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SLC25A19-Related Thiamine Metabolism Dysfunction

Synonym: SLC25A19 Deficiency

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Summary

Clinical characteristics

SLC25A19-related thiamine metabolism dysfunction (SLC25A19 deficiency) is characterized by two phenotypes: Amish lethal microcephaly and thiamine metabolism dysfunction syndrome 4 (THMD-4).

Amish lethal microcephaly is characterized by severe congenital microcephaly, developmental delay, seizures, 2-oxoglutaric aciduria, and often premature death.

THMD-4 is characterized by febrile illness-associated episodic encephalopathy, progressive polyneuropathy, and bilateral striatal necrosis.

Diagnosis/testing

The diagnosis of SLC25A19 deficiency is established in a proband with suggestive findings and biallelic pathogenic variants in *SLC25A19* identified by molecular genetic testing.

Management

Targeted therapy: Oral thiamine treatment (400-600 mg daily) starting at diagnosis. Thiamine dose must be increased (by 25%) during febrile illness, surgery, or acute decompensation.

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Supportive care: Acute encephalopathic episodes may require admission to an ICU to manage seizures and increased intracranial pressure; during acute decompensations thiamine may be increased to double the regular dose (up to 1,500 mg daily) and given intravenously. Anti-seizure medication is used to control seizures. Treatment of dystonia is symptomatic and includes administration of trihexyphenidyl or L-dopa. Rehabilitation, physiotherapy, occupational therapy, and speech therapy as needed, and adaptation of educational programs to meet individual needs. Management of routine childhood illnesses to avoid acidosis and/or fever. Education of the family regarding the importance of lifelong compliance with medical therapy.

Surveillance: Clinical review of neurologic status every six months; annual assessment of developmental progress and educational needs; assessment of growth and nutritional needs, mobility and therapy needs, and social support and care coordination needs at each visit.

Agents/circumstances to avoid: Contact with individuals with communicable respiratory diseases; the anti-seizure medication sodium valproate.

Evaluation of relatives at risk: It is appropriate to clarify the status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of thiamine treatment.

Genetic counseling

SLC25A19 deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SLC25A19* 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 *SLC25A19* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for SLC25A19 deficiency are possible.

GeneReview Scope

SLC25A19-Related Thiamine Metabolism Dysfunction: Included Phenotypes [1]
• Amish lethal microcephaly • Thiamine metabolism dysfunction syndrome 4 (THMD-4)

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

Diagnosis

SLC25A19-related thiamine metabolism dysfunction (SLC25A19 deficiency) is characterized by two phenotypes: Amish lethal microcephaly and thiamine metabolism dysfunction syndrome 4 (THMD-4).

Suggestive Findings

Amish lethal microcephaly should be suspected in probands with the following findings:

- Severe congenital microcephaly
- Developmental delay
- Seizures
- Lactic acidosis
- Highly elevated (≥10-fold increase) levels of acid 2-ketoglutarate on urine organic acids

THMD-4 should be suspected in probands with the following findings:

- Acute episodic encephalopathy and weakness triggered by fever
- Hypotonia with developmental delay
- Seizures
- Progressive peripheral neuropathy
- Lactic acidosis
- Brain MRI shows T_2 hyperintensity and necrosis in the caudate and putamen in all individuals. The thalamus, brain stem, and cortex may also demonstrate T_2 hyperintensities and necrosis.

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 SLC25A19 deficiency **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *SLC25A19* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic *SLC25A19* variants of uncertain significance (or of one known *SLC25A19* pathogenic variant and one *SLC25A19* variant of uncertain significance) does not establish or rule out the diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of SLC25A19 deficiency has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SLC25A19* 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.530G>C (p.Gly177Ala) pathogenic variant can be performed first in individuals of Amish ancestry (see Table 6).

A multigene panel that includes *SLC25A19* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of SLC25A19 deficiency has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 *SLC25A19*-Related Thiamine Metabolism Dysfunction

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
SLC25A19	Sequence analysis [3]	<100% [4]
	Gene-targeted deletion/duplication analysis [5]	1 reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. One large *SLC25A19* deletion has been reported to date [Lionel et al 2018].

Clinical Characteristics

Clinical Description

The two phenotypes observed in *SLC25A19*-related thiamine metabolism dysfunction (SLC25A19 deficiency) are Amish lethal microcephaly and thiamine metabolism dysfunction syndrome 4 (THMD-4).

Amish Lethal Microcephaly

Amish lethal microcephaly is characterized by severe congenital microcephaly, developmental delay, seizures, 2-oxoglutaric aciduria, and often premature death. The phenotype shows little variability [Kelley et al 2002, Siu et al 2010].

