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SLC39A14 Deficiency

Synonym: *SLC39A14*-Related Early-Onset Dystonia-Parkinsonism

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Summary

Clinical characteristics

SLC39A14 deficiency is characterized by evidence between ages six months and three years of delay or loss of motor developmental milestones (e.g., delayed walking, gait disturbance). 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 succumbed in their first decade due to secondary complications such as respiratory infections.

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 variants in *SLC39A14* 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 and language/feeding specialist and nutritionist 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. 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.

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

Surveillance: Routine monitoring of:

- Height and weight using age- and gender-appropriate growth charts;
- Swallowing and diet to assure adequate nutrition;
- Ambulation and speech;
- Whole-blood manganese levels and brain MRI 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 diagnosis are possible.

Diagnosis

Suggestive Findings

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

- **Clinical findings.** Infantile or early-childhood onset of:
  - 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.
- **Neuroimaging.** Brain MRI findings characteristic of manganese deposition (Figure 1) including T_1-weighted hyperintensity of the following:
  - Globus pallidus and striatum, with thalamic sparing;

    Note: Basal ganglia changes on T_1-weighted imaging are accompanied by T_2-weighted hypointensity.

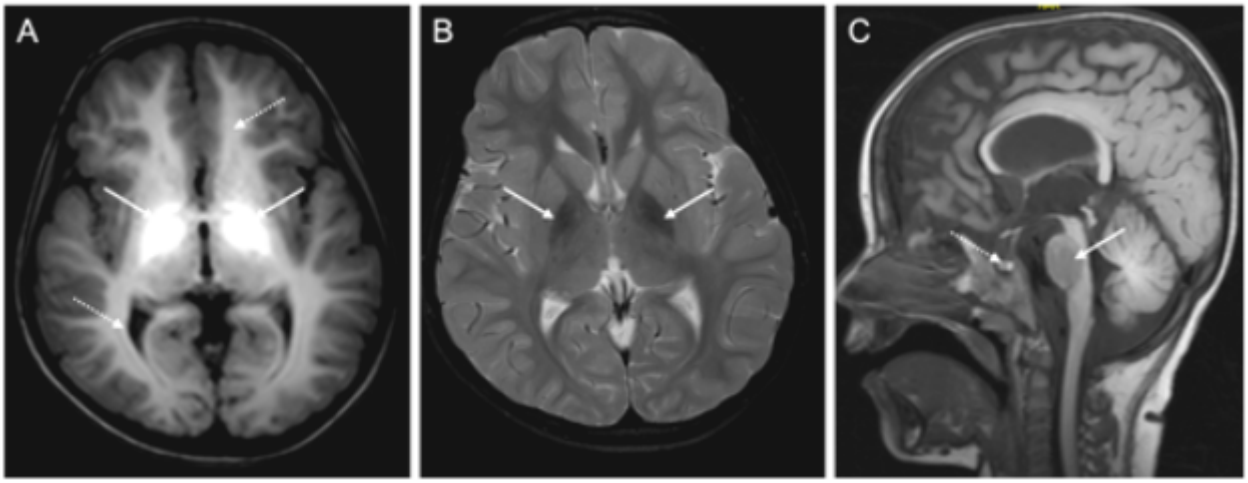

Figure 1. A. Axial T_1-weighted image showing the hyperintensity of the globus pallidus (white arrows), and the cerebral white matter (dashed arrows)

B. Axial T_2-weighted image showing the hypointensity of the globus pallidus (white arrows)

C. Sagittal T_1-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)

  - 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 identification of biallelic pathogenic variants in *SLC39A14* on molecular genetic testing [Tuschl et al 2016] (see Table 1).

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

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of SLC39A14 deficiency is likely to be broad, 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** and use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *SLC39A14* is performed first. If only one pathogenic variant is found, gene-targeted deletion/duplication analysis could be considered; however, to date no exon or whole-gene deletions have been reported.

- **A multigene panel** that includes *SLC39A14* and other genes of interest (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 provides the best opportunity to identify the genetic cause of condition at the most reasonable cost while limiting identification of pathogenic variants in genes that do not explain the underlying phenotype. (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 other movement disorders, molecular genetic testing approaches can include a combination of **genomic testing** (comprehensive genomic sequencing; recommended) or **gene-targeted testing** (multigene panel; to consider).

