



## SLC39A14 Deficiency

Synonyms: **Hypermanganesemia with Dystonia 2 (HMNDYT2); SLC39A14-Related Early-Onset Dystonia-Parkinsonism**

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## Summary

### Clinical characteristics

SLC39A14 deficiency is typically characterized by evidence of delay or loss of motor developmental milestones (e.g., delayed walking, gait disturbance) between ages six months and three years. Early in the disease course, children show axial hypotonia followed by dystonia, spasticity, dysarthria, bulbar dysfunction, and signs of parkinsonism including bradykinesia, hypomimia, and tremor. By the end of the first decade, they develop severe, generalized, pharmaco-resistant dystonia, limb contractures, and scoliosis, and lose independent ambulation. Cognitive impairment appears to be less prominent than motor disability. Some affected children have died in their first decade due to secondary complications such as respiratory infections. One individual with disease onset during the late teens has been reported, suggesting that milder adult presentation can occur.

### Diagnosis/testing

The diagnosis of SLC39A14 deficiency is established in a proband with progressive dystonia-parkinsonism (often combined with other signs such as spasticity and parkinsonian features), characteristic neuroimaging findings, hypermanganesemia, and biallelic pathogenic (or likely pathogenic) variants in *SLC39A14* identified on molecular genetic testing.

### Management

*Treatment of manifestations:* Symptomatic treatment includes physiotherapy and orthopedic management to prevent contractures and maintain ambulation; use of adaptive aids (walker or wheelchair) for gait abnormalities; and use of assistive communication devices. Support by a speech-language pathologist, feeding specialist, and nutritionist to assure adequate nutrition and to reduce the risk of aspiration. When an adequate

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oral diet can no longer be maintained, gastrostomy tube placement should be considered. Antispasticity medications (baclofen and botulinum toxin) and L-dopa have had limited success. While chelation therapy with intravenous administration of disodium calcium edetate early in the disease course shows promise, additional studies are warranted.

*Prevention of primary manifestations:* Unknown, but disodium calcium edetate chelation therapy shows promise; additional studies are warranted.

*Surveillance:* At each visit assess growth, swallowing, and diet to assure adequate nutrition; assess development including ambulation and speech; neurologic examination including scoring of movement disorder severity; consider whole-blood manganese levels and brain MRI as available to assess treatment response and disease progression.

*Agents/circumstances to avoid:*

- Environmental manganese exposure (i.e., contaminated drinking water, occupational manganese exposure in welding/mining industries, contaminated ephedrone preparations)
- High manganese content of total parenteral nutrition
- Foods very high in manganese including: cloves; saffron; nuts; mussels; dark chocolate; pumpkin, sesame, and sunflower seeds

*Evaluation of relatives at risk:* Molecular genetic testing for the familial *SLC39A14* pathogenic variants of apparently asymptomatic younger sibs of an affected individual allows early identification of sibs who would benefit from prompt initiation of treatment and preventive measures.

## Genetic counseling

*SLC39A14* deficiency is inherited in an autosomal recessive manner. Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder. 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 *SLC39A14* pathogenic variants have been identified in an affected family member, carrier testing of at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

## Diagnosis

### Suggestive Findings

*SLC39A14* deficiency **should be suspected** in probands with typical clinical, neuroimaging, and laboratory findings [Tuschl et al 2016, Garg et al 2022]:

**Clinical findings.** Infantile or early-childhood onset of the following:

- Delay in acquisition of developmental motor milestones or loss of developmental motor milestones
- Progressive pharmaco-resistant dystonia
- Parkinsonism signs (tremor, bradykinesia, hypomimia)
- Bulbar dysfunction
- Dysarthria

Note: One individual with onset of dystonia during the second decade has been reported, suggesting that milder presentations with juvenile or adult onset may also occur [Namnah et al 2020].

**Neuroimaging.** Brain MRI findings characteristic of manganese deposition (Figure 1) including T<sub>1</sub>-weighted hyperintensity of the following:

- Globus pallidus and striatum, with thalamic sparing
- Note: Basal ganglia changes on T<sub>1</sub>-weighted imaging are accompanied by T<sub>2</sub>-weighted hypointensity.
- White matter including the cerebellum, spinal cord, and dorsal pons, with sparing of the ventral pons
- Anterior pituitary gland

**Laboratory findings.** Hypermanganesemia. Whole-blood manganese levels are markedly elevated, usually above 1,000 nmol/L (normal reference range <320 nmol/L).

