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Hypermanganesemia with Dystonia 1

Synonyms: Dystonia/Parkinsonism, Hypermanganesemia, Polycythemia, and Chronic Liver Disease; HMNDYT1

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Summary

Clinical characteristics

Hypermanganesemia with dystonia 1 (HMNDYT1) is characterized by the following:

- A movement disorder resulting from manganese accumulation in the basal ganglia
- Whole-blood manganese concentrations that often exceed 2000 nmol/L (normal: <320 nmol/L)
- Polycythemia
- Hepatomegaly with variable hepatic fibrosis/cirrhosis

Neurologic findings can manifest in childhood (ages 2-15 years) as four-limb dystonia, leading to a characteristic high-stepping gait ("cock-walk gait"), dysarthria, fine tremor, and bradykinesia or on occasion spastic paraplegia; or in adulthood as parkinsonism (shuffling gait, rigidity, bradykinesia, hypomimia, and monotone speech) unresponsive to L-dopa treatment.

Diagnosis/testing

The diagnosis of HMNDYT1 is established in a proband with suggestive findings and biallelic pathogenic variants in *SLC30A10* identified by molecular genetic testing.

Management

Treatment of manifestations: Regular chelation therapy with intravenous disodium calcium edetate improves blood manganese levels and neurologic findings and halts liver disease. In addition, supplementation with oral iron therapy (despite normal serum iron levels) can reduce blood manganese levels and resolve polycythemia. The potential for complications from chelation therapy and/or iron supplementation can be lessened by careful monitoring. Physical therapy (to prevent contractures and maintain ambulation), occupational therapy, and/or

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speech therapy and use of adaptive aids and assistive communication devices are recommended. Progressive dystonia may necessitate a gastrostomy tube for adequate nutrition and a tracheostomy may be needed to prevent aspiration pneumonia.

Prevention of primary manifestations: Chelation therapy and iron supplementation may prevent primary disease manifestations in affected asymptomatic sibs.

Agents/circumstances to avoid: Foods very high in manganese: cloves; saffron; nuts; mussels; dark chocolate; and pumpkin, sesame, and sunflower seeds.

Evaluation of relatives at risk: Because chelation therapy and iron supplementation could prevent primary disease manifestations in affected asymptomatic individuals, it is recommended that at-risk sibs of a proband be evaluated either by molecular genetic testing (if the pathogenic variants in the family are known) or by periodic monitoring of whole-blood manganese concentration and hemoglobin.

Genetic counseling

HMNDYT1 is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *SLC30A10* 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 inheriting neither of the familial pathogenic variants. Once the *SLC30A10* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members and prenatal and preimplantation genetic testing are possible.

Diagnosis

Hypermanganesemia with dystonia 1 (HMNDYT1) presents as a movement disorder associated with manganese accumulation in the basal ganglia. No consensus clinical diagnostic criteria have been published.

Suggestive Findings

HMNDYT1 **should be suspected** in individuals with typical clinical, brain MRI, and laboratory findings and family history.

Clinical Findings

An early- and a late-onset form exist:

- **Childhood-onset form** (between ages 2 and 15 years). Usually four-limb dystonia, leading to a characteristic high-stepping gait ("cock-walk gait"), dysarthria, fine tremor, and bradykinesia [Tuschl et al 2012, Quadri et al 2015] or on occasion spastic paraplegia [Gospe et al 2000]
- **Adult-onset form.** Parkinsonism (shuffling gait, rigidity, bradykinesia, hypomimia, and monotone speech) unresponsive to L-dopa treatment [Quadri et al 2012]

Brain MRI

T_1-weighted images show characteristic hyperintensity of the basal ganglia including the globus pallidus; putamen; and caudate, subthalamic, and dentate nuclei with sparing of the thalamus and ventral pons. When the disease is extensive, white matter and anterior pituitary involvement can be present (Figure 1).

T_2-weighted images show corresponding hypointensity changes. However, these changes are often less pronounced and, hence, may be reported as normal (see Figure 1).

Note: Normalization of manganese blood levels (see Management) improves findings on brain MRI [Quadri et al 2012, Stamelou et al 2012, Tuschl et al 2012].

