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SLC6A3-Related Dopamine Transporter Deficiency Syndrome

Synonym: DAT Deficiency

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Summary

Clinical characteristics

SLC6A3-related dopamine transporter deficiency syndrome (DTDS) is a complex movement disorder with a continuum that ranges from classic early-onset DTDS (by age 6 months) to atypical later-onset DTDS (in childhood, adolescence, or adulthood).

Classic early-onset DTDS: Infants typically manifest nonspecific findings (irritability, feeding difficulties, axial hypotonia, and/or delayed motor development) followed by a hyperkinetic movement disorder (with features of chorea, dystonia, ballismus, orolingual dyskinesia). Over time, affected individuals develop parkinsonism-dystonia characterized by bradykinesia (progressing to akinesia), dystonic posturing, distal tremor, rigidity, and reduced facial expression. Limitation of voluntary movements leads to severe motor delay. Episodic status dystonicus, exacerbations of dystonia, and secondary orthopedic, gastrointestinal, and respiratory complications are common. Many affected individuals appear to show relative preservation of intellect with good cognitive development.

Atypical later-onset DTDS: Normal psychomotor development in infancy and early childhood. Attention-deficit/hyperactivity disorder (ADHD) is reported in childhood followed by later-onset manifestations of parkinsonism-dystonia with tremor, progressive bradykinesia, variable tone, and dystonic posturing. The long-term prognosis of this form of DTDS is currently unknown.

Diagnosis/testing

The diagnosis of *SLC6A3*-related DTDS is established in a proband with characteristic clinical, laboratory, and imaging findings and either biallelic loss-of-function pathogenic variants in *SLC6A3* or, rarely, a heterozygous dominant-negative pathogenic variant in *SLC6A3* identified by molecular genetic testing.

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Management

Treatment of manifestations: Treatment to control chorea and dyskinesia in early stages of the disease includes tetrabenazine and benzodiazepines. Dystonia is more difficult to control, and treatment often includes the dopamine agonists pramipexole and ropinirole as first-line agents; adjuncts such as trihexyphenidyl, baclofen, gabapentin, and clonidine for severe dystonia; and chloral hydrate and benzodiazepines for exacerbations of dystonia or status dystonicus. Movement disorders can be exacerbated by pain or discomfort, so diagnosis and treatment of all sources of pain and discomfort (e.g., dental caries, hip dislocation, scoliosis, pressure sores) is essential. Supportive management and developmental support includes: nutrition management and feeding support for oral feeding issues; alternative and augmentative communication devices when needed; medical management of tone issues and regular physical therapy to reduce the risk of contractures and fractures; focal botulinum toxin for contractures; standard treatments for pulmonary infections; influenza vaccine, prophylactic antibiotics, and chest physiotherapy to prevent pulmonary infections; chloral hydrate, melatonin, and other sedatives as needed for sleep issues; anti-serotoninergic agents for vomiting; standard treatments for gastroesophageal reflux, constipation, and ADHD.

Surveillance: Every six to 12 months: neurologic assessment; nutrition, swallowing, and speech-language assessment; physiotherapy evaluation for postural and tone issues; evaluation for hip dislocation and spinal deformity; physical and occupational therapy evaluation to assess mobility, activities of daily living, and need for adaptive devices; assessment of the frequency of respiratory infections and presence of sleep issues; assessment for vomiting, gastrointestinal reflux, and constipation; assessment for manifestations of ADHD. Annually: ophthalmology examination for eye movement disorders and refractive errors.

Agents/circumstances to avoid: Although the dopamine agonists bromocriptine and pergolide could be considered, the associated increased risk of pulmonary, retroperitoneal, and pericardial fibrosis makes them less desirable than the newer dopamine agonists. Drugs with anti-dopaminergic side effects (e.g., some antihistamines, sedatives, and dimenhydrinate) may exacerbate movement disorders. The antiemetics metoclopramide, prochlorperazine, and other medicines with anti-dopaminergic effects may exacerbate movement disorders.

Genetic counseling

In most individuals reported to date, *SLC6A3*-related DTDS is caused by biallelic loss-of-function pathogenic variants and inherited in an autosomal recessive manner. Autosomal dominant *SLC6A3*-related DTDS caused by a heterozygous dominant-negative *SLC6A3* pathogenic variant has been reported in one individual to date.

Autosomal recessive inheritance: If both parents are known to be heterozygous for an *SLC6A3* loss-of-function 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. Carrier testing for at-risk relatives requires prior identification of the *SLC6A3* pathogenic variants in the family.