## Establishing the Diagnosis

The diagnosis of SLC39A14 deficiency is **established** in a proband with progressive dystonia (often combined with other signs such as spasticity and parkinsonian features), characteristic neuroimaging findings, hypermanganesemia, and biallelic pathogenic (or likely pathogenic) variants in *SLC39A14* identified by molecular genetic testing [Tuschl et al 2016] (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SLC39A14* variants of uncertain significance (or of one known *SLC39A14* pathogenic variant and one *SLC39A14* variant of uncertain significance) does not establish or rule out the diagnosis.

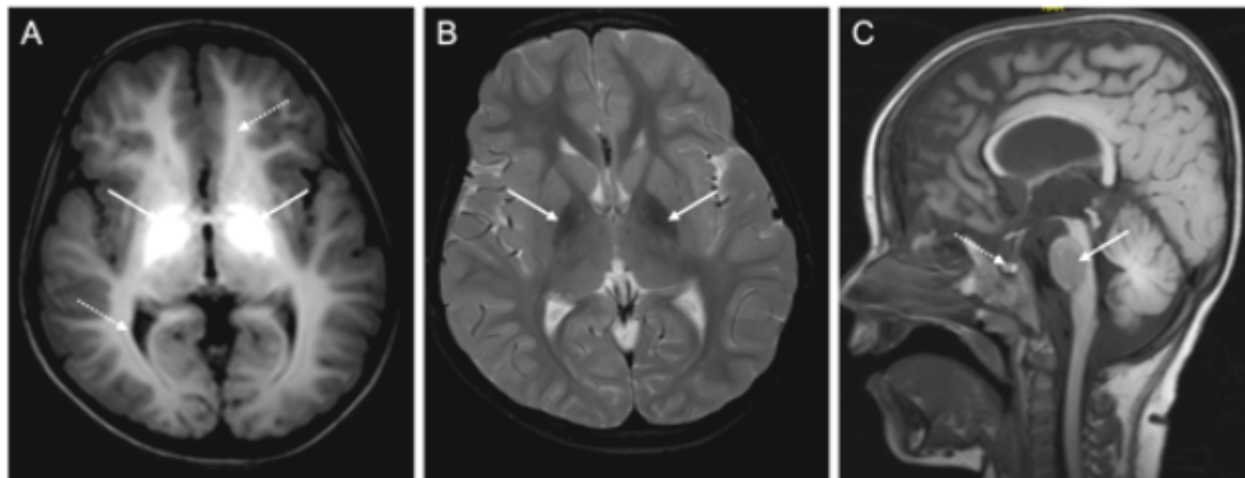
Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or a multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing does not. Children with the suggestive clinical, laboratory, and neuroimaging findings could be diagnosed using gene-targeted testing (see Option 1), whereas those with early-onset dystonia-parkinsonism indistinguishable from other inherited disorders with parkinsonism-dystonia are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

When the clinical, laboratory, and brain MRI findings suggest the diagnosis of SLC39A14 deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SLC39A14* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. If only one or no pathogenic variant is found, gene-targeted deletion/duplication analysis could be considered; however, to date no exon or whole-gene deletions of *SLC39A14* have been reported.
- **A multigene panel** that includes *SLC39A14* and other genes of interest (see Differential Diagnosis) may 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.



**Figure 1.** A. Axial T<sub>1</sub>-weighted image showing the hyperintensity of the globus pallidus (white arrows), and the cerebral white matter (dashed arrows)

B. Axial T<sub>2</sub>-weighted image showing the hypointensity of the globus pallidus (white arrows)

C. Sagittal T<sub>1</sub>-weighted image showing the hyperintensity of the white matter in the cerebellum, spinal cord, and dorsal pons with sparing of the ventral pons (white arrow), and the anterior pituitary (dashed arrow)

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 other movement disorders, **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 SLC39A14 Deficiency

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Detectable by Method
SLC39A14	Sequence analysis <sup>3</sup>	100% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	None reported

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. Tuschl 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

SLC39A14 deficiency has only recently been identified in 30 individuals from 23 families [Tuschl et al 2016, Anazi et al 2017, Marti-Sanchez et al 2018, Juneja et al 2018, Zeglam et al 2019, Namnah et al 2020, Alhasan et al 2022, Garg et al 2022, Lee & Shin 2022]; therefore, information on the phenotypic spectrum and disease progression is limited.