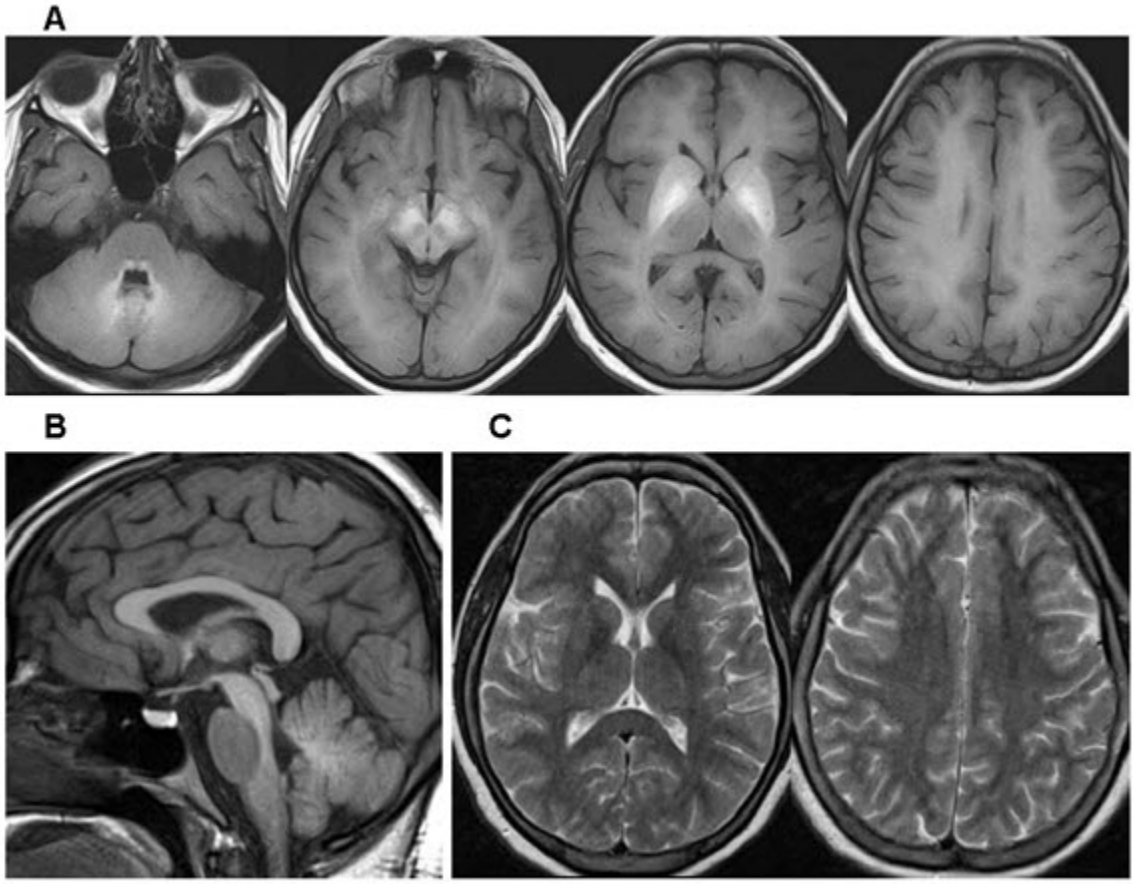

Figure 1. Representative brain MRI of an affected individual

A. Transaxial T_1-weighted images. Note abnormally high signal return from all white matter as well as more prominent signal return from the putamen and globus pallidus bilaterally.

B. Sagittal T_1-weighted image. Note abnormally high signal return from the anterior pituitary and all of the white matter, particularly corpus callosum, midbrain, dorsal pons and medulla.

C. Transaxial T_2-weighted images. Note abnormally low signal return from the globus pallidus in the same distribution as the regions of highest signal return on T_1-weighted images.

Laboratory Findings

Hypermanganesemia

- Whole-blood manganese concentrations are elevated in all affected individuals. Average in affected individuals is greater than 2,000 nmol/L (normal: <320 nmol/L).
- In contrast, blood manganese concentration in acquired hypermanganesemia is usually less than 2,000 nmol/L.

Corroborative laboratory features

- **Polycythemia.** Manganese induces expression of the gene encoding erythropoietin [Ebert & Bunn 1999]. Characteristically, affected individuals are polycythemic. Hemoglobin concentrations reported in the literature range from 15.9 to 22.5 g/dL (mean: 18.6 g/dL). Some individuals studied have had elevated erythropoietin levels [Gospe et al 2000, Quadri et al 2012, Tuschl et al 2012].
- **Markers of depleted iron stores.** Manganese and iron compete for the same serum-binding protein (transferrin) and membranous transporter protein (divalent metal transporter 1). Therefore, affected

individuals show low serum ferritin concentration and serum iron levels while total iron-binding capacity is elevated [Quadri et al 2012, Tuschl et al 2012].

