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Tyrosine Hydroxylase Deficiency

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Summary

Clinical characteristics

Tyrosine hydroxylase (TH) deficiency is associated with a broad phenotypic spectrum. Based on severity of symptoms/signs as well as responsiveness to levodopa therapy, clinical phenotypes caused by pathogenic variants in *TH* are divided into (1) TH-deficient dopa-responsive dystonia (the mild form of TH deficiency), (2) TH-deficient infantile parkinsonism with motor delay (the severe form), and (3) TH-deficient progressive infantile encephalopathy (the very severe form).

- In individuals with TH-deficient dopa-responsive dystonia (DYT5b, DYT-TH), onset is between age 12 months and 12 years; initial symptoms are typically lower-limb dystonia and/or difficulty in walking. Diurnal fluctuation of symptoms (worsening of the symptoms toward the evening and their alleviation in the morning after sleep) may be present.
- In most individuals with TH-deficient infantile parkinsonism with motor delay, onset is between age three and 12 months. In contrast to TH-deficient DRD, motor milestones are overtly delayed in this severe form. Affected infants demonstrate truncal hypotonia and parkinsonian symptoms and signs (hypokinesia, rigidity of extremities, and/or tremor).
- In individuals with TH-deficient progressive infantile encephalopathy, onset is before age three to six months. Fetal distress is reported in most. Affected individuals have marked delay in motor development, truncal hypotonia, severe hypokinesia, limb hypertonia (rigidity and/or spasticity), hyperreflexia, oculogyric crises, ptosis, intellectual disability, and paroxysmal periods of lethargy (with increased sweating and drooling) alternating with irritability.

Diagnosis/testing

The diagnosis of TH deficiency is established in a proband by identification of biallelic pathogenic variants in *TH* by molecular genetic testing.

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Management

Treatment of manifestations:

- All individuals with TH-deficient DRD demonstrate complete responsiveness of symptoms to levodopa (with a decarboxylase inhibitor).
- Individuals with TH-deficient infantile parkinsonism with motor delay demonstrate a marked response to levodopa. However, in contrast to TH-deficient DRD, the responsiveness is generally not complete and/or it takes several months or even years before the full effects of treatment become established. Some individuals are hypersensitive to levodopa and prone to side effects (i.e., dopa-induced dyskinesias which develop at initiation of levodopa treatment).
- Individuals with TH-deficient progressive infantile encephalopathy are extremely sensitive to levodopa therapy. In this very severe form, treatment with levodopa is often limited by intolerable dyskinesias.

Prevention of primary manifestations: Levodopa therapy from early infancy may prevent manifestations of some symptoms and signs in TH-deficient infantile parkinsonism with motor delay; however, no levodopa trials in the early postnatal period of infants with this type of TH deficiency and biallelic *TH* pathogenic variants have been reported.

Prevention of secondary complications: Side effects associated with levodopa (e.g., gastroesophageal reflux, vomiting, significant suppression of appetite) may be ameliorated with dose adjustment and supportive intervention.

Surveillance: Examination by a movement disorder specialist in pediatric or adult neurology at least several times yearly.

Agents/circumstances to avoid: The prokinetic agent Reglan® and other related antidopaminergic agents.

Evaluation of relatives at risk: Sibs of affected individuals should be examined for mild dystonic and/or parkinsonian symptoms or unexplained gait disorders. It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from treatment.

Genetic counseling

TH deficiency is inherited in an autosomal recessive manner. Heterozygotes (carriers) are generally asymptomatic. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if both *TH* pathogenic variants in a family are known.