Onset occurs typically between ages six months and three years. Affected children present with delay or loss of motor developmental milestones (e.g., delayed walking, gait disturbance) [Tuschl et al 2016, Garg et al 2022].

Early in the disease course, children show axial hypotonia followed by dystonia, spasticity, dysarthria, bulbar dysfunction, and signs of parkinsonism including bradykinesia, hypomimia, and tremor.

By the end of the first decade, children develop severe, generalized, pharmaco-resistant dystonia, limb contractures, scoliosis, and loss of independent ambulation.

Although there appears to be relative cognitive sparing (psychometric testing has not been possible), a degree of learning disability is present in all children.

Some affected children die in their first decade due to secondary complications such as respiratory infections.

More recently, one affected individual with a milder phenotype has been described with onset of movement disorder at age 18 years and independent ambulation and survival into late adulthood [Namnah et al 2020].

**Neuropathology.** The neuropathologic findings in one individual with SLC39A14 deficiency [Tuschl et al 2016] included:

- Extensive gliosis and neuronal loss in the globus pallidus and dentate nucleus;
- Preservation of neurons in the cerebral and cerebellar cortex as well as the caudate, putamen, and thalamus;
- A vacuolated myelinopathy with patchy axonal loss in the cerebral and cerebellar white matter.

### Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

### Prevalence

The disease prevalence is not established. To date only 30 individuals with SLC39A14 deficiency from 23 families have been identified. These 23 families are from different ethnic backgrounds and the majority are consanguineous [Tuschl et al 2016, Anazi et al 2017, Marti-Sanchez et al 2018, Juneja et al 2018, Zeglam et al 2019, Namnah et al 2020, Alhasan et al 2022, Garg et al 2022, Lee & Shin 2022].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC39A14*.

## Differential Diagnosis

**Table 2.** Hereditary Disorders of Interest in the Differential Diagnosis of SLC39A14 Deficiency

Gene	Differential Disorder	MOI	Features of Differential Disorder	
			Overlapping w/SLC39A14 deficiency	Distinguishing from SLC39A14 deficiency
<b>Hereditary disorder of manganese homeostasis</b> (See also <b>acquired hypermanganesemia</b> below the table.)				
<i>SLC30A10</i>	<a href="#">Hypermanganesemia with dystonia 1 (HMNDYT1)</a>	AR	Dystonia-parkinsonism; hypermanganesemia; brain MRI features consistent w/ manganese deposition	Presents w/polycythemia, abnormal iron indices, & liver disease in addition to neurologic phenotype; on liver MRI, absence of Mn deposition in liver w/T <sub>1</sub> hyperintensity
<b>Early-onset NBIA disorders</b> (See <a href="#">NBIA Overview</a> .)				
<i>ATP13A2</i>	<a href="#">Kufor-Rakeb syndrome</a>	AR	Parkinsonism-dystonia; T <sub>2</sub> -weighted hypointensity of the globus pallidus on brain MRI	Usually present w/additional clinical features (e.g., pigmentary retinopathy, optic atrophy, oculomotor abnormalities, axonal neuropathy, cognitive decline, seizures); on brain MRI, absence of T <sub>1</sub> -weighted hyperintensity of the globus pallidus due to Mn deposition
<i>C19orf12</i>	<a href="#">MPAN</a>			
<i>COASY</i>	<a href="#">CoPAN</a>			
<i>FA2H</i>	<a href="#">FAHN</a>			
<i>PANK2</i>	<a href="#">PKAN</a>			
<i>PLA2G6</i>	<a href="#">PLAN</a>			
<i>WDR45</i>	<a href="#">BPAN</a>	XL		
<b>Disorder of copper metabolism</b>				
<i>ATP7B</i>	<a href="#">Wilson disease</a>	AR	Parkinsonism-dystonia	Liver disease, psychiatric symptoms, low serum ceruloplasmin & high non-ceruloplasmin-bound serum copper; no Mn deposition on brain MRI
<b>Inherited forms of dystonia</b> (See <a href="#">Dystonia Overview</a> .)				
<i>KMT2B</i>	<a href="#">KMT2B-related dystonia</a>	AD	Early-onset generalized dystonia	No features consistent w/Mn deposition on brain MRI; absence of hypermanganesemia
<i>MECR</i>	<a href="#">MECR-related neurologic disorder</a>	AR		Optic atrophy; no features consistent w/Mn deposition on brain MRI
<i>TOR1A</i>	<a href="#">DYT1 early-onset isolated dystonia</a>	AD		No features consistent w/Mn deposition on brain MRI; absence of hypermanganesemia