Autosomal dominant inheritance: Each child of an individual with *SLC6A3*-related DTDS has a 50% chance of inheriting the dominant-negative *SLC6A3* pathogenic variant.

Once the *SLC6A3* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

SLC6A3-Related Dopamine Transporter Deficiency Syndrome: Included Phenotypes
• Classic early-onset dopamine transporter deficiency syndrome (DTDS) • Atypical later-onset DTDS

Diagnosis

Suggestive Findings

Classic early-onset and atypical later-onset *SLC6A3*-related dopamine transporter deficiency syndrome (DTDS) **should be suspected** in individuals with the following clinical and laboratory findings.

Clinical Findings

Classic early-onset DTDS

- **Predominant features in infancy**
  - Onset usually within the first six months of life
  - Early nonspecific clinical findings of irritability and difficulty feeding
  - Axial hypotonia
  - Delay in motor milestones
  - Hyperkinetic movement disorder (chorea, ballismus, dystonia, orolingual dyskinesia) typically evident in infancy and early childhood; may persist into late childhood and adolescence
  - Eye movement disorders including recurrent oculogyric crises, saccade initiation failure, ocular flutter, and eyelid myoclonus
- **Predominant features in childhood/adolescence**
  - Parkinsonism-dystonia including dystonic postures, resting and action tremor, difficulty initiating movements, bradykinesia, paucity of facial expression, and rigidity
  - Severe delay in motor milestones
  - Eye movement disorders including recurrent oculogyric crises, saccade initiation failure, ocular flutter, and eyelid myoclonus

Atypical later-onset DTDS

- **Predominant features**
  - Onset from childhood to adulthood (4th decade)
  - Attention-deficit/hyperactivity disorder (ADHD)
  - Resting and action tremor
  - Dysarthria
  - Parkinsonism-dystonia

Laboratory Findings

Cerebrospinal fluid (CSF) neurotransmitter analysis. To date, almost all individuals with classic early-onset *SLC6A3*-related DTDS have a distinct pattern:

- Raised homovanillic acid level (HVA, metabolite derived from dopamine) with normal 5-hydroxyindoleacetic acid level (5-HIAA, metabolite derived from serotonin). The HVA:5-HIAA ratio in *SLC6A3*-related DTDS is >4.0 (range 5.0-13.0) (normal range 1.0-4.0).
- Normal pterin profile

SPECT imaging using the ligand ioflupane (DaTSCAN). To date, all individuals with *SLC6A3*-related DTDS who were evaluated with DaTSCAN had very abnormal results with absent/reduced tracer uptake in the basal ganglia.

Establishing the Diagnosis

The diagnosis of *SLC6A3*-related DTDS **is established** in a proband with characteristic clinical findings (especially parkinsonism-dystonia), CSF HVA:5-HIAA ratio >4.0, DaTSCAN showing reduced tracer uptake (supportive but not essential for diagnosis) [Kurian et al 2011b], and either of the following identified by molecular genetic testing (see Table 1):

- Biallelic loss-of-function pathogenic variants in *SLC6A3*

OR

- A heterozygous dominant-negative *SLC6A3* pathogenic variant known to cause autosomal dominant DTDS (e.g., p.Lys619Asn)

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis. (3) Although the CSF HVA:5-HIAA ratio is almost universally elevated, an atypical presentation without elevated CSF HVA:5-HIAA ratio has been described.

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). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *SLC6A3*-related DTDS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *SLC6A3* 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 *SLC6A3* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by ADHD, tremor, dysarthria, and/or parkinsonism-dystonia, **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 *SLC6A3*-Related Dopamine Transporter Deficiency Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SLC6A3	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	2 individuals [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Large deletions have been described: a homozygous multiexon deletion [Kurian et al 2011b] and a microdeletion/translocation encompassing *SLC6A3* [Kurian, personal communication 2023].

Clinical Characteristics

Clinical Description

SLC6A3-related dopamine transporter deficiency syndrome (DTDS) typically presents in infancy and atypically later in childhood, adolescence, or adulthood. In early-onset *SLC6A3*-related DTDS, nonspecific findings of irritability, feeding difficulties, axial hypotonia, and/or delayed motor development are followed by onset of hyperkinetic movement disorder, abnormal eye movements, and childhood parkinsonism-dystonia. Later-onset *SLC6A3*-related DTDS is characterized by normal psychomotor development in infancy and early childhood. Attention-deficit/hyperactivity disorder (ADHD) is reported in childhood followed by later-onset manifestations of parkinsonism-dystonia with tremor, progressive bradykinesia, variable tone, and dystonic posturing. *SLC6A3*-related DTDS is rare, with fewer than 60 affected individuals identified to date [Kurian et al 2009, Kurian et al 2011b, Hansen et al 2014, Ng et al 2014b, Yildiz et al 2017, Herborg et al 2021, Ng et al 2021, Ng et al 2023].