GeneReview Scope

Tyrosine Hydroxylase Deficiency: Included Phenotypes [1]
• TH-deficient dopa-responsive dystonia • TH-deficient infantile parkinsonism with motor delay • TH-deficient progressive infantile encephalopathy

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

Diagnosis

Tyrosine hydroxylase (TH) deficiency is associated with a wide phenotypic spectrum. Based on severity of symptoms and signs as well as responsiveness to levodopa therapy, the three clinical phenotypes attributable to

pathogenic variants in *TH* are: TH-deficient dopa-responsive dystonia (DYT5b, DYT-TH ; the mild form of TH deficiency); TH-deficient infantile parkinsonism with motor delay (the severe form); and TH-deficient progressive infantile encephalopathy (the very severe form).

Since clinical suspicion is a key to the diagnosis of TH deficiency, physicians should be aware of this broad phenotypic spectrum.

Suggestive Findings

The diagnosis of TH deficiency **should be suspected** in an individual with the following clinical and laboratory features.

Clinical

- Lower-limb dystonia
- Generalized dystonia
- Other forms of dystonia
- Postural and/or rest tremor
- Slowness of movements
- Rigidity in affected limbs
- Postural instability
- Diurnal fluctuation (worsening of the symptoms toward the evening and their alleviation in the morning after sleep)
- Hypokinesia
- Truncal hypotonia
- Developmental motor delay
- Hyperreflexia
- Spasticity in affected limbs
- Extensor plantar responses
- The striatal toe
- Myoclonic jerks
- Oculogyric crises
- Bilateral ptosis
- Intellectual disability
- Autonomic disturbances
- Fetal distress
- Feeding difficulties
- Growth retardation (head circumference, height, and/or weight)
- Dystonic crises
- Lethargy-irritability crises

Laboratory (cerebrospinal fluid)

- Reduced homovanillic acid (HVA)
- Normal 5-hydroxyindoleacetic acid (5-HIAA)
- Reduced HVA/5-HIAA ratio
- Reduced 3-methoxy-4-hydroxy-phenylethyleneglycol (MHPG; a metabolite of noradrenaline)
- Normal total biopterin (BP) (most of which exists as tetrahydrobiopterin [BH_4])
- Normal total neopterin (NP) (the by-products of the GTP cyclohydrolase 1 [GTPCH1] reaction)

This pattern of CSF neurotransmitter metabolites and pterins supports the clinical diagnosis of TH deficiency [Bräutigam et al 1998, Furukawa et al 1998a, Furukawa & Kish 1999, Wevers et al 1999, Willemsen et al 2010].

If CSF pterin analysis reveals low BP and NP levels, GTPCH1-deficient disorders (including GTPCH1-deficient dopa-responsive dystonia; see Differential Diagnosis) should be considered; reduced levels of BP and NP have been confirmed in autopsied brains with GTPCH1 dysfunction [Furukawa et al 1999, Furukawa et al 2002].

Establishing the Diagnosis

The diagnosis of TH deficiency **is established** in a proband by identification of biallelic pathogenic variants in *TH* (see Table 1).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *TH* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *TH* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel 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. (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.
- **More comprehensive genomic testing** (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 Tyrosine Hydroxylase Deficiency

Gene [1]	Method	Number of Probands with Pathogenic Variant(s) [2] Detected by Method
TH	Sequence analysis [3]	73 individuals [4, 5]
	Gene-targeted deletion/duplication analysis [6]	1 individual [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Note that sequence variants in the TH promoter region have been associated with TH deficiency at c.-69, c.-70, and c.-71 [Ribasés et al 2007, Verbeek et al 2007, Ormazabal et al 2011, Stamelou et al 2012, Ortez et al 2015]. Detection of these variants is dependent on the design of the sequencing assay.
5. See references in Clinical Description and Molecular Genetics.
6. 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.
7. Ormazabal et al [2011]

Clinical Characteristics

Clinical Description

Tyrosine hydroxylase (TH) deficiency is associated with a wide phenotypic spectrum. Based on the severity of symptoms and signs as well as responsiveness to levodopa therapy, the three clinical phenotypes from mildest to most severe are: TH-deficient dopa-responsive dystonia (DRD) (DYT5b, DYT-TH); TH-deficient infantile parkinsonism with motor delay; and TH-deficient progressive infantile encephalopathy (see Table 2). In addition, several atypical severe forms have been recognized.