- **Recommended testing.** Comprehensive genomic testing (when 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.
- **Testing to consider.** A multigene panel that includes *SLC39A14* and other genes of interest (see Differential Diagnosis) may be considered; however, given the rarity of SLC39A14 deficiency, many panels for inherited dystonia-parkinsonism and/or this complex neurologic phenotype may not include this gene. For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in SLC39A14 Deficiency

Gene [1]	Test Method	Proportion of Probands with Pathogenic Variants [2] Detectable by This Method
SLC39A14	Sequence analysis [3]	7/7 [6]
	Gene-targeted deletion/duplication analysis [4]	None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. No data on detection rate of gene-targeted deletion/duplication analysis are available.
6. Five reported consanguineous families [Tuschl et al 2016] and two other families, one consanguineous and one non-consanguineous [Author, personal observation]

Clinical Characteristics

Clinical Description

SLC39A14 deficiency has only recently been identified in 11 individuals from seven families [Tuschl et al 2016; Author, personal observation]; therefore, information on the phenotypic spectrum and disease progression is limited.

Onset occurs between ages six months and three years. Affected children present with delay or loss of motor developmental milestones (e.g., delayed walking, gait disturbance).

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, 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 succumb in their first decade due to secondary complications such as respiratory infections.

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 11 individuals with SLC39A14 deficiency from seven families have been identified. These seven families are from different ethnic backgrounds and six are consanguineous [Tuschl et al 2016; Author, personal observation].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of SLC39A14 Deficiency

Disorder		Gene(s)	MOI	Clinical Features of This Disorder	
				Overlapping with SLC39A14 Deficiency	Distinguishing from SLC39A14 Deficiency
Disorders of manganese homeostasis	Dystonia/parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease (SLC30A10 deficiency)	*SLC30A10*	AR	• Dystonia-parkinsonism • Hypermanganesemia • Brain MRI features consistent w/ manganese deposition	• Presents with polycythemia, abnormal iron indices, & liver disease in addition to the neurologic phenotype • Absence of Mn deposition in the liver w/T_1 hyperintensity on liver MRI
	Acquired hypermanganesemia [1]	N/A	N/A		• Often presents w/ psychiatric symptoms • History of Mn exposure from environmental sources, parenteral nutrition, or contaminated ephedrone preparations
	Acquired hepatocerebral degeneration [2]	N/A	N/A		• Liver disease is the predominant feature; it precedes development of neurologic symptoms.
Early-onset NBIA disorders (see NBIA Overview)	PKAN	*PANK2*	AR	• Parkinsonism-dystonia • T_2-weighted hypointensity of the globus pallidus on brain MRI	• Usually presents w/ additional clinical features (e.g., pigmentary retinopathy, optic atrophy, oculomotor abnormalities, axonal neuropathy, cognitive decline, seizures) • Lacks the T_1-weighted hyperintensity of the globus pallidus on brain MRI due to Mn deposition
	PLAN	*PLA2G6*	AR		
	MPAN	*C19orf12*	AR		
	BPAN	*WDR45*	XL		
	FAHN	*FA2H*	AR		
	Kufor-Rakeb syndrome	*ATP13A2*	AR		
	CoPAN	*COASY*	AR		
Disorders of copper metabolism	Wilson disease	*ATP7B*	AR	• Parkinsonism-dystonia	• Liver disease, psychiatric symptoms, low serum ceruloplasmin & high non-ceruloplasmin-bound serum copper • No Mn deposition on brain MRI
Inherited forms of dystonia (see Dystonia Overview)	DYT1 early-onset isolated dystonia	*TOR1A*	AD	• Early-onset generalized dystonia	• No features consistent w/Mn deposition on brain MRI • Absent hypermanganesemia
	KMT2B-related early-onset dystonia	*KMT2B*	AD		
	MECR-related childhood-onset dystonia and optic atrophy [3]	*MECR*	AR		• Additional optic atrophy • No features consistent w/Mn deposition on brain MRI

Table 2. continued from previous page.

Disorder		Gene(s)	MOI	Clinical Features of This Disorder	
				Overlapping with SLC39A14 Deficiency	Distinguishing from SLC39A14 Deficiency
	SLC6A3-related dopamine transporter deficiency syndrome	*SLC6A3*	AR	• Parkinsonism-dystonia	• No features consistent w/Mn deposition on brain MRI
	Tyrosine hydroxylase-deficient dopa-responsive dystonia	*TH*	AR		
	GTP cyclohydrolase 1-deficient dopa-responsive dystonia	*GCH1*	*AD*		
	Sepiapterin reductase deficiency dopa-responsive dystonia	*SPR*	AR		
Inherited Forms of Parkinson Disease (see Parkinson Disease Overview)					
Inherited neurodegenerative/metabolic disorders (see Dystonia Overview, Table 4 for hereditary neurodegenerative or metabolic disorders characterized by complex dystonia)				• Complex dystonia	• No features consistent w/Mn deposition on brain MRI

AD = autosomal dominant; AR = autosomal recessive; BPAN = beta-propeller protein-associated neurodegeneration; CoPAN = COASY protein-associated neurodegeneration; 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

1. Mortimer et al [2012], Santos et al [2014], Janocha-Litwin et al [2015]
2. Miletić et al [2014]
3. Heimer et al [2016]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with SLC39A14 deficiency, the following evaluations are recommended:

- Neurologic examination for dystonia, parkinsonism, and spasticity, including evaluation of ambulation and speech
- Assessment for physiotherapy, occupational therapy, and/or speech therapy
- Evaluation of swallowing and nutritional status
- Brain MRI, if not performed as part of the diagnostic evaluation
- Assessment of whole-blood manganese levels, if not performed as part of the diagnostic evaluation
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Symptomatic treatment. Early initiation of physiotherapy 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 and language/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. Disodium calcium edetate, which primarily promotes the urinary excretion of manganese, was given intravenously (20 mg/kg/dose) twice daily for five days each month to a female age five years with SLC39A14 deficiency [Tuschl et al 2016]. After six months of treatment, neurologic manifestations improved and the child regained the ability to walk.

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 as 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, hepatoxicity, 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 $<3.5x10^9$/L
- Neutrophil count is $<2.0x10^9$/L
- Platelet count is $<150x10^9$/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).

Surveillance

Routine monitoring of:

- Height and weight using age and gender appropriate growth charts;
- Swallowing and diet to assure adequate nutrition;
- Ambulation and speech;
- Whole-blood manganese levels and brain MRI to assess treatment response and disease progression.

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

Molecular genetic testing of apparently asymptomatic younger sibs of an affected individual for the familial *SLC39A14* pathogenic variants allows early identification of 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 in the US and www.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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

SLC39A14 deficiency is inherited in an autosomal recessive manner. Six of the seven families reported to date were consanguineous.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *SLC39A14* 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. 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 a *SLC39A14* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC39A14* pathogenic variants in the family. Carrier testing for reproductive partners of known carriers is appropriate, particularly if consanguinity is likely.

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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.

No specific resources for SLC39A14 Deficiency have been identified by *GeneReviews* staff.

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

Table A. continued from previous page.

SLC39A14	8p21.3	Zinc transporter 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 Genetic 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 by facilitating manganese uptake into the liver for subsequent excretion in bile.

Biallelic *SLC39A14* pathogenic variants are thought to impair hepatic manganese uptake and lead to accumulation of manganese in the blood. Subsequent deposition of manganese in the brain, particularly the globus pallidus, results in manganese toxicity and causes progressive dystonia (often combined with other signs such as spasticity and parkinsonian features) [Tuschl et al 2016].

Gene structure. *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).

Pathogenic variants. Homozygous or compound heterozygous *SLC39A14* pathogenic variants documented in seven families include missense, nonsense and deletion variants (see Table 3).

Pathogenic variants are predicted to (1) cause a significantly truncated protein because of a frameshift and premature stop codon, (2) affect an evolutionary highly conserved area of the protein, or (3) lead to abnormal splicing. Therefore, these sequence changes have detrimental effects on protein function [Tuschl et al 2016].

Table 3. *SLC39A14* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.292T>G	p.Phe98Val	NM_015359.4 NP_056174.2
c.313G>T	p.Glu105Ter	
c.367C>T	p.Gln123Ter	
c.477_478delCA	p.Ser160CysfsTer5	
c.512G>A	p.Gly171Glu	
c.1147G>A	p.Gly383Arg	
c.1407C>G	p.Asn469Lys	
c.751-9C>G [1, 2]	p.His251ProfsTer26 [1]	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. cDNA analysis confirmed an eight-nucleotide insertion (c.751_752insCTTCCAGC) from intron 5 indicating that this variant creates a new splice-acceptor site [Author, personal observation].
2. g.22,273,273C>G (GRCh37/hg19)

Normal gene product. *SLC39A14* encodes three protein isoforms. Isoforms 1 (NP_001121903) and 2 (NP_056174) have 492 amino acids; isoform 3 (NP_001128626) has 481 amino acids. They contain eight transmembrane domains, a histidine-rich motif (HXHXHX), and a metalloprotease motif (H/EEXPHEXGD) required for metal transport [Taylor et al 2005, Tominaga et al 2005].

Only isoforms 1 and 2 have been studied in detail; both localize to the plasma membrane and transport manganese, iron, zinc, and cadmium. While isoform 1 is ubiquitously expressed, expression of isoform 2 is restricted to liver, gastrointestinal tract, kidney, and pancreas with no expression in the brain. Isoform 2 is thought to act as the main regulator of manganese homeostasis, facilitating hepatic manganese uptake for biliary excretion [Tuschl et al 2016].

Abnormal gene product. *SLC39A14* pathogenic variants described in affected individuals (Table 3) have deleterious effects on protein function. While wild-type SLC39A14 expressed in HEK-293 cells facilitates manganese uptake, mutated SLC39A14 results in greatly reduced manganese uptake [Tuschl et al 2016].

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Chapter Notes

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