Table 2. continued from previous page.

Gene	Differential Disorder	MOI	Features of Differential Disorder	
			Overlapping w/SLC39A14 deficiency	Distinguishing from SLC39A14 deficiency
<i>GCH1</i>	GTPCH1-deficient DRD	AD	Parkinsonism-dystonia	No features consistent w/Mn deposition on brain MRI
<i>SLC6A3</i>	<i>SLC6A3</i> -related dopamine transporter deficiency syndrome	AR		
<i>SPR</i>	Sepiapterin reductase deficiency	AR		
<i>TH</i>	Tyrosine hydroxylase deficiency	AR		

AD = autosomal dominant; AR = autosomal recessive; BPAN = beta-propeller protein-associated neurodegeneration; CoPAN = COASY protein-associated neurodegeneration; DYT = dystonia; DRD = dopa-responsive dystonia; FAHN = fatty acid hydroxylase-associated neurodegeneration. Mn = manganese; MOI = mode of inheritance; MPAN = mitochondrial membrane protein-associated neurodegeneration; NBIA = neurodegeneration with brain iron accumulation; PKAN = pantothenate kinase-associated neurodegeneration; PLAN = *PLA2G6*-associated neurodegeneration; XL = X-linked

Additional hereditary disorders in the differential diagnosis of SLC39A14 deficiency include **inherited forms of Parkinson disease** associated with parkinsonism-dystonia (see [Parkinson Disease Overview](#)) and **inherited neurodegenerative/metabolic disorders associated with complex dystonia** (see [Dystonia Overview, Table 4](#)). Both categories of disorders can be distinguished from SLC39A14 deficiency by the absence of features consistent with Mn deposition on brain MRI.

Acquired conditions in the differential diagnosis of SLC39A14 deficiency include **acquired hypermanganesemia** and **acquired hepatocerebral degeneration**. Like SLC39A14 deficiency, these disorders of manganese homeostasis are associated with dystonia-parkinsonism, hypermanganesemia, and brain MRI features consistent with manganese deposition.

- Unlike SLC39A14 deficiency, acquired hypermanganesemia often presents with psychiatric symptoms and a history of Mn exposure from environmental sources, parenteral nutrition, or contaminated ephedrone preparations [Mortimer et al 2012, Santos et al 2014, Janocha-Litwin et al 2015].
- Unlike SLC39A14 deficiency, liver disease is the predominant feature in acquired hepatocerebral degeneration and it precedes development of neurologic symptoms [Miletić et al 2014].

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with SLC39A14 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 SLC39A14 Deficiency

System/Concern	Evaluation	Comment
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>• Neurologic exam for dystonia, parkinsonism, &amp; spasticity</li> <li>• Brain MRI</li> <li>• Assessment of whole-blood manganese levels</li> </ul>	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
<b>Development</b>	Developmental assessment	<ul style="list-style-type: none"> <li>To incl motor, adaptive, cognitive, &amp; speech/language eval</li> <li>Eval for early intervention / special education</li> </ul>
<b>Musculoskeletal</b>	Orthopedics / physical medicine & rehab / PT & OT eval	<p>To incl assessment of:</p> <ul style="list-style-type: none"> <li>Gross motor &amp; fine motor skills</li> <li>Contractures, clubfoot, &amp; kyphoscoliosis</li> <li>Mobility, ADL, &amp; need for adaptive devices</li> <li>Need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills)</li> </ul>
<b>Gastrointestinal/Feeding</b>	Gastroenterology / nutrition / feeding team eval	<ul style="list-style-type: none"> <li>To incl eval of aspiration risk &amp; nutritional status</li> <li>Consider eval for gastric tube placement in those w/ dysphagia &amp;/or aspiration risk.</li> </ul>
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform affected persons & their families re nature, MOI, & implications of SLC39A14 deficiency to facilitate medical & personal decision making
<b>Family support &amp; resources</b>	<p>Assess need for:</p> <ul style="list-style-type: none"> <li>Community or online resources such as <a href="#">Parent to Parent</a>;</li> <li>Social work involvement for parental support;</li> <li>Home nursing referral.</li> </ul>	