Classic Early-Onset *SLC6A3*-Related DTDS

Movement disorder. Typically, infants present between birth and age six months [Kurian et al 2009, Kurian et al 2011b]. In the early stages, children manifest the nonspecific findings of irritability, axial hypotonia, and delayed motor development. In infancy a heterogeneous movement disorder is prominent, with features of chorea, dystonia, dystonia-parkinsonism, and ballismus. The early hyperkinesia often becomes less prominent over time, with subsequent development of parkinsonism-dystonia. Bradykinesia progressing to akinesia is common, as well as dystonic posturing, distal tremor, rigidity, and hypomimia (reduced facial expression). Voluntary movements become limited, leading to severe motor delay.

During the first years of life some children have episodic status dystonicus. Prolonged periods of crying and irritability – without discernable triggers – are also described. Disrupted sleep patterns are common. Exacerbations of dystonia are also common, often related to intercurrent illness, infection, and/or dehydration.

Orolingual dyskinesia in infants contributes to feeding difficulties. Alternative feeding strategies using nasogastric tubes or percutaneous endoscopic gastrostomy become necessary due to progressive bulbar dysfunction. The majority develop anarthria and need alternative and augmentative communication devices for effective communication.

Eye movement abnormalities. Many infants also develop an eye movement disorder, which may manifest as recurrent oculogyric crises, saccade initiation failure, ocular flutter, or eyelid myoclonus.

Secondary orthopedic, pulmonary, and gastrointestinal complications are common [Kurian & Assmann 2015].

- **Orthopedic complications.** Many develop spinal deformities, often necessitating surgery. Fixed limb contractures, osteoporotic bone fractures, and hip dislocation are also described. Optimum management of tone with medical therapies, regular physiotherapy evaluation, and use of orthotics reduce the risk of contracture development.
- **Pulmonary complications.** Reduced axial tone, spinal abnormalities, and bulbar dysfunction compromise respiratory function, leading to an increased risk of recurrent chest infections and aspiration pneumonia.
- **Gastrointestinal complications** include vomiting, gastroesophageal reflux disease, and constipation likely related to gastrointestinal dysmotility.

Cognition. Although more data are needed, it appears that many affected individuals show relative preservation of intellect with good cognitive development.

Prognosis. A number of children with classic early-onset *SLC6A3*-related DTDS die in late childhood / early adolescence from unexplained sudden death in sleep or respiratory complications.

Atypical Later-Onset *SLC6A3*-Related DTDS

To date, five individuals with atypical later-onset DTDS have been described. Four had biallelic loss-of-function *SLC6A3* pathogenic variants and one had a heterozygous dominant-negative variant in *SLC6A3*. They had normal psychomotor development in infancy and early childhood, attaining independent ambulation and spoken language [Hansen et al 2014, Ng et al 2014b, Herborg et al 2021]. Manifestations of ADHD in childhood have been reported. Later in childhood, adolescence, or adulthood, they developed manifestations of parkinsonism-dystonia with tremor, progressive bradykinesia, variable tone, and dystonic posturing.

Genotype-Phenotype Correlations

It is not yet clear whether genotype-phenotype correlations exist for *SLC6A3*-related DTDS. From published functional data on pathogenic missense variants, children with classic early-onset DTDS have lower levels of residual transporter activity than those with the atypical later-onset DTDS [Hansen et al 2014, Ng et al 2014b].

Prevalence

While there are no current estimates on prevalence, *SLC6A3*-related DTDS is ultra-rare, with fewer than 60 affected individuals identified to date [Kurian et al 2009, Kurian et al 2011b, Hansen et al 2014, Ng et al 2014b, Yildiz et al 2017, Herborg et al 2021, Ng et al 2021, Ng et al 2023].

Genetically Related (Allelic) Disorders

Heterozygous *SLC6A3* loss-of-function variants have been rarely identified in individuals with attention-deficit/hyperactivity disorder, bipolar disorder, and autism spectrum disorder [Reith et al 2022, Ng et al 2023]. However, an increased incidence of these disorders has not been reported in the heterozygous parents of

individuals with biallelic *SLC6A3* loss-of-function variants, nor does there appear to be an increased risk of early-onset parkinsonism in heterozygous parents.