None of the symptoms and signs of TH deficiency improve without proper treatment with levodopa (see Management).

Mild Form: TH-Deficient DRD (DYT5b, DYT-TH)

Clinical features of more than 15 individuals with molecularly confirmed TH-deficient DRD have been reported [Castaigne et al 1971, Rondot & Ziegler 1983, Rondot et al 1992, Knappskog et al 1995, Lüdecke et al 1995, Swaans et al 2000, Furukawa et al 2001, Furukawa et al 2004b, Schiller et al 2004, Verbeek et al 2007, Wu et al 2008, Willemsen et al 2010, Haugarvoll & Bindoff 2011, Yeung et al 2011, Sun et al 2014, Yan et al 2017].

The perinatal and postnatal periods are normal. Early psychomotor development is normal. Onset of symptoms is generally between ages 12 months and 12 years. Initial symptoms are usually lower-limb dystonia and/or difficulty in walking. In general, gradual progression to generalized dystonia occurs. Bradykinesia and tremor (mainly postural) can be observed. A variable degree of rigidity is detected in affected limbs. There is a tendency to fall. Without treatment individuals with TH-deficient DRD become wheelchair bound.

In addition to dystonic and parkinsonian elements, many affected individuals have some clinical features suggestive of pyramidal signs (hyperreflexia, spasticity, and/or extensor plantar responses). Plantar responses become flexor after beginning levodopa therapy, suggesting that the previous findings may be consistent with a dystonic phenomenon (the striatal toe) rather than a Babinski response.

Intellect is not impaired in individuals with TH-deficient DRD. Of note, Schiller et al [2004] reported one individual with TH-deficient DRD and mild cognitive impairment attributed to Rh incompatibility.

In rare instances, sustained upward ocular deviations (oculogyric crises) are observed.

Diurnal fluctuation of symptoms (worsening of the symptoms toward the evening and their alleviation in the morning after sleep) has been reported in approximately one third of individuals with TH-deficient DRD (a much lower incidence than observed in GTP cyclohydrolase 1-deficient dopa-responsive dystonia).

DRD is characterized by a dramatic and sustained response to relatively low doses of levodopa [Nygaard 1993, Furukawa 2004]. All individuals with TH-deficient DRD demonstrate complete responsiveness of symptoms to levodopa therapy. (Note: The term "levodopa therapy," without further specification, is herein used to indicate oral administration of levodopa with a decarboxylase inhibitor.) Such an excellent response in the absence of any motor adverse effects of chronic levodopa therapy (e.g., wearing-off and on-off phenomena and dopa-induced dyskinesias) for more than 30 years has been confirmed in at least five individuals with TH-deficient DRD [Swaans et al 2000, Schiller et al 2004].

Severe Form: TH-Deficient Infantile Parkinsonism with Motor Delay

Approximately 50 individuals with molecularly confirmed TH-deficient infantile parkinsonism with motor delay have been reported [Lüdecke et al 1996, Bräutigam et al 1998, Surtees & Clayton 1998, van den Heuvel et al 1998, Wevers et al 1999, de Rijk-Van Andel et al 2000, Grattan-Smith et al 2002, Yeung et al 2006, Ribasés et al 2007, Verbeek et al 2007, Clot et al 2009, Doummar et al 2009, Pons et al 2010, Willemsen et al 2010, Haugarvoll & Bindoff 2011, Najmabadi et al 2011, Ormazabal, et al 2011, Yeung et al 2011, Chi et al 2012, Giovanniello et al 2012, Pons et al 2013, Ortez et al 2015, Zhang et al 2017].

In general, the pregnancies of affected individuals are uncomplicated. Perinatal and early postnatal periods are usually normal. Onset in most children is between ages three and 12 months. In contrast to TH-deficient DRD, in this severe form, motor milestones are overtly delayed in infancy.