Congenital microcephaly has been reported in all affected infants. Head circumference is typically more than two standard deviations (SD) below the mean and occasionally more than six SD below the mean, with an extremely underdeveloped cranial vault as a result of the small brain size. The anterior and posterior fontanels are closed at birth, and ridging from premature sutural fusion may be evident.

Seizures have occurred in some affected infants. Seizures were generalized tonic-clonic and responded well to phenobarbital.

Developmental delay. All individuals have profound developmental delay, and most died before age one year. The single affected individual described by Siu et al [2010] was started on a high-fat diet and thiamine. At age seven years, he had profound developmental delay, severe microcephaly, and was fed via gastrostomy tube.

Craniofacial features. Apart from the small head size and craniofacial distortions caused by profound microcephaly, moderate micrognathia was noted in most individuals, and one infant had a cleft soft palate.

Metabolic disturbances. 2-ketoglutaric acidosis has been demonstrated in a number of Amish infants with this disorder. Mild hepatomegaly has been observed in several affected individuals, usually during acute illnesses associated with metabolic acidosis.

Other neurologic manifestations. Many affected infants have difficulty maintaining body temperature.

Brain and/or spine imaging has not been done in most affected individuals. In those who underwent head imaging, reported findings include corpus callosum dysgenesis, large cisterna magma, and hypoplastic cerebellar vermis. Spine MRI demonstrated closed spinal dysraphism in one individual [Siu et al 2010].

Prognosis. After the first two or three months of life, increasing irritability of unknown cause commonly develops [Kelley et al 2002]. Although no changes in physical or neurologic examination accompany the irritability, the Lancaster Amish children who show increased irritability are more likely to die within 24-48 hours of developing their next viral illness. The average life span of an affected infant is between ages five and six months among the Lancaster Amish; the affected Amish Mennonite child reported by Siu et al [2010] was alive (albeit with severe developmental delay) at age seven years.

Neuropathology. A partial autopsy of an affected infant age four months showed severity of the malformation was more pronounced in the anterior portion of the brain. Frontal lobes are smooth and rudimentary. Increasing convolution and lamination progress occipitotemporally. Regions that were most hypoplastic were most disorganized histologically [Strauss et al 2002]. No pathology on the individual reported by Siu et al [2010] was available.

Thiamine Metabolism Dysfunction Syndrome 4 (THMD-4)

THMD-4 is characterized by febrile illness-associated episodic encephalopathy, progressive polyneuropathy, and bilateral striatal necrosis.

Acute encephalopathic episodes are triggered by febrile illness. All affected individuals reached normal developmental milestones until their first encephalopathic episode. Triggers for these episodes included trauma and vaccination. Most individuals developed episodes between ages 12 months and six years. Acute encephalopathic episodes were characterized by gait difficulties, dysphagia, dysphonia, seizures, lethargy, and encephalopathy including coma.

Lack of or delayed thiamine treatment following the first acute encephalopathic episode was associated with early death or severe neurologic sequalae including dystonia, hypotonia, and developmental delay. Early supplementation with thiamine was associated with a good prognosis, with full recovery in most individuals; a few individuals had residual deficits.

Development. Typically, all individuals reached normal developmental milestones until their first acute encephalopathic episode. Following the episode, individuals developed neurodevelopmental regression, which was reversible if thiamine treatment was started promptly.

Seizures were usually observed during the acute encephalopathic episodes. They were described as focal or generalized.

Metabolic disturbances. Lactic acidosis is reported during acute encephalopathic episodes.

Progressive axonal motor and/or sensory neuropathy. Affected individuals developed recurrent episodes of acute flaccid paralysis following febrile illness. Usually, the onset is between ages one and two years. Nerve

conduction studies demonstrated motor/sensory axonal polyneuropathy. Untreated individuals showed flaccid quadriparesis with absent deep tendon reflexes. Early thiamine treatment was associated with full recovery.

Brain MRI examination showed bilateral symmetrical T_2 hyperintensity and necrosis in the caudate and putamen in all individuals. Bilateral T_2 hyperintensity and necrosis of the thalamus, cerebellum, cortical, and subcortical regions were also reported. Follow-up brain MRI in older individuals showed volume loss and gliosis of the striatum.

Prognosis is largely related to early supplementation of thiamine. Early thiamine treatment was associated with good outcomes; delayed or no treatment with thiamine was associated with early death or neurologic sequalae including dystonia, spasticity, and cognitive delay.