Differential Diagnosis

Hereditary (see Table 2) and acquired disorders can present clinically with the manifestations of classic early-onset and atypical later-onset *SLC6A3*-related dopamine transporter deficiency syndrome (DTDS).

Table 2. Genes of Interest in the Differential Diagnosis of *SLC6A3*-Related Dopamine Transporter Deficiency Syndrome

Gene	Disorder	MOI	Comment
Neurotransmitter disorders including:			
DDC	Aromatic L-amino acid decarboxylase deficiency	AR	Clinical features assoc w/*SLC6A3*-related DTDS (progressive parkinsonism-dystonia, eye movement disorder, axial hypotonia, & delayed motor development) may be similar to those seen in other neurotransmitter disorders. [1, 2]
DNACJ12	Hyperphenylalaninemia, non-BH4 deficient (OMIM 617384)	AR	
GCH1	GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD)	AD	
	Dystonia w/motor delay (See GTPCH1-Deficient DRD, Genetically Related Disorders.)	AR	
PTS	Hyperphenylalaninemia, BH4 deficient, A (OMIM 261640)	AR	
QDPR	Hyperphenylalaninemia, BH4 deficient, C (OMIM 261630)	AR	
SLC18A2	Infantile-onset parkinsonism-dystonia 2 (OMIM 618049)	AR	
SPR	Sepiapterin reductase deficiency	AR	
TH	Tyrosine hydroxylase deficiency	AR	
Mitochondrial diseases including:			
DLAT *DLD* *PDHA1* *PDHB* *PDHX* *PDP1* *PDK3*	Primary pyruvate dehydrogenase complex deficiency	XL AR [3]	The phenotypic features of the mitochondriocytopathies overlap w/*SLC6A3*-related DTDS. [4] ↑ HVA levels are also observed in some mitochondrial disorders. [5] See also Primary Mitochondrial Disorders Overview.
PC	Pyruvate carboxylase deficiency	AR	
POLG	AR *POLG*-related disorders	AR	
Metabolic syndromes including:			

Table 2. continued from previous page.

Gene	Disorder	MOI	Comment
CBS	Homocystinuria caused by cystathionine beta-synthase deficiency (classic homocystinuria)	AR	Metabolic syndromes incl lysosomal storage diseases can mimic *SLC6A3*-related DTDS. [6]
GLB1	GM1 gangliosidosis (See *GLB1*-Related Disorders.)	AR	
HPRT1	Lesch-Nyhan disease (See *HPRT1* Disorders.)	XL	
NPC1 *NPC2*	Niemann-Pick disease type C	AR	
PAH	Untreated phenylketonuria (See Phenylalanine Hydroxylase Deficiency.)	AR	
Monogenic movement disorders associated with infantile-onset dyskinesia/hyperkinesia including:			
ADCY5	*ADCY5* dyskinesia	AD AR [7]	Monogenic movement disorders assoc w/infantile-onset dyskinesia/hyperkinesia may be reminiscent of early disease manifestations of classic early-onset *SLC6A3*-related DTDS. [2]
ATP1A3	*ATP1A3*-related neurologic disorders	AD	
ATP8A2	Cerebellar ataxia, impaired intellectual development, & disequilibrium syndrome 4 (OMIM 615268)	AR	
FOXG1	Rett syndrome, congenital variant (OMIM 613454)	AD	
GNAO1	*GNAO1*-related disorder	AD	
PRRT2	*PRRT2*-related paroxysmal kinesigenic dyskinesia w/infantile convulsions (See *PRRT2*-Associated Paroxysmal Movement Disorders.)	AD AR [8]	
SLC2A1	Glucose transporter type 1 deficiency syndrome	AD AR [9]	
SYT1	*SYT1*-related disorder (OMIM 618218)	AD	
Monogenic juvenile parkinsonism syndromes including:			
ATP1A3	*ATP1A3*-related neurologic disorders	AD	Monogenic juvenile parkinsonism syndromes may mimic classic early-onset & atypical later-onset *SLC6A3*-related DTDS. [2, 6]
ATXN2	SCA2	AD	
ATXN3	SCA3	AD	
DNAJC6	PARK-*DNAJC6*	AR	
FBXO7	PARK-*FBXO7* (See Parkinson Disease Overview.)	AR	
HTT	Juvenile Huntington disease	AD	
MAPT	*MAPT*-related frontotemporal dementia	AD	
PRKN (PARK2)	PARK-*Parkin*	AR	

Table 2. continued from previous page.