All affected individuals demonstrate truncal hypotonia as well as parkinsonian symptoms and signs (e.g., hypokinesia, rigidity of extremities, tremor). Although dystonia is recognized in most, it tends to be less prominent. Brisk deep tendon reflexes, spasticity, and/or extensor plantar responses are frequently detected. Deep tendon reflexes have been reported to be normal or reduced in some.

Oculogyric crises are often observed. Ptosis and other features of mild autonomic dysfunction can be observed. Intellectual disability is found in many of the affected individuals.

Typical diurnal fluctuation of symptoms is not observed in most individuals with TH-deficient infantile parkinsonism with motor delay. Of note, diurnal variation of axial hypotonia but not of limb dystonia has been described in one affected individual [Clot et al 2009, Doummar et al 2009].

Individuals with TH-deficient infantile parkinsonism with motor delay demonstrate a marked response to levodopa. However, in contrast to TH-deficient DRD, the responsiveness is generally not complete and/or it takes several months or even years for the full effects of treatment to become established. For example, four individuals reported by de Rijk-Van Andel et al [2000] still had clumsy gait and intellectual impairment four to five years after beginning levodopa therapy. One child, who had received levodopa from age six months, showed motor and speech delay at age three years [Lüdecke et al 1996]; when examined at age four years, this child was reported to have no developmental delay and no neurologic abnormalities [Surtees & Clayton 1998].

Some affected individuals are hypersensitive to levodopa (combined with a decarboxylase inhibitor) and are prone to intolerable side effects (e.g., severe dopa-induced dyskinesias which develop at initiation of levodopa treatment); because of this hypersensitivity, such individuals require very low initial doses of levodopa [Clot et al 2009, Doummar et al 2009, Yeung et al 2011].

Very Severe Form: TH-Deficient Progressive Infantile Encephalopathy

More than 15 individuals with molecularly confirmed TH-deficient progressive infantile encephalopathy have been reported [Bräutigam et al 1999, de Lonlay et al 2000, Dionisi-Vici et al 2000, Janssen et al 2000, Häussler et al 2001, Hoffmann et al 2003, Møller et al 2005, Zafeiriou et al 2009, Willemsen et al 2010, Yeung et al 2011, Chi et al 2012, Szentiványi et al 2012, Pons et al 2013, Tristán-Noguero et al 2016, Leuzzi et al 2017].

The onset of TH-deficient progressive infantile encephalopathy is before age three to six months. Fetal distress is reported in most; infants may demonstrate feeding difficulties, hypotonia, and/or growth retardation affecting head circumference, height, and/or weight from birth. Determining the age of onset is sometimes difficult because of complicated perinatal events.

Affected individuals have marked delay in motor development, truncal hypotonia, severe hypokinesia, limb hypertonia (rigidity and/or spasticity), hyperreflexia with extensor plantar responses, oculogyric crises, bilateral ptosis, intellectual disability, and paroxysmal periods of lethargy (with increased sweating and drooling) alternated with irritability – referred to as "lethargy-irritability crises" [Willemsen et al 2010].

In general, dystonia is not a prominent clinical feature of TH-deficient progressive infantile encephalopathy; however, in the most severely affected infants, dystonic crises (every 4-5 days) have been reported [Zafeiriou et al 2009, Willemsen et al 2010]. Other abnormal involuntary movements (tremor and/or myoclonic jerks) can be observed in some.

Although autonomic disturbances occur, especially in the periods of lethargy-irritability crises, the clinical characteristics of impaired production of peripheral catecholamines (e.g., abnormalities in the maintenance of blood pressure) are not present [Hoffmann et al 2003, Willemsen et al 2010].

Usually, typical diurnal fluctuation of symptoms is not recognized in TH-deficient progressive infantile encephalopathy.

