to reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a *SUCLG1* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SUCLG1* pathogenic variants in the family.

## Related Genetic Counseling Issues

**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). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

Once the *SUCLG1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

# 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
- **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.** SUCLG1-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *SUCLG1* | 2p11.2 | Succinate--CoA ligase [ADP/GDP-forming] subunit alpha, mitochondrial | SUCLG1 database | SUCLG1 | SUCLG1 |

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 SUCLG1-Related Mitochondrial DNA Depletion Syndrome, Encephalomyopathic Form with Methylmalonic Aciduria (View All in OMIM)

| | |
|---|---|
| 245400 | MITOCHONDRIAL DNA DEPLETION SYNDROME 9 (ENCEPHALOMYOPATHIC TYPE WITH METHYLMALONIC ACIDURIA); MTDPS9 |
| 611224 | SUCCINATE-CoA LIGASE, GDP/ADP-FORMING, SUBUNIT ALPHA; SUCLG1 |

## Molecular Pathogenesis

Succinyl-CoA ligase (SUCL) is a mitochondrial heterodimeric enzyme of the Krebs cycle that is composed of an alpha subunit, encoded by *SUCLG1*, and a beta subunit, encoded by either *SUCLA2* or *SUCLG2*. SUCL catalyzes the reversible conversion of succinyl-CoA and ADP or GDP to succinate and ATP or GTP. When the alpha subunit forms a heterodimer with *SUCLA2*-encoded beta subunits, the resulting SUCL enzyme utilizes ADP to generate ATP. In contrast, when the alpha subunit forms a heterodimer with *SUCLG2*-encoded beta subunits, the resulting SUCL enzyme utilizes GDP to generate GTP.

SUCL also forms a complex with the mitochondrial nucleoside diphosphate kinase (see **Abnormal gene product**).

**Gene structure.** *SUCLG1* contains nine exons (NM_003849.3).

**Pathogenic variants.** The spectrum of reported *SUCLG1* pathogenic variants includes missense, splice site, frameshift deletion, and nonsense variants. Missense variants are the most common, accounting for about half of pathogenic variants.

**Normal gene product.** *SUCLG1* encodes the succinyl-CoA ligase [ADP/GDP-forming] subunit alpha of SUCL, which has 346 amino acid residues (NP_003840.2).

**Abnormal gene product.** Pathogenic *SUCLG1* variants lead to dysfunctional SUCL protein. As SUCL forms a complex with the mitochondrial nucleoside diphosphate kinase, the lack of this complex in SUCL deficiency can disturb the kinase function, resulting in decreased mitochondrial nucleotide synthesis and, therefore, decreased mtDNA synthesis leading to mtDNA depletion. In addition, because SUCL deficiency results in impaired conversion of succinyl-CoA to succinate, succinyl-CoA accumulates and is converted to methylmalonyl-CoA by methylmalonyl-CoA mutase, leading to the accumulation of methylmalonic acid (MMA) [El-Hattab & Scaglia 2013].

# Chapter Notes

## Revision History

- 30 March 2017 (bp) Review posted live
- 20 October 2016 (aeh) Original submission

# References

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