Gene	Disorder	MOI	Comment
PARK7 (DJ1)	PARK-*DJ1* (See Parkinson Disease Overview.)	AR	
PINK1	PARK-*PINK1*	AR	
PRKRA	DYT-PRKRA (See Hereditary Dystonia Overview.)	AR	
RAB39B	Waisman syndrome (OMIM 311510)	XL	
SNCA	PARK-*SNCA* (See Parkinson Disease Overview.)	AD	
SPG11	Spastic paraplegia 11	AR	
SYNJ1	PARK-*SYNJ1* (See Parkinson Disease Overview.)	AR	
TAF1	X-linked dystonia-parkinsonism	XL	
VPS13C	PARK-*VPS13C* (See Parkinson Disease Overview.)	AR	
WARS2	*WARS2*-related movement disorder (See WARS2 Deficiency.)	AR	
Disorders of brain metal accumulation including:			
ATP13A2 *C19orf12* *COASY* *CP* *DCAF17* *FA2H* *FTL* *PANK2* *PLA2G6* *WDR45*	Neurodegeneration w/brain iron accumulation disorders	AR AD XL	Disorders of brain metal accumulation may mimic *SLC6A3*-related DTDS.
ATP7B	Wilson disease	AR	
SLC30A10	Hypermanganesemia w/dystonia 1	AR	
SLC39A14	SLC39A14 deficiency (hypermanganesemia w/dystonia 2)	AR	
Other childhood disorders that can feature parkinsonism:			
NUP62 *VAC14*	Monogenic causes of striatal necrosis (OMIM PS271930)	AR	Monogenic striatonigral degeneration may cause similar dystonia-parkinsonism. [2]
CLN2 *CLN3* *CLN6*	Neuronal ceroid lipofuscinoses [2] (NCL) (OMIM 204200, 204500, 601780)	AR	Infantile & late-infantile NCL may mimic *SLC6A3*-related DTDS. [2]
SCN1A	*SCN1A*-related Dravet syndrome (See *SCN1A* Seizure Disorders.)	AD	Predominantly early-onset epilepsies, but w/later parkinsonism & non-epileptiform disorders [2]
STXBP1	*STXBP1* encephalopathy w/epilepsy (OMIM 612164)	AD (AR)	
CLTC	*CLTC*-related intellectual developmental disorder (OMIM 617854)	AD	Other monogenic disorders that present in childhood, typically w/symptoms other than dystonia-parkinsonism, though that can feature parkinsonism often later in the disease course [2]

Table 2. continued from previous page.

Gene	Disorder	MOI	Comment
CSF1R	Leukoencephalopathy w/neuroaxonal spheroids [2]	AD	
DHDDS	*DHDDS*-related developmental delay & seizures ± movement abnormalities (OMIM 617836)	AD	
HEXA	Tay-Sachs disease (See *HEXA* Disorders.)	AR	
LYST	Chediak-Higashi syndrome	AR	
MECP2	*MECP2*-related classic Rett syndrome (See *MECP2* Disorders.)	XL	
PGK1	Phosphoglycerate kinase 1 deficiency (OMIM 300653)	XL	
SLC20A2	*SLC20A2*-related primary familial brain calcification [2]	AD	
TBC1D24	*TBC1D24*-related disorders	AR[10]	
TMEM240	Spinocerebellar ataxia 21 (OMIM 607454)	AD	
ZFYVE26	HSP-*ZFYVE26*	AR	

AD = autosomal dominant; AR = autosomal recessive; DRD = dopa-responsive dystonia; DTDS = dopamine transporter deficiency syndrome; DYT = dystonia; HSP = hereditary spastic paraplegia; HVA = homovanillic acid; MOI = mode of inheritance; PARK = Parkinson disease; SCA = spinocerebellar ataxia; XL = X-linked

1. Kurian et al [2011a], Ng et al [2015]

2. Morales-Briceño et al [2020]

3. *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.

4. Garcia-Cazorla et al [2008]

5. Pineda et al [2006], Hasselmann et al [2010]

6. Garcia-Cazorla & Duarte [2014]

7. *ADCY5* dyskinesia is typically inherited in an autosomal dominant manner. Autosomal recessive inheritance has been reported in two families.