Individuals with TH-deficient progressive infantile encephalopathy are extremely sensitive to levodopa therapy; thus, treatment with levodopa is often limited by intolerable dyskinesias. Some develop severe dyskinesias even at doses of 0.2 to 1.5 mg/kg/day levodopa (combined with a decarboxylase inhibitor); no or only minimal improvement can be detected in these individuals [de Lonlay et al 2000, Hoffmann et al 2003, Zafeiriou et al 2009]. Two such individuals died at ages 2.5 years and nine years [Hoffmann et al 2003, Willemsen et al 2010].

Table 2. Characteristics of the Three Phenotypes of TH Deficiency

Clinical Phenotype	Severity	Age at Onset	Effect of Levodopa
TH-deficient dopa-responsive dystonia	Mild	12 mos-12 yrs	Dramatic & sustained
TH-deficient infantile parkinsonism with motor delay	Severe	3-12 mos	Incomplete [1]
TH-deficient progressive infantile encephalopathy	Very severe	<3-6 mos	Little to none [2]

1. Effect is generally incomplete, or levodopa treatment takes months/years to achieve full effect.
2. Levodopa treatment is often limited by intolerable dopa-induced dyskinesias which develop at initiation of the therapy.

Atypical Severe Forms

TH-deficient myoclonus-dystonia. Stamelou et al [2012] reported three sibs with severe TH deficiency who presented with truncal hypotonia, developmental motor delay, generalized dystonia, and prominent myoclonic jerks in infancy. The proband in this family had a normal birth but was floppy with poor head control at age six months. After beginning levodopa treatment at age 13 years, all of her symptoms (including cognitive dysfunction) markedly improved. She could walk some steps with help but had generalized dystonia, choreoathetoid movements, slowing in finger-tapping, and myoclonic jerks even five years after starting levodopa therapy.

TH deficiency with a biphasic clinical course. Giovanniello et al [2007] reported one individual with moderate-severe TH deficiency showing a biphasic course. Psychomotor development was normal in early infancy. In the second year of life he demonstrated toe-walking, frequent falls, and developmental language delay. At age 11 years, he developed involuntary movements over the course of a few months. When examined at age 13 years, he had generalized choreoathetosis, myoclonic jerks, expressionless face, dysarthria, gaze paresis, oculogyric crises, and borderline intellectual function. He showed hypersensitivity to levodopa and could be treated only with very low doses.

TH deficiency with exacerbation by viral infections. Diepold et al [2005] reported one individual with developmental psychomotor delay, truncal hypotonia, parkinsonism, and dystonic posturing of the hands. These symptoms were induced and/or exacerbated by viral infections (e.g., exanthema subitum, an active infection of Epstein-Barr virus). Although he demonstrated a remarkable response to levodopa, this individual still had truncal hypotonia and developmental delay six months after starting levodopa treatment.

Neuroimaging

In all individuals with TH-deficient DRD and in most individuals with TH-deficient infantile parkinsonism with motor delay, brain MRI is normal. Brain MRI demonstrated no abnormalities in the basal ganglia of two individuals with TH-deficient DRD even 38 and 43 years after onset of the disorder [Schiller et al 2004].

In individuals with TH-deficient progressive infantile encephalopathy, brain MRI often reveals mild-moderate cerebral and/or cerebellar atrophy. In one individual with this very severe form, no abnormalities were observed on two brain MRIs in the first year of life; however, the third brain MRI at age 2.5 years showed periventricular white matter changes and symmetric high signal abnormalities in the superior cerebellar peduncles and dorsal pons [Zafeiriou et al 2009].

Neurochemistry

In a 16-week-old miscarried human fetus found to be heterozygous for *TH* variants p.Arg328Trp and p.Thr399Met, protein levels of dopaminergic markers (including TH) in the mesencephalon and pons were reported to be lower than those in an age-matched control fetus [Tristán-Noguero et al 2016]. The same *TH* pathogenic variants were identified in her sister, who developed TH-deficient progressive infantile encephalopathy [Møller et al 2005].