It is unknown whether life span in individuals with THMD-4 is abnormal. One reported individual is alive at age 18 years [Bottega et al 2019], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

c.530G>C (p.Gly177Ala) is the only *SLC25A19* variant reported in individuals with Amish lethal microcephaly to date. This variant is associated with a severe phenotype.

In those with other *SLC25A19* variants and THMD-4, no genotype-phenotype correlations have been identified.

Nomenclature

Thiamine metabolism dysfunction syndrome 4 may also be referred to as *SLC25A19*-related bilateral striatal degeneration and progressive polyneuropathy based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

Amish lethal microcephaly has been found primarily in the Old Order Amish who have ancestors from Lancaster County, Pennsylvania. At least 61 affected infants have been born to 33 nuclear families in the past 40 years. In this population, incidence is approximately one in 500 births.

THMD-4 is a rare disorder, with only 16 individuals reported to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC25A19*.

Differential Diagnosis

Amish Lethal Microcephaly

Microcephaly has a wide variety of causative factors. It can be syndromic or isolated, environmental or genetic, congenital or acquired [Battaglia & Carey 2003]. Metabolic testing (including urine organic acids, plasma amino acids, lactate, pyruvate, and electrolytes) is indicated for all children with congenital microcephaly. Further specific evaluations are performed as indicated based on the results of this testing.

The primary microcephalies are a group of rare, phenotypically and etiologically heterogeneous disorders of brain growth characterized by (1) a head circumference two or more standard deviations (SD) below the mean

at birth and three or more SD below the mean by age one year, and (2) mild-to-severe intellectual disability. Additional clinical or neuroimaging features can be associated. Most primary microcephalies are inherited in an autosomal recessive manner. To date, pathogenic variants in more than 100 genes are known to cause primary microcephaly (for review, see Jayaraman et al [2018]). (See also *WDR62* Primary Microcephaly and *ASPM* Primary Microcephaly.)

The degree of microcephaly is much greater in Amish lethal microcephaly than in any of these other genetically defined microcephaly syndromes. Additionally, 2-ketoglutaric aciduria is a good clue for the diagnosis of Amish lethal microcephaly, as 2-ketoglutaric aciduria has not been reported as a finding in other genetically defined microcephaly syndromes.

Alpha-ketoglutarate. Among other genetic malformation syndromes, a similar level of urinary 2-ketoglutarate is also characteristic of DOORS (*d*eafness, *o*nychodystrophy, *o*steodystrophy, intellectual disability [formerly known as mental *r*etardation], *s*eizures) syndrome, caused by biallelic pathogenic variants in *TBC1D24*. Microcephaly is noted in one third of individuals with DOORS syndrome. (See *TBC1D24*-Related Disorders.)

Thiamine Metabolism Dysfunction Syndrome 4

Table 2. Genes of Interest in the Differential Diagnosis of Thiamine Metabolism Dysfunction Syndrome 4

Gene	Disorder	MOI	Clinical Characteristics / Comment
>350 genes [1]	Primary mitochondrial disorders	AR AD XL Mat	↑ levels of urinary 2-ketoglutarate are common in wide variety of disorders of mitochondrial dysfunction, incl those caused by mutation of both mtDNA & nuclear DNA genes.
BCKDHA *BCKDHB* *DBT* *IVD* *MCEE* *MMAA* *MMAB* *MMADHC* *MMUT* *PCCA* *PCCB* [2]	Organic acid disorders (e.g., isolated methylmalonic acidemia, maple syrup urine disease, propionic acidemia)	AR	Major clinical features are developmental delay, seizures, lethargy, coma, hypotonia, vomiting, poor weight gain, growth deficiency, hepatomegaly, respiratory distress, cardiac dysfunction, hypoglycemia, & acidosis.
DLD	Dihydrolipoamide dehydrogenase deficiency	AR	↑ levels of urinary alpha-ketoglutarate may be seen in persons w/pathogenic variants in the alpha-ketoglutarate dehydrogenase complex.
NUP62	Infantile striatonigral degeneration (OMIM 271930)	AR	Early-onset dystonia &/or Leigh-like syndrome [3]
OGDH	Alpha-ketoglutarate dehydrogenase deficiency (OMIM 203740)	AR	↑ levels of urinary alpha-ketoglutarate may be seen in persons w/pathogenic variants in the alpha-ketoglutarate dehydrogenase complex.
SLC19A3	Biotin-thiamine-responsive basal ganglia disease (thiamine metabolism dysfunction syndrome 2)	AR	Classic presentation is in childhood & is characterized by recurrent subacute encephalopathy manifesting as confusion, seizures, ataxia, dystonia, supranuclear facial palsy, external ophthalmoplegia, &/or dysphagia, which – if left untreated – can eventually lead to coma & even death. Dystonia & cogwheel rigidity are nearly always present. Prompt administration of biotin & thiamine early in disease course results in partial or complete improvement w/in days in childhood & adult presentations. ↑ excretion of alpha-ketoglutarate in urinary organic acid assays can be observed.