8. *PRRT2*-associated paroxysmal movement disorders (*PRRT2*-PxMD) is caused by a *PRRT2* heterozygous pathogenic variant (~99% of affected individuals); the 16p11.2 recurrent deletion that includes *PRRT2* (<1% of affected individuals); or biallelic *PRRT2* pathogenic variants (<1% of affected individuals, typically those with a more severe phenotype). *PRRT2*-PxMD caused by a heterozygous *PRRT2* pathogenic variant or, rarely, the 16p11.2 recurrent deletion is inherited in an autosomal dominant manner. Rarely *PRRT2*-PxMD is inherited in an autosomal recessive manner.

9. Glucose transporter type 1 deficiency syndrome (Glut1 DS) is most commonly inherited in an autosomal dominant manner. Rarely, Glut1 DS is inherited in an autosomal recessive manner.

10. Most *TBC1D24*-related disorders are inherited in an autosomal recessive manner.

Cerebral palsy. The early hyperkinetic features of classic early-onset *SLC6A3*-related DTDS can mimic dyskinetic cerebral palsy and later features may be reminiscent of spastic/dystonic cerebral palsy. Details of the pre- and perinatal history and brain MRI, as well as the diagnostic testing specific for *SLC6A3*-related DTDS, may be helpful in differentiating these conditions.

Other. Acquired causes that should be considered include: meningoencephalitis; autoimmune, hypoxia, toxin, drug-induced, and post-infectious causes of striatal necrosis; structural brain lesions; marrow transplant-related leukoencephalopathy; and tumors [Garcia-Cazorla & Duarte 2014, Morales-Briceño et al 2020].

Management

No clinical practice guidelines for *SLC6A3*-related dopamine transporter deficiency syndrome (DTDS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *SLC6A3*-related DTDS, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. *SLC6A3*-Related Dopamine Transporter Deficiency Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Movement disorder	Neurologic assessment of the movement disorder	
Orolingual dyskinesia	• Eval of caloric intake & feeding by nutritionist • Speech-language therapy assessment of swallowing, drooling, & communication	In those w/classic early-onset *SLC6A3*-related DTDS
Eye movement abnormalities	Ophthalmology assessment of vision & eye movements	
Orthopedic	• Orthopedic assessment for fixed contractures / joint dislocations • Hip & spine x-rays to evaluate for hip dislocation & spinal deformity	
Pulmonary	• Assess frequency of respiratory infections. • Assess for evidence of sleep disturbance due to movement disorder. • Consider sleep study to assess nocturnal respiratory pattern.	
Gastrointestinal	Assess for vomiting, GERD, & constipation.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SLC6A3*-related DTDS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent in those w/early-onset *SLC6A3*-related DTDS; • Social work involvement; • Home nursing referral.	

DTDS = dopamine transporter deficiency syndrome; GERD = gastroesophageal reflux disease; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *SLC6A3*-related DTDS. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4) [Ng et al 2014a, Kurian & Assmann 2015].

Table 4. *SLC6A3*-Related Dopamine Transporter Deficiency Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Chorea/Dyskinesia	• Tetrabenazine & benzodiazepines may be useful in early stages of the disease. • Chloral hydrate may also help during exacerbations.	Note: Avoidance of long-term use of chloral hydrate is recommended if possible. [1]
Dystonia-parkinsonism	• Dopamine agonists pramipexole & ropinirole are first-line agents. • Adjuncts, such as the anticholinergic trihexyphenidyl, are often needed. • Baclofen, gabapentin, & clonidine may be used for severe dystonia. • Benzodiazepines & chloral hydrate can be useful for exacerbations. • Although the role of atypical tranquilizers (e.g., zopiclone) is not yet established, they have been used successfully in some persons. • Surgical interventions (e.g., intrathecal baclofen, deep brain stimulation) have been used rarely late in the disease course when dystonia is severe; therapeutic benefit is limited. [2] • Avoid & treat risk factors that exacerbate the movement disorder such as discomfort, poor body positioning, & pain (e.g., dental caries, hip dislocation, scoliosis, pressure sores). • PT/OT to provide suitable aids for mobility & home adaptations • Melatonin & other sedatives as needed for sleep issues	Dystonia is more difficult to control than other manifestations as affected persons rarely respond to levodopa/carbidopa & any response is usually modest & not sustained.
Status dystonicus	• Standard protocols are used in an intensive care setting. • Anesthetic agents • GABA-ergic medication incl GABA-A receptor agonists (benzodiazepines), GABA-enhancing medications (gabapentin, phenobarbitone), & GABA-B receptor agonists (baclofen) • Anticholinergics • Alpha-adrenergic agents (e.g., clonidine both enterally & intravenously) • For severe life-threatening or medically intractable status dystonicus, consider intrathecal baclofen & pallidal deep brain stimulation.	
Orolingual dyskinesia	• Nutrition mgmt to ensure adequate caloric intake • Early referral for nasogastric feeding or percutaneous gastrostomy for oral feeding issues • Alternative & augmentative communication devices for effective communication	
Orthopedic manifestations	• Medical mgmt of tone issues & regular PT to ↓ risk of contractures • Focal botulinum toxin for emerging limb contractures & to prevent hip dislocation • Mgmt of bone density to ↓ risk of fractures	
Pulmonary complications	• Standard treatments for pulmonary infections • Influenza vaccine, prophylactic antibiotics, & chest PT for persons prone to chest infections esp during winter months	
Gastrointestinal complications	• For treatment of vomiting, antiemetics such as anti-serotoninergic agents (e.g., ondansetron) potentially have fewer side effects than other agents. • Standard treatments for GERD & constipation	
ADHD	Standard treatment approaches should be used for ADHD.	