- **Chronic liver disease.** Hepatic involvement may be present with variable severity and is not pathognomonic for this disease; when present, however, hepatic involvement should further suggest the diagnosis:
  - The majority of affected individuals reported to date have evidence of hepatic involvement that includes hepatomegaly, elevated transaminases (alanine transaminase, aspartate transaminase), and unconjugated hyperbilirubinemia.
  - Liver ultrasound examination or MRI can confirm hepatomegaly and features of liver cirrhosis.
  - Pathologic features on liver biopsy / postmortem examination in six affected individuals included fibrosis, steatosis, and micronodular cirrhosis.
  - Note: One individual with hepatomegaly and micronodular cirrhosis had no laboratory evidence of hepatic dysfunction [Gospe et al 2000, Tuschl et al 2008, Quadri et al 2012, Tuschl et al 2012, Lechpammer et al 2014].
  - Hepatic manganese content is highly elevated. Rhodanine staining confirms deposition of manganese in hepatocytes. Copper and zinc content can also be affected with mild elevation in hepatic levels [Gospe et al 2000, Tuschl et al 2008, Quadri et al 2012, Tuschl et al 2012, Lechpammer et al 2014].

Family History

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 HMNDYT1 **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *SLC30A10* 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 likely pathogenic variants. (2) Identification of biallelic *SLC30A10* variants of uncertain significance (or of one known *SLC30A10* pathogenic variant and one *SLC30A10* 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 with atypical findings or in whom the diagnosis of HMNDYT1 has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *SLC30A10* 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.

A multigene panel that includes *SLC30A10* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

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 Hypermanganesemia with Dystonia 1

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SLC30A10	Sequence analysis [3]	48/50 (96%) [4]
	Gene-targeted deletion/duplication analysis [5]	2/50 (4%) [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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. Quadri et al [2012], Tuschl et al [2012], Avelino et al [2014], Quadri et al [2015], Mukhtiar et al [2016], Anagianni & Tuschl [2019], Tavasoli et al [2019], Yapici et al [2019], Lambrianides 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.

Clinical Characteristics

Clinical Description

To date, 48 individuals have been identified with biallelic pathogenic variants in *SLC30A10* [Anagianni & Tuschl 2019, Tavasoli et al 2019, Yapici et al 2019, Lambrianides et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Hypermanganesemia with Dystonia 1: Frequency of Select Features

Feature	Frequency			Comment
	Nearly all	Common	Infrequent	
Dystonia, dysarthria, and parkinsonism	●			
Hypermanganesemia	●			
Polycythemia	●			
Liver disease		●		
Pica in childhood			●	
Darker skin tone			●	
Spastic diplegia			●	Reported in 1 person to date [Gospe et al 2000]

Neurologic Findings

Childhood onset. In the childhood-onset form of hypermanganesemia with dystonia 1 (HMNDYT1), affected individuals present with neurologic signs between ages two and 15 years. Many become wheelchair bound in their teens.

The neurologic signs and symptoms of the childhood-onset form are primarily extrapyramidal and include dystonia, dysarthria, and rigidity. Four-limb dystonia manifests with difficulties walking and a high-stepping gait ("cock walk gait"), dystonic posturing, and painful extensor spasms. Fine motor impairment causes problems with writing and drawing and inability to perform rapid alternating movements of the hands (dysdiadochokinesis). Dystonia of the tongue can lead to dysarthria [Quadri et al 2012, Tuschl et al 2012, Quadri et al 2015]. Dystonia may lead to progressive swallowing difficulties and aspiration which may require gastrostomy/tracheostomy insertion.

Isolated corticospinal tract involvement has been described in one affected individual. Typical neurologic signs of spastic paraparesis (e.g., spasticity, hyperreflexia, extensor plantar responses) were found [Gospe et al 2000].

Adult onset. Quadri et al [2012] reported two brothers who presented at ages 47 years and 57 years with progressive gait disturbance and bradykinesia. Neurologic examination showed features of parkinsonism including hypomimia, monotone speech, mild rigidity, global bradykinesia, wide-based gait with freezing and starting hesitation, and moderate postural instability without evidence of tremor, dystonia, or cerebellar or pyramidal disturbances. Treatment with L-dopa and dopamine agonists did not improve neurologic findings.

Sensorimotor axonal polyneuropathy has been described in two affected individuals with the late-onset neurologic presentation [Quadri et al 2012].

Hypermanganesemia

Whole-blood manganese concentrations are elevated in the majority of affected individuals.

Due to limited data, the onset of hypermanganesemia is not accurately known. Raised whole-blood manganese concentrations have been recorded in affected children as young as age three years [Quadri et al 2015]; however, given that clinical manifestations can be apparent in the first two years of life, it is expected that hypermanganesemia develops concurrently with or prior to onset of clinical manifestations.

Hypermanganesemia due to environmental overexposure (including parenteral nutrition) and acquired hepatocerebral degeneration in persons with end-stage liver disease must be excluded. See Differential Diagnosis.

Quadri et al [2012] reported one affected individual whose blood manganese concentration was only minimally increased on one occasion; similarly, Lambrianides et al [2020] reported an affected individual with evidence of manganese deposition on brain MRI but normal blood manganese levels in adulthood. Therefore, normal blood manganese levels do not exclude a diagnosis of HMNDYT1 when the clinical suspicion is strong.