Genotype-Phenotype Correlations

Individuals who are homozygous or compound heterozygous for a single-nucleotide variant in the promoter region of *TH* have not developed the very severe form of TH deficiency [Ribasés et al 2007, Verbeek et al 2007, Ormazabal et al 2011, Stamelou et al 2012, Ortez et al 2015].

No additional genotype-phenotype correlations have been identified in individuals with TH deficiency.

Penetrance

Penetrance appears to be complete in individuals with biallelic *TH* pathogenic variants.

In contrast to autosomal dominant GTPCH1-deficient DRD [Furukawa et al 1998b, Segawa et al 2003], there is no predominance of clinically affected females in autosomal recessive TH-deficient DRD.

Prevalence

The prevalence of TH deficiency has not been clearly documented. DRD has been reported to account for an estimated 5%-10% of primary dystonia in childhood or adolescence [Nygaard et al 1988].

Nomenclature

DYT5b and DYT-TH are other designations for TH-deficient dopa-responsive dystonia (see Dystonia Overview).

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The major differential diagnoses for tyrosine hydroxylase (TH) deficiency include several types of dystonia, early-onset parkinsonism, cerebral palsy or spastic paraplegia, and primary and secondary deficiencies of CSF neurotransmitter metabolites.

Dystonia. For a differential diagnosis of dystonia, see Dystonia Overview.

GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD, DYT5a, DYT-GCH1) is characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of oral administration of levodopa. The average age of onset is approximately six years. This disorder typically presents with gait disturbance caused by foot dystonia, later development of parkinsonism, and diurnal fluctuation of symptoms. In general, gradual progression to generalized dystonia is observed. More than 80% of individuals with DRD have pathogenic variants in *GCH1* (which encodes GTPCH1) [Furukawa et al 2013]. Brain and CSF concentrations of total biopterin (BP) and total neopterin (NP) are low in GTPCH1-deficient DRD (see Suggestive Findings, **Laboratory**). When the phenotypes associated with GTPCH-deficient DRD and TH-deficient DRD overlap significantly, the two disorders can be distinguished by molecular genetic testing and the pattern of CSF pterins and neurotransmitter metabolites. GTPCH1-deficient DRD is inherited in an autosomal dominant manner with incomplete penetrance.

DYT1 early-onset isolated dystonia (DYT1, DYT-TOR1A) is characterized by childhood or adolescent onset of dystonic muscle contractions causing posturing of a foot, leg, or arm. The dystonia is first apparent with specific actions such as writing or walking. Over time, the contractions frequently become evident with less specific actions and spread to other body regions. No other neurologic abnormalities are present, except for postural arm tremor. Disease severity varies considerably even within the same family. A heterozygous GAG deletion in *TOR1A* is identified in most affected individuals. DYT1 is inherited in an autosomal dominant manner with reduced penetrance.

Early-onset parkinsonism. Individuals with early-onset parkinsonism responding to levodopa, especially those with onset before age 20 years, often develop gait disturbance attributable to foot dystonia as the initial symptom. Thus, early in the disease course, clinical differentiation between individuals with early-onset parkinsonism with dystonia and individuals with DRD is difficult. The most reliable clinical distinction between early-onset parkinsonism and DRD is the subsequent occurrence of motor-adverse effects of chronic levodopa therapy (e.g., wearing-off and on-off phenomena and dopa-induced dyskinesias) in early-onset parkinsonism. Under optimal doses, individuals with DRD on long-term levodopa treatment do not develop these complications. However, this is a retrospective difference. An investigation of the nigrostriatal dopaminergic terminals by positron emission tomography (PET) or single photon emission computed tomography (SPECT) can differentiate early-onset parkinsonism (markedly reduced) from DRD (normal or near normal) [Furukawa & Kish 2015]. Cerebrospinal fluid concentration of BP is reduced and NP is normal in early-onset parkinsonism [Furukawa et al 1996], including the autosomal recessive form caused by *PRKN* pathogenic variants (see Parkin Type of Early-Onset Parkinson Disease and Parkinson Disease Overview).