ADHD = attention-deficit/hyperactivity disorder; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

1. Wyness et al [2023]

2. Kurian et al [2009]

Surveillance

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

Table 5. *SLC6A3*-Related Dopamine Transporter Deficiency Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Movement disorder	Neurologic assessment of the movement disorder	At each visit, every 6-12 mos
Orolingual dyskinesia	• Dietitian/nutritionist assessment to ensure adequate caloric intake • Swallowing assessment to evaluate risk for aspiration • Speech-language assessment of communication needs	
Ophthalmology	Assessment for eye movement disorders & refractive error to maximize visual function	Every 12 mos
Orthopedic	• PT eval of postural issues & tone • Eval for early evidence of hip dislocation &/or spinal deformity • PT/OT eval to assess mobility, ADL, & need for adaptive devices	Every 6-12 mos
Pulmonary	• Assess frequency of respiratory infections. • Assess for evidence of sleep disturbance due to movement disorder.	At each visit
Gastrointestinal	Assess for vomiting, GERD, & constipation.	At each visit
Neuropsychiatric	Assessment for ADHD	At each visit in persons w/ atypical later-onset *SLC6A3*-related DTDS

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; DTDS = dopamine transporter deficiency syndrome; GERD = gastroesophageal reflux disease; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Although dopamine agonists are used as first-line treatment of dystonia in *SLC6A3*-related DTDS, bromocriptine and pergolide are generally avoided due to increased risk of pulmonary, retroperitoneal, and pericardial fibrosis.

Drugs with anti-dopaminergic side effects (e.g., some antihistamines, sedatives, and dimenhydrinate) may exacerbate movement disorders.

The antiemetics metoclopramide, prochlorperazine, and other medicines with anti-dopaminergic effects may exacerbate movement disorders and alternatives should be used (e.g., anti-serotonergic agents).

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

In most individuals reported to date, *SLC6A3*-related dopamine transporter deficiency syndrome (DTDS) is caused by biallelic loss-of-function pathogenic variants and inherited in an autosomal recessive manner. Autosomal dominant *SLC6A3*-related DTDS caused by a heterozygous dominant-negative *SLC6A3* pathogenic variant has been reported in one individual to date.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive *SLC6A3*-related DTDS are presumed to be heterozygous for an *SLC6A3* loss-of-function pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *SLC6A3* 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.
- Individuals who are heterozygous for an *SLC6A3* loss-of-function pathogenic variant 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 *SLC6A3* 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.
- Individuals who are heterozygous for an *SLC6A3* loss-of-function pathogenic variant are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- To date, there are no reports of individuals with *SLC6A3*-related classic early-onset DTDS having children, but this may be a theoretic possibility for those with atypical later-onset DTDS.
- Unless an affected individual's reproductive partner also has *SLC6A3*-related DTDS or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SLC6A3*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC6A3* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *SLC6A3* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- In the one individual reported to date autosomal dominant *SLC6A3*-related DTDS, the proband had the disorder as the result of a paternally inherited dominant-negative *SLC6A3* pathogenic variant (clinical data are not available for the heterozygous father) [Herborg et al 2021].
- If a proband with autosomal dominant *SLC6A3*-related DTDS appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *SLC6A3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SLC6A3* pathogenic variant but are clinically unaffected, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *SLC6A3*-related DTDS because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant *SLC6A3*-related DTDS has a 50% chance of inheriting the *SLC6A3* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SLC6A3* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygous, or are at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC6A3* pathogenic variant(s) have been identified in an affected family member, prenatal 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.