ADL = activities of daily living; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy;

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

## Treatment of Manifestations

### Symptomatic Treatment

Early initiation of physical therapy and orthopedic management aims to prevent contractures and maintain ambulation. As needed, individuals should be referred for adaptive aids (e.g., a walker or wheelchair for gait abnormalities) and assistive communication devices.

Support by a speech-language pathologist, feeding specialist, and nutritionist is indicated to assure adequate nutrition and to reduce the risk of aspiration. When an adequate oral diet can no longer be maintained, gastrostomy tube placement should be considered. Gastric feeding tube and/or tracheostomy may be required to prevent aspiration pneumonia.

Note that symptomatic treatment with L-dopa and antispasticity medications including benzodiazepines, baclofen, and botulinum toxin has been attempted with limited success. There has been partial but poorly sustained response to trihexyphenidyl at high doses of 20 mg/day and intrathecal baclofen of 1,500-2,000 µg/day in two older sibs reported by Tuschl et al [2016].

### Chelation Therapy

There is evidence that disodium calcium edetate, which primarily promotes the urinary excretion of manganese, can improve neurologic symptoms and slow the disease progression [Tuschl et al 2016, Garg et al 2022, Lee & Shin 2022]. Disodium calcium edetate is administered intravenously (20 mg/kg/dose) twice daily for five consecutive days each month.



A female age five years with SLC39A14 deficiency showed improvement of neurologic manifestations with regain of her ability to walk after six months of disodium calcium edetate treatment [Tuschl et al 2016]. In contrast, treatment of a female age 17 years with advanced disease (severe generalized dystonia with prominent oromandibular involvement, contractures, and scoliosis) did not affect disease progression; she continued to deteriorate with worsening tremor and stiffness. Hence, it is likely necessary to initiate chelation treatment early in the disease course.

It is anticipated that chelation therapy will need to be lifelong.

Potential adverse effects of disodium calcium edetate chelation therapy include thrombocytopenia and leukopenia, nephrotoxicity, hepatotoxicity, hypocalcemia, and trace metal and vitamin deficiencies [Lamas et al 2012]. Monitoring includes the following:

- Complete blood count
- Assessment of renal function including urinalysis assessed at baseline and monthly thereafter. Monitoring may be extended to every other month once on a stable dose.
- Assessment of liver function
- Measurement of the concentrations of electrolytes, calcium, magnesium, and phosphate
- Measurement of the concentrations of trace metals (manganese, zinc, copper, and selenium)
- Assessment of iron status

Treatment may need to be discontinued if:

- White blood count is  $<3.5 \times 10^9/L$
- Neutrophil count is  $<2.0 \times 10^9/L$
- Platelet count is  $<150 \times 10^9/L$
- $>2+$  proteinuria is detected on more than one occasion (with no evidence of infection)

The above cut-off values are based on guidelines for D-penicillamine treatment [Chakravarty et al 2008]. Because chelation treatment with disodium calcium edetate may prevent early death and reduce morbidity in SLC39A14 deficiency, lower cut-off values may be acceptable. For each affected individual, the benefits of clinical treatment need to be carefully weighed against the risk of adverse effects.

## Prevention of Primary Manifestations

Chelation therapy with disodium calcium edetate may prevent primary disease manifestations in affected sibs who are asymptomatic (see Treatment of Manifestations, Chelation Therapy).