Note: Blood manganese concentrations of heterozygotes (i.e., carriers of one *SLC30A10* pathogenic variant) are within normal limits or are mildly elevated. Gospe et al [2000] reported a borderline high blood manganese concentration of 380 nmol/L in an obligate heterozygous parent and Tuschl et al [2012] reported levels between 380 and 649 nmol/L in three heterozygous parents (normal: <320 nmol/L).

Polycythemia

All affected individuals reported to date had polycythemia at the time of diagnosis. Polycythemia can precede the onset of neurologic manifestations; therefore, affected individuals often undergo repeat phlebotomies prior to identification of the correct diagnosis [Quadri et al 2012, Tuschl et al 2012]. Polycythemia has been described in affected children from age three years; earlier presentation of polycythemia cannot be ruled out due to insufficient data. Individuals in whom neurologic symptoms do not manifest until late adulthood have had polycythemia since as early as the third decade. Polycythemia can resolve on treatment with chelation therapy or iron. There is evidence from one patient whose polycythemia resolved without treatment during advanced stage of disease [Lechpammer et al 2014].

Liver Disease

The spectrum of hepatic involvement ranges from mild hepatomegaly to hepatic failure in early adulthood [Tuschl et al 2012]. However, pure neurologic phenotypes presenting with dystonia alone have also been reported [Quadri et al 2012].

In the majority of affected individuals, transaminases are mildly elevated [Quadri et al 2012, Tuschl et al 2012]. To date, three affected individuals died of complications of liver cirrhosis between ages 18 and 46 years. As most of the affected individuals known to the authors are still in their teens or early adulthood, no long-term follow-up data are available.

Significant phenotypic variability with regard to hepatic involvement is apparent even within the same family: The two brothers reported by Quadri et al [2012], who are now in their sixties and severely affected by dystonia, did not show hepatic involvement. Both had normal liver function and liver ultrasound examination throughout their lives. However, while the affected sister had minimal neurologic involvement, she developed liver cirrhosis in the third decade and died of liver failure at age 46 years.

Other

Intellect appears normal in all affected individuals. Quadri et al [2012] described one individual who developed cognitive and behavioral problems, thought to be alcohol related. While environmental manganese exposure is known to cause cognitive and psychiatric disturbances ("manganese madness") including emotional lability, hallucinations, and compulsive behavior [Racette et al 2012], this has not yet been observed in individuals with hypermanganesemia with dystonia 1.

Pica. Several affected individuals had pica during early childhood [Brna et al 2011; Brna, unpublished data].

Darker skin tone. Some affected individuals have been described to have a purple or dark skin discoloration to an extent that parents are able to distinguish affected and unaffected children prior to the manifestation of clinical symptoms [Authors, unpublished data].

Pathology

Postmortem studies in an individual with SLC30A10 deficiency showed yellow-gray mottling of the basal ganglia associated with severe neuronal loss, astrocytosis, myelin loss, spongiosis, and rhodanine-positive deposits particularly in the globus pallidus, while other basal ganglia were affected to a lesser extent. Gliosis of the white matter and axonal loss of the corticospinal tracts were observed [Lechpammer et al 2014].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

A total of 48 affected individuals from 25 families are known worldwide [Quadri et al 2012, Tuschl et al 2012, Avelino et al 2014, Quadri et al 2015, Mukhtiar et al 2016, Anagianni & Tuschl 2019, Tavasoli et al 2019, Yapici et al 2019, Lambrianides et al 2020]. The prevalence is yet to be determined.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants *SLC30A10*.

Differential Diagnosis

Acquired hypermanganesemia. Overexposure to manganese is known to be neurotoxic and causes "manganism" – a distinct syndrome of extrapyramidal movement disorder (dystonia/parkinsonism) combined with high signal intensity of the basal ganglia on T_1-weighted MR images of the brain resulting from manganese accumulation in the basal ganglia [Racette et al 2012].

- Environmental exposure has been described in workers in mining and welding industries who inhale manganese-laden dust or fumes, in individuals ingesting contaminated drinking water, and in drug addicts who use intravenous methcathinone contaminated with potassium permanganate [Bouchard et al 2011, Racette et al 2012, Ordak et al 2022].
- Total parenteral nutrition has been associated with manganese toxicity because the control mechanisms of manganese absorption in the gut and subsequent hepatic excretion are bypassed [Chalela et al 2011].
- Acquired hepatocerebral degeneration is observed in those with advanced hepatic cirrhosis or portosystemic shunts, in which impaired biliary excretion of manganese results in manganese accumulation in the basal ganglia, causing a debilitating movement disorder [Meissner & Tison 2011].