- **DTDS Foundation**
  www.dtdsfoundation.org
- **MedlinePlus**
  Dopamine transporter deficiency syndrome
- **International Working Group on Neurotransmitter Related Disorders (iNTD) Patient Registry**
  About iNTD

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. SLC6A3-Related Dopamine Transported Deficiency Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC6A3	5p15.33	Sodium-dependent dopamine transporter	SLC6A3 @ LOVD	SLC6A3	SLC6A3

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 SLC6A3-Related Dopamine Transported Deficiency Syndrome (View All in OMIM)

126455	SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, DOPAMINE), MEMBER 3; SLC6A3
613135	PARKINSONISM-DYSTONIA 1, INFANTILE-ONSET; PKDYS1

Molecular Pathogenesis

To date, functional investigations indicate that *SLC6A3*-related dopamine transporter deficiency syndrome (DTDS) results from loss of transporter function [Kurian et al 2009, Kurian et al 2011b, Hansen et al 2014, Ng et al 2014b, Ng et al 2021]. *SLC6A3* encodes the dopamine transporter (DAT) that is expressed predominantly within the substantia nigra (projecting to the striatum) and in the midbrain ventral tegmental area (projecting to the hippocampus, nucleus accumbens, and corticolimbic areas). DAT has a crucial role in mediating reuptake of dopamine from the synaptic cleft, thereby controlling dopamine homeostasis by regulating the duration and amplitude of synaptic dopaminergic transmission.

A number of nonsense variants, splice site changes, and deletions have been reported in *SLC6A3*-related DTDS, and it is likely that for these pathogenic variants nonsense-mediated decay or absent/truncated protein are mechanistic factors in disease. Reported missense substitutions result in mutated proteins that impair DAT through a number of mechanisms including (1) reduced transporter activity, (2) impaired dopamine recognition and/or binding affinity, (3) decreased cell surface expression or accelerated turnover of the transporter, and (4) abnormal post-translational protein modification with impaired glycosylation [Kurian et al 2009, Kurian et al

2011b, Hansen et al 2014, Ng et al 2014b, Herborg et al 2021, Ng et al 2021]. Abnormal DAT protein folding and transporter oligomerization are also postulated to play a role.

SLC6A3 pathogenic variants therefore impair the normal physiologic recycling of dopamine leading to presynaptic dopamine depletion. Excess dopamine in the synaptic cleft is metabolized to homovanillic acid (HVA), which can be detected on cerebrospinal fluid (CSF) analysis. High levels of synaptic dopamine may have downstream signaling effects on postsynaptic dopamine receptors and are also likely to suppress tyrosine hydroxylase activity through action on D2 autoreceptors, thereby inhibiting presynaptic dopamine synthesis [Blackstone 2009].

A DAT knockout mouse model shows several features described in humans, including reduced growth, early hyperkinesia, and difficulties with feeding. Over time, the mice develop abnormal clasping and kyphosis with progressive bradykinesia, reminiscent of the parkinsonism-dystonia phenotype in humans [Giros et al 1996]. Recent preclinical studies investigating targeted gene therapy delivered to the midbrain of knockout mice has shown rescue of the motor phenotype [Ng et al 2021].

Mechanism of disease causation. In most individuals the mechanism is loss of transporter function due to biallelic *SLC6A3* pathogenic variants. One individual with heterozygous *SLC6A3* pathogenic variant p.Lys619Asn presented with atypical later-onset DTDS; functional modeling of the variant demonstrated dominant-negative reduction in transporter function [Herborg et al 2021].

Table 6. SLC6A3 Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001044.5 NP_001035.1	c.1857G>C	p.Lys619Asn	Assoc w/AD *SLC6A3*-related DTDS [Herborg et al 2021]

AD = autosomal dominant; DTDS = dopamine transporter deficiency syndrome
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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Prof Kurian (manju.kurian@ucl.ac.uk) is actively involved in clinical research regarding individuals with *SLC6A3*-related dopamine transporter deficiency syndrome (DTDS). She would be happy to communicate with persons who have any questions regarding diagnosis of *SLC6A3*-related DTDS or other considerations.

Contact Prof Kurian to inquire about review of *SLC6A3* variants of uncertain significance.

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