Table 2. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics / Comment
TPK1	Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type) (OMIM 614458)		Episodic encephalopathy, ataxia, dystonia, spasticity, 2-ketoglutaric aciduria [4]

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MOI = mode of inheritance; XL = X-linked
1. McCormick et al [2018]
2. More than 65 organic acids are known [Ramsay et al 2018]; listed genes represent those associated with the selected organic acidemias in the **Disorder** column.
3. The term "Leigh-like syndrome" is often used for individuals with clinical and other features that are strongly suggestive of Leigh syndrome but who do not fulfill the stringent diagnostic criteria because of atypical neuropathology (variation in the distribution or character of lesions or with the additional presence of unusual features such as extensive cortical destruction), atypical or normal neuroimaging, normal blood and cerebrospinal fluid lactate levels, or incomplete evaluation. The heterogeneous clinical presentation that occurs in Leigh syndrome is also present in Leigh-like syndromes. (See Mitochondrial DNA-Associated Leigh Syndrome and NARP and Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview.)
4. See Mitochondrial DNA-Associated Leigh Syndrome and NARP.

Management

No clinical practice guidelines for *SLC25A19*-related thiamine metabolism dysfunction (SLC25A19 deficiency) have been published.

Evaluation Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with SLC25A19 deficiency, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *SLC25A19*-Related Thiamine Metabolism Dysfunction

System/Concern	Evaluation	Comment
Neurologic	• Neurologic eval • Urine organic acids	• To incl brain MRI • Consider EEG if seizures are a concern. • Consider serum lactate & blood gas.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SLC25A19 deficiency 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.	

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

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Oral thiamine treatment (400-600 mg daily) is critical from the time of diagnosis. The dose must be increased during febrile illness, surgery, or acute decompensation (by 25%). This treatment is lifelong. It prevents metabolic decompensation and improves outcomes [Samur et al 2022].

In Amish lethal microcephaly, thiamine supplementation is usually without benefit. One individual showed stabilization of his symptoms with thiamine treatment [Siu et al 2010].

Supportive Care

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 4).

Table 4. Treatment of Manifestations in Individuals with *SLC25A19*-Related Thiamine Metabolism Dysfunction

Manifestation/ Concern	Treatment	Considerations/Other
Acute encephalopathic episodes	• May require admission to ICU to manage seizures & ↑ intracranial pressure. • ↑ thiamine to 2x the daily dose (up to 1,500 mg daily); can administer thiamine intravenously.	
Epilepsy	• Standardized treatment w/ASM by experienced neurologist. • The few children w/Amish lethal microcephaly who were treated responded well to phenobarbital.	• Many ASMs may be effective. • Valproate must be avoided. • Education of parents/ caregivers [1]
Dystonia	Symptomatic treatment incl administration of trihexyphenidyl or L-dopa	
Spasticity	• Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls • Infants w/Amish lethal microcephaly have responded to benzodiazepine anxiolytics.	Consider need for positioning & mobility devices, disability parking placard.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Infection/Fever	Routine childhood illnesses should be managed to minimize acidosis assoc w/acute illnesses.	
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 in survivors.

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.
  - 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.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

To monitor existing manifestations, the individual's response to targeted therapy and supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with *SLC25A19*-Related Thiamine Metabolism Dysfunction

System/Concern	Evaluation	Frequency
Neurologic	Assess for new seizures or changes in seizures, changes in tone, movement disorders.	Every 6 mos
Development	Monitor developmental progress & educational needs.	At each visit
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
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).	

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Avoidance of contact with individuals with communicable respiratory diseases is appropriate.

Avoid sodium valproate as an anti-seizure medication.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing for the *SLC25A19* pathogenic variants in the family in order to identify as early as possible those who would benefit from prompt initiation of thiamine treatment.

For at-risk newborn sibs when prenatal testing was not performed, prior to genetic testing, or while it is under way, urine organic acids and pyruvate and lactate levels should be considered.

Supplementation with pharmacologic doses of thiamine (vitamin B_1) (400-600 mg/day compared to US recommended dietary allowance of 1.5 mg/day) is recommended as early as possible for at-risk sibs until their genetic status can be determined.

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

SLC25A19-related thiamine metabolism dysfunction (SLC25A19 deficiency) 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 an *SLC25A19* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC25A19* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic, have normal urinary excretion of 2-ketoglutarate, and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC25A19* 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.
- Intrafamilial clinical variability has not been reported to date.