Other conditions to consider in the differential diagnosis of hypermanganesemia with dystonia 1 (HMNDYT1) include the following:

- **SLC39A14 deficiency** (*SLC39A14*-related early-onset parkinsonism-dystonia, hypermanganesemia with dystonia 2 [HMNDYT2]): a manganese transporter defect caused by impaired manganese uptake into the liver and gut;
- **Wilson disease**
- **Parkinson disease** and its differential diagnoses (atypical degenerative parkinsonisms [multiple-system atrophy, progressive supranucleal palsy], vascular parkinsonism, and drug-induced parkinsonism)
- **Hereditary dystonia**
- **Neurodegenerative diseases associated with dystonia** (including organic acidemias [i.e. glutaric, methylmalonic, propionic, 3-hydroxyisobutyryl-CoA hydrolase deficiency])
- **Cerebral palsy**

Table 3 lists associated genes and clinical characteristics of SLC39A14 deficiency and Wilson disease and provides selected examples of genes known to be involved in monogenic Parkinson disease, hereditary dystonia, neurodegenerative diseases associated with dystonia, and hereditary spastic paraplegia (which can resemble spastic diplegic cerebral palsy in individuals with onset in early childhood).

Table 3. Hereditary Disorders in the Differential Diagnosis of Hypermanganesemia with Dystonia 1

Gene	Diff Dx Disorder	MOI	Clinical Characteristics
Disorders of metal metabolism			
SLC39A14	SLC39A14 deficiency (HMNDYT2)	AR	Manganese transporter defect caused by impaired manganese uptake into liver. Affected persons present w/hypermanganesemia & rapidly progressive childhood-onset PD-DYT due to cerebral manganese deposition. Brain MRI appears the same as in HMNDYT1. Distinguishing features: absence of liver disease & polycythemia due to lack of hepatic manganese deposition (can be assessed by liver MRI)
ATP7B	Wilson disease	AR	Disorder of copper metabolism that can present w/hepatic, neurologic, or psychiatric disturbances (or a combination) from age 3 yrs to >50 yrs. Neurologic presentations incl mvmt disorders or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement).
Monogenic Parkinson disease [1] & hereditary disorders in the DiffDx of Parkinson disease			
ATP13A2 *DNAJC6* *FBXO7* *PODXL* *SLC6A3* *SYNJ1*	Juvenile-onset Parkinson disease (PD) [3]	AR	Age of onset of PD generally <20 yrs. Clinical presentation often incl addl signs incl dystonia, spasticity, & dementia.
GBA1 (*GBA*) *LRRK2* *PARK7* *PINK1* *PRKN* *SNCA* *VPS13C* *VPS35*	Early-onset adult & late-onset adult Parkinson disease [2]	AD AR	PD is characterized by rest tremor, muscle rigidity, slowed movement, & often postural instability. Onset is typically unilateral & may incl other abnormal movements (e.g., postural or action tremor & limb dystonia). Common assoc non-motor findings incl insomnia, depression, anxiety, REM sleep behavior disorder, fatigue, constipation, dysautonomia, & hyposmia. As part of a prodromal phase, non-motor features may predate formal diagnosis of PD by yrs.
ATN1	DRPLA	AD	Progressive disorder of ataxia, myoclonus, epilepsy, & progressive intellectual deterioration in children; ataxia, choreoathetosis, & dementia or character changes in adults. Clinical presentation varies w/age of onset. Cardinal features in adults: ataxia, choreoathetosis, dementia; in children: progressive intellectual deterioration, behavioral changes, myoclonus, epilepsy
HTT	Huntington disease	AD	Progressive disorder of motor, cognitive, & psychiatric disturbances. Mean age of onset 35-44 yrs. Affected persons may present w/neurologic manifestations or psychiatric changes.
Hereditary dystonia (selected examples of early-onset dystonia &/or dopa-responsive dystonia)			
GCH1	GTP cyclohydrolase 1-deficient dopa-responsive dystonia	AD AR	Childhood-onset dystonia & dramatic & sustained response to low doses of oral administration of levodopa. Most common presenting findings: posturing or irregular tremor of a leg or arm (due to dystonic muscle contractions)
KMT2B	*KMT2B*-related dystonia	AD	Complex childhood-onset mvmt disorder. Typically presents w/ progressive disease course evolving commonly from lower-limb focal dystonia into generalized dystonia w/prominent cervical, cranial, & laryngeal involvement

Table 3. continued from previous page.