## Surveillance

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

**Table 4.** Recommended Surveillance for Individuals with SLC39A14 Deficiency

System/Concern	Evaluation	Frequency
<b>Feeding</b>	<ul style="list-style-type: none"> <li>• Measurement of growth parameters</li> <li>• Eval of nutritional status &amp; safety of oral intake</li> </ul>	At each visit
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>• Monitor development incl ambulation &amp; speech.</li> <li>• Neurologic exam (scoring of mvmt disorder severity)</li> </ul>	
	To assess treatment response & disease progression: <ul style="list-style-type: none"> <li>• Whole-blood manganese levels</li> <li>• Brain MRI</li> </ul>	To be considered on an individual basis & based on available resources

## Agents/Circumstances to Avoid

The following should be avoided:

- Environmental manganese exposure (i.e., contaminated drinking water, occupational manganese exposure in welding/mining industries, contaminated ephedrone preparations)
- High manganese content of total parenteral nutrition
- Foods very high in manganese including: cloves; saffron; nuts; mussels; dark chocolate; and pumpkin, sesame, and sunflower seeds

## Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic younger sibs of an affected individual in order to identify as early as possible sibs who would benefit from prompt initiation of treatment and preventive measures (see Agents/Circumstances to Avoid).

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

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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

SLC39A14 deficiency is inherited in an autosomal recessive manner.

### Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *SLC39A14* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC39A14* 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 and are not at risk of developing the disorder.

### Sibs of a proband

- If both parents are known to be heterozygous for an *SLC39A14* 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.** The offspring of an individual with *SLC39A14* deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *SLC39A14*.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC39A14* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC39A14* pathogenic variants in the family.

## Related Genetic Counseling Issues

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

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- *SLC39A14* molecular genetic testing for reproductive partners of known carriers is appropriate, particularly if consanguinity is likely. (The majority of families with *SLC39A14* deficiency reported to date have been consanguineous.)

## Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC39A14* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **MedlinePlus**  
[Hypermanganesemia with dystonia](#)
- **American Parkinson Disease Association (APDA)**  
**Phone:** 800-223-2732  
**Fax:** 718-981-4399  
**Email:** [apda@apdaparkinson.org](mailto:apda@apdaparkinson.org)  
[www.apdaparkinson.org](http://www.apdaparkinson.org)
- **Dystonia Medical Research Foundation**  
**Phone:** 312-755-0198; 800-377-DYST (3978)  
**Fax:** 312-803-0138  
**Email:** [dystonia@dystonia-foundation.org](mailto:dystonia@dystonia-foundation.org)  
[dystonia-foundation.org](http://dystonia-foundation.org)
- **Parkinson's Foundation**  
**Phone:** 800-4PD-INFO (473-4636)  
**Email:** [contact@parkinson.org](mailto:contact@parkinson.org)  
[www.parkinson.org](http://www.parkinson.org)

## 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.** SLC39A14 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
<i>SLC39A14</i>	8p21.3	Metal cation symporter ZIP14	SLC39A14	SLC39A14

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 SLC39A14 Deficiency ([View All in OMIM](#))

608736	SOLUTE CARRIER FAMILY 39 (ZINC TRANSPORTER), MEMBER 14; SLC39A14
617013	HYPERMANGANESEMIA WITH DYSTONIA 2; HMNDYT2

## Molecular Pathogenesis

*SLC39A14* encodes a divalent metal transporter that is required for cellular uptake of manganese [Tuschl et al 2016]. It plays a crucial role as a regulator of manganese homeostasis within the liver and the gut, facilitating biliary manganese excretion and reduced intestinal manganese absorption [Winslow et al 2020].

Biallelic *SLC39A14* pathogenic variants are thought to impair hepatic manganese uptake and homeostatic control of intestinal manganese absorption. Subsequently, manganese accumulates in the blood and is deposited

in the brain, particularly the globus pallidus, resulting in manganese toxicity and causing progressive dystonia (often combined with other signs such as spasticity and parkinsonian features) [Tuschl et al 2016, Winslow et al 2020].

**Mechanism of disease causation.** Loss of function

**SLC39A14-specific laboratory technical considerations.** *SLC39A14* comprises nine exons and encodes four transcripts. Two transcripts differ by an alternative 5'UTR (NM\_001128431.2 and NM\_001135153). Alternative splicing of exon 4 and 9 generates two alternative transcripts (NM\_015359.4 and NM\_001135154.1).

## Chapter Notes

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