- Heterozygotes (carriers) are asymptomatic, have normal urinary excretion of 2-ketoglutarate, and are not at risk of developing the disorder.

Offspring of a proband

- Amish lethal microcephaly is lethal before reproductive age.
- To date, individuals with thiamine metabolism dysfunction syndrome 4 are not known to reproduce.

Other family member. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC25A19* pathogenic variant.

Carrier Detection

Carrier testing for at-risk family members requires prior identification of the *SLC25A19* 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. Amish lethal microcephaly has been found primarily in the Old Order Amish who have ancestors in Lancaster County, Pennsylvania. In this population, incidence is approximately one in 500 births (see Table 6).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *SLC25A19* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for SLC25A19 deficiency are possible.

Fetal ultrasound examination. Three fetal ultrasound examinations performed after 20 weeks' gestation in two pregnancies of babies ultimately found to have Amish lethal microcephaly revealed marked deceleration of head growth [Kelley et al 2002]. The sensitivity and specificity of fetal ultrasound for the prenatal diagnosis of Amish lethal microcephaly has not been evaluated.

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.

- **MedlinePlus**
  Microcephaly
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801

Bethesda MD 20824
Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
Microcephaly Information Page

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. SLC25A19-Related Thiamine Metabolism Dysfunction: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC25A19	17q25.1	Mitochondrial thiamine pyrophosphate carrier	SLC25A19 database	SLC25A19	SLC25A19

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 SLC25A19-Related Thiamine Metabolism Dysfunction (View All in OMIM)

606521	SOLUTE CARRIER FAMILY 25 (MITOCHONDRIAL THIAMINE PYROPHOSPHATE CARRIER), MEMBER 19; SLC25A19
607196	MICROCEPHALY, AMISH TYPE; MCPHA
613710	THIAMINE METABOLISM DYSFUNCTION SYNDROME 4 (BILATERAL STRIATAL DEGENERATION AND PROGRESSIVE POLYNEUROPATHY TYPE); THMD4

Molecular Pathogenesis

SLC25A19 encodes the mitochondrial thiamine pyrophosphate (TPP) carrier. TPP, the active form of thiamine, is an essential cofactor for transketolase in the cytoplasm. It is attached to 2-hydroxyacyl-CoA lyase (HACL1) in the cytoplasm before this enzyme is transported into the peroxisomes. Also, TPP is transported by the mitochondrial TPP carrier into mitochondria, where it binds to pyruvate dehydrogenase and stimulates conversion of pyruvate to acetyl-CoA and binds to alpha-ketoglutarate and branched-chain alpha-keto acid dehydrogenase, entering the tricarboxylic acid cycle for energy production and biosynthesis.

SLC25A19 pathogenic variants lead to a drastic depletion in mitochondrial TPP levels, which is causative for two different clinical diseases: Amish lethal microcephaly and thiamine metabolism dysfunction syndrome 4.

A bacterially expressed human SLC25A19 protein containing the p.Gly177Ala substitution reconstituted in proteoliposomes was unable to catalyze the exchange of alpha-S^{35}-dATP (deoxyadenosine triphosphate) for ADP (adenosine diphosphate), TPP, or TMP (thiamine monophosphate) at 37 °C and had reduced activity at 25 °C [Rosenberg et al 2002].

Knockout mouse embryos homozygous for a null allele of *Slc25a19* have a neural tube closure defect, yolk sac erythropoietic failure, and elevated alpha-ketoglutarate in the amniotic fluid, and are lethal by embryonic day 12 [Lindhurst et al 2006]. Fibroblasts generated from E10.5 mouse embryos had normal levels of mitochondrial ribo- and deoxyribonucleoside triphosphates, but TPP and TMP were not detectable in their mitochondria. Ribo- and deoxyribonucleoside triphosphate levels were also normal in mitochondria of lymphoblasts from individuals with Amish lethal microcephaly; TPP and TMP levels were markedly reduced, indicating that the p.Gly177Ala substitution is a hypomorphic allele. Activity of the pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase complexes was greatly reduced in both the mouse and human cells, which explains the alpha-ketoglutaric aciduria in individuals with Amish lethal microcephaly and emphasizes the importance of oxidative metabolism in early embryogenesis.

Mechanism of disease causation. Loss of function

Table 6. Notable *SLC25A19* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_021734.5 NP_068380.3	c.530G>C	p.Gly177Ala	Founder variant in Amish community of Lancaster County, Pennsylvania [Rosenberg et al 2002]

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

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