Gene	Diff Dx Disorder	MOI	Clinical Characteristics
SPR	Sepiapterin reductase deficiency	AR	Rare cause of partially dopa-responsive childhood-onset dystonia characterized by axial hypotonia, motor & speech delay, weakness, & oculogyric crises; symptoms show diurnal fluctuation & sleep benefit.
TH	TH-deficient dopa-responsive dystonia (See Tyrosine Hydroxylase Deficiency.)	AR	Age of onset 12 mos-2 yrs. Initial manifestations: typically lower-limb dystonia &/or difficulty in walking. Diurnal fluctuation of symptoms may be present.
THAP1	DYT-THAP1	AD	Although some phenotypic overlap w/DYT-TOR1A is observed, the onset of DYT-THAP1 is later (mean age 19 yrs) & cranial involvement is more prominent esp in muscles of the tongue, larynx, & face; dysphonia is a predominant feature.
TOR1A	DYT1 early-onset isolated dystonia	AD	Typically presents in childhood or adolescence & only on occasion in adulthood. Most common presenting findings: posturing or irregular tremor of a leg or arm (due to dystonic muscle contractions)
Neurodegenerative diseases assoc w/dystonia			
ATP13A2 *C19orf12* *COASY* *CP* *DCAF17* *FA2H* *FTL* *PANK2* *PLA2G6* *WDR45*	Neurodegeneration with brain iron accumulation disorders	AR AD XL [3]	Characterized by abnormal accumulation of iron in basal ganglia. Generalized cerebral atrophy & cerebellar atrophy are frequently observed. Hallmark clinical manifestations: progressive dystonia & dysarthria, spasticity, parkinsonism, neuropsychiatric abnormalities, optic atrophy or retinal degeneration. Although cognitive decline occurs in some genetic types, more often cognition is relatively spared. Onset from infancy to adulthood.
DLAT *DLD* *PDHA1* *PDHB* *PDHX* *PDP1* *PDK3*	Primary pyruvate dehydrogenase complex deficiency (PDCD)	XL AR [4]	Most commonly manifests as syndrome of neurologic signs (congenital microcephaly, hypotonia, epilepsy, &/or ataxia), abnormal brain imaging (dysgenesis of corpus callosum, Leigh syndrome), & metabolic abnormalities (↑ plasma pyruvate, lactic acidemia, &/or metabolic acidosis). DD is nearly universal. Mean age of diagnosis of primary PDCD typically~45 mos (median ~20 mos).
GBA1 (*GBA*)	Gaucher disease (GD)	AR	GD types 2 & 3 are characterized by presence of primary neurologic disease. Disease w/onset age <2 yrs, limited psychomotor development, & rapidly progressive course w/death by age 1-2 yrs is classified as GD type 2. Persons w/GD type 3 may have onset <2 yrs, but often more slowly progressive course, w/survival into 3rd-4th decade.
NPC1 *NPC2*	Niemann-Pick disease type C	AR	Principal manifestations are age dependent. Perinatal period & infancy: features are predominantly visceral, w/hepatosplenomegaly, jaundice, & (in some) pulmonary infiltrates. Late infancy onward: presentation dominated by neurologic manifestations. The youngest children may present w/hypotonia & DD, w/subsequent emergence of ataxia, dysarthria, dysphagia, &, in some, epileptic seizures, dystonia, & gelastic cataplexy.
Hereditary spastic paraplegia (selected examples of more commonly involved genes)			

Table 3. continued from previous page.

Gene	Diff Dx Disorder	MOI	Clinical Characteristics
ATL1 *KIF1A* *REEP1* *SPAST*	Autosomal dominant HSP [5]	AD	The predominant signs & symptoms of HSP are lower-extremity weakness & spasticity. When symptoms begin in very early childhood, they may be non-progressive & resemble spastic diplegic cerebral palsy.
CYP7B1 *SPG11* *SPG7*	Autosomal recessive HSP [5]	AR	

DD = developmental delay; DiffDx = differential diagnosis; DYT = dystonia; HSP = hereditary spastic paraplegia; HMNDYT1 = hypermanganesemia with dystonia 1; PD = Parkinson disease
1. An estimated 5%-10% of all Parkinson disease is attributed to pathogenic variants in single genes (monogenic Parkinson disease).
2. Early-onset adult Parkinson disease (PD) = onset at age 20-50 years. Late-onset adult PD = onset after age 50 years.
3. Seven of the ten genetically defined types of neurodegeneration with brain iron accumulation are inherited in an autosomal recessive manner. Exceptions: neuroferritinopathy, an autosomal dominant disorder caused by a pathogenic variant in *FTL*; mitochondrial membrane protein-associated neurodegeneration (MPAN), an autosomal recessive or autosomal dominant disorder caused by mutation of *C19orf12*; and beta-propeller protein-associated neurodegeneration (BPAN), an X-linked disorder.
4. PDHA1- and *PDK3*-related primary pyruvate dehydrogenase complex deficiency (PDCD) are inherited in an X-linked manner. Primary PDCD caused by pathogenic variants in *DLAT*, *DLD*, *PDHB*, *PDHX*, or *PDP1* is inherited in an autosomal recessive manner.
5. To date, more than 80 genetic types of hereditary spastic paraplegia (HSP) have been defined by genetic linkage analysis and identification of HSP-related gene variants. Autosomal dominant, autosomal recessive, X-linked, and maternally inherited (mitochondrial) forms of HSP have been identified.

Management

No clinical practice guidelines for hypermanganesemia with dystonia 1 (HMNDYT1) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with HMNDYT1, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Hypermanganesemia with Dystonia 1

System/Concern	Evaluation	Comment
Neurologic status	• Neurologic exam for dystonia, parkinsonism, & spasticity • Incl eval of (1) ambulation & speech & (2) swallowing & nutritional status	
	Assessment for needs for PT, OT, &/or speech therapy	
	Brain MRI as baseline	Improvement may be seen w/normalization of manganese blood levels.
Hypermanganesemia	Whole-blood manganese levels	Establish baseline.
Liver disease	Liver function tests, liver ultrasound exam, & liver biopsy if indicated	Consultation w/hepatologist is advised.
Iron status	Total iron binding capacity, ferritin	Monitoring of iron supplementation
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of HMNDYT1 in order to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental/family support; • Home nursing referral.	

MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Hypermanganesemia with Dystonia 1

Manifestation/Concern	Treatment	Considerations/Other
Hypermanganesemia	Chelation therapy w/intravenous disodium calcium edetate	• Regular chelation therapy can stabilize blood manganese levels, improve neurologic symptoms, & halt liver disease. • See Adverse Effects of Chelation Therapy.
	Short term. The response of a person to disodium calcium edetate is determined by a single 5-day course of 2x/d disodium calcium edetate at 20 mg/kg/dose (made up in 250 mL of 0.9% sodium chloride, given intravenously over 1 hr) & daily measurement of plasma manganese concentration & 24-hr urine manganese levels. Note: To avoid hypocalcemia, administer disodium calcium edetate infusions slowly over ≥1 hr. If calcium level (corrected for albumin concentration) is low, administer infusions over a longer time span (i.e., >3 hrs).	
	Long term. If chelation therapy proves effective in the short term, monthly 5-day courses of disodium calcium edetate (IV 20 mg/kg/dose 2x/day) are recommended & expected to lower blood manganese levels & normalize hemoglobin concentration & iron indices.	• Chelation therapy should be continued lifelong. • CBC & renal function incl urinalysis are assessed at baseline & then monthly. • Monitoring may be extended to every 2 mos once on stable dose. • While on treatment, monitor every 2 mos incl: serum concentration of electrolytes, calcium, phosphate, magnesium; renal & liver function; full blood count; & serum concentrations of trace metals incl zinc, copper, & selenium to ensure no secondary effects on these metals. • If available, blood manganese levels can be monitored at similar intervals.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hypermanganesemia & polycythemia	Iron therapy: supplementation w/iron given orally per standard protocols for iron supplementation for iron deficiency	• Iron is a competitive inhibitor of intestinal manganese uptake; despite normal iron levels, iron therapy can ↓ blood manganese levels & resolve polycythemia. • To avoid iron toxicity, monitor serum iron & total iron binding capacity regularly; if serum iron >80% of total iron binding capacity, stop or ↓ iron supplementation.
Dystonia, dysarthria, & rigidity	PT (to prevent contractures & maintain ambulation), OT, &/or speech therapy; use of adaptive aids (e.g., walker or wheelchair for gait abnormalities) & assistive communication devices	Symptomatic treatment w/anti-spasticity medications & L-dopa has been attempted w/limited success.
Inadequate nutrition due to progressive dystonia	Gastrostomy tube placement once an adequate oral diet can no longer be maintained	To prevent assoc aspiration pneumonia, a tracheostomy may be required.

CBC = complete blood count; IV = intravenous; OT = occupational therapy; PT = physical therapy

Adverse Effects of Chelation Therapy

Adverse effects of chelation therapy with disodium calcium edetate include hypocalcemia, nephrotoxicity, trace metal and vitamin deficiency, and thrombocytopenia and leukopenia [Lamas et al 2012].

Treatment may need to be discontinued if the following occur:

- White blood count $<3.5x10^9$/L
- Neutrophils $<2x10^9$/L
- Platelets $<150x10^9$/L
- >2+ proteinuria on >1 occasion (and no evidence of infection)

The above cut-off values are based on guidelines for D-penicillamine treatment [Chakravarty et al 2008]. The clinical treatment benefit needs to be carefully weighed against occurring adverse effects for each affected individual.

Prevention of Primary Manifestations

Chelation therapy and iron supplementation may prevent primary disease manifestations in affected sibs who are asymptomatic (see Treatment of Manifestations).

Surveillance

Table 6. Recommended Surveillance for Individuals with Hypermanganesemia with Dystonia 1

System/Concern	Evaluation	Frequency
Hypermanganesemia & chronic liver disease	Liver function tests; hemoglobin; iron indices; whole-blood manganese (if available)	Every 3 mos
	Follow up w/neurologist & hepatologist (w/repeat assessment of brain MRI & liver ultrasound & biopsy)	When clinically indicated by worsening liver function &/or for monitoring treatment at least every 6-12 mos

Agents/Circumstances to Avoid

Foods very high in manganese (cloves; saffron; nuts; mussels; dark chocolate; pumpkin, sesame, and sunflower seeds) should be avoided.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic sibs of a proband in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Chelation therapy and iron supplementation can potentially prevent primary disease manifestations in affected sibs who are asymptomatic (see Treatment of Manifestations).

Periodic monitoring of whole-blood manganese concentration and hemoglobin is recommended if the genetic status of a sib is unknown (i.e., if a sib has not undergone molecular genetic testing for the *SLC30A10* pathogenic variants identified in the proband).

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

Pregnancy Management

For an affected fetus, no prenatal treatment is recommended as the disease does not manifest before early childhood.

For an affected mother, no data or information on pregnancy management are available.

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

Hypermanganesemia with dystonia 1 (HMNDYT1) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *SLC30A10* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SLC30A10* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:

- One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
- Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.

- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *SLC30A10* 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 inheriting neither of the familial pathogenic variants.
- Significant phenotypic variability may be observed between affected sibs, particularly with regard to liver disease, which may be absent or mild in some individuals while their sibs develop chronic liver disease and associated complications.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- No data on fertility in individuals with HMNDYT1 are available.
- Assuming that reproduction is possible, the offspring of an affected individual are obligate heterozygotes (carriers) for a pathogenic variant in *SLC30A10*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC30A10* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLC30A10* 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.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC30A10* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for a pregnancy at increased risk 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 Liver Foundation**
  Phone: 800-465-4837 (HelpLine)
  www.liverfoundation.org
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.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. Hypermanganesemia with Dystonia 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC30A10	1q41	Calcium/manganese antiporter SLC30A10	SLC30A10 @ LOVD	SLC30A10	SLC30A10

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 Hypermanganesemia with Dystonia 1 (View All in OMIM)

611146	SOLUTE CARRIER FAMILY 30 (ZINC TRANSPORTER), MEMBER 10; SLC30A10
613280	HYPERMANGANESEMIA WITH DYSTONIA 1; HMNDYT1

Molecular Pathogenesis

SLC30A10 is a member of the SLC30 solute carrier subfamily of the cation diffusion facilitator (CDF) family. Human SLC30A10 is a protein of 485 amino acids [Tuschl et al 2012]. The protein is a transmembrane manganese transporter expressed in liver and brain that facilitates manganese efflux at the cell surface [Leyva-Illades et al 2014]. Quadri et al [2012] showed that *SLC30A*10 expression and the levels of the encoded protein are under strict control by extracellular manganese levels in vitro. Exposure to high manganese concentrations leads to significant increase of *SLC30A10* mRNA and protein expression.

Pathogenic variants in *SLC30A10* have deleterious effects on protein function. While wild type *SLC30A10* expressed in manganese-sensitive yeast cells rescues growth in high manganese concentrations, *SLC30A10* with missense and nonsense sequence changes fails to restore manganese resistance [Tuschl et al 2012]. Furthermore, *SLC30A10* pathogenic variants lead to loss of immunoreactivity in liver and brain tissues of affected individuals and fail to traffic to the cell surface [Quadri et al 2012, Lechpammer et al 2014, Leyva-Illades et al 2014]. In

humans, impaired function of SLC30A10 results in accumulation of manganese in liver and brain [Gospe et al 2000, Lechpammer et al 2014].

Mechanism of disease causation. Hypermanganesemia with dystonia 1 (HMNDYT1) occurs by a loss-of-function mechanism. Pathogenic variants are predicted to either (1) cause a significantly truncated protein because of a frameshift and premature stop codon or large deletion, or (2) affect an evolutionary highly conserved area of the protein. Therefore, these sequence changes have detrimental effects on protein function [Quadri et al 2012, Tuschl et al 2012].

SLC30A10 localizes to the apical domain of hepatocytes and enterocytes where it facilitates manganese excretion. Studies in mice have confirmed that loss of SLC30A10 function leads to impaired biliary and intestinal manganese elimination with subsequent accumulation of manganese in the liver and brain [Mercadante et al 2019, Taylor et al 2019]. Furthermore, SLC30A10 expressed in the brain protects from any increase in manganese and neurotoxicity [Taylor et al 2019].

Chapter Notes

Author Notes

The authors are studying the mechanisms underlying manganese neurotoxicity and inherited manganese transporter defects at the University College London (UCL) Great Ormond Street Institute of Child Health.

Tuschl Lab website: zebrafishucl.org/tuschl

Dr Karin Tuschl UCL website: www.ucl.ac.uk

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