Cerebral palsy or spastic paraplegia. Some individuals with DRD are initially diagnosed as having cerebral palsy or spastic paraplegia [Tassin et al 2000, Furukawa et al 2001, Grimes et al 2002]. Dystonic extension of the big toe (the striatal toe), which occurs spontaneously or is induced by plantar stimulation, may be misinterpreted as an extensor plantar response (see Hereditary Spastic Paraplegia Overview).

Primary deficiencies of CSF neurotransmitter metabolites include autosomal recessive BH_4-related enzyme deficiencies (so-called BH_4 deficiencies, including recessively inherited GTPCH1 deficiency). Individuals with recessively inherited BH_4 deficiencies develop BH_4-dependent hyperphenylalaninemia in the first six months of life; an exception is sepiapterin reductase deficiency (SRD) (in which BH_4 is synthesized through the salvage pathway in peripheral tissue). Individuals with autosomal recessive BH_4 deficiencies typically present with severe neurologic dysfunction (e.g., psychomotor retardation, convulsions, microcephaly, swallowing difficulties, hypersomnia, cognitive impairment, truncal hypotonia, limb hypertonia, paroxysmal stiffening, involuntary movements, oculogyric crises); diurnal fluctuation of symptoms and dystonia partially responding to levodopa can be seen in some, especially those with SRD [Hanihara et al 1997, Furukawa & Kish 1999, Bonafé et al 2001, Furukawa 2004, Neville et al 2005, Abeling et al 2006, Roze et al 2006, Arrabal et al 2011, Dill et al 2012, Friedman et al 2012, Marras et al 2012]. In contrast to individuals with TH deficiency and GTPCH1-deficient DRD, oral administration of both levodopa and 5-hydroxytryptophan is necessary for individuals with SRD because of dopamine and serotonin deficits [Friedman 2016, Furukawa et al 2016]. Arrabal et al [2011] reported one family with a strikingly mild phenotype (without motor and cognitive delay) of SRD associated with compound heterozygous pathogenic variants in *SPR* (which encodes SR). Even in this family, an affected family member showed markedly decreased levels of HVA and 5-HIAA in CSF. BH_4 treatment and neurotransmitter replacement therapy (levodopa and 5-hydroxytriptophan) are indispensable for those with other autosomal recessive BH_4-related enzyme deficiencies.

Sepiapterin reductase deficiency (SRD). The phenotypic spectrum of SRD, which ranges from significant motor and cognitive deficits to only minimal findings, has not been completely elucidated. Clinical features in the majority of affected individuals include motor and speech delay, axial hypotonia, dystonia, weakness, and oculogyric crises; individuals with SRD can show some diurnal fluctuation and sleep benefit. Other common features include parkinsonian symptoms and signs (tremor, bradykinesia, masked face, limb rigidity), hyperreflexia, intellectual disability, psychiatric and/or behavioral abnormalities, autonomic dysfunction, and sleep disturbances (hypersomnolence, difficulty initiating or maintaining sleep, and drowsiness). SRD is inherited in an autosomal recessive manner.

Secondary deficiencies of CSF neurotransmitter metabolites have been observed in other neurodegenerative disorders including spinocerebellar ataxia type 2, neuronal ceroid-lipofuscinosis, Menkes kinky hair disease (see *ATP7A*-Related Copper Transport Disorders), and in association with hypoxic ischemic encephalopathy.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with tyrosine hydroxylase (TH) deficiency, the following are recommended if they have not already been completed:

- Clinical examination to assess the severity of motor disturbances
- Evaluation for associated psychiatric symptoms or cognitive impairments
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

In individuals with TH deficiency, initial use of a levodopa (combined with a decarboxylase inhibitor) dose of 0.5-3 mg/kg (body weight)/day, divided into three to six doses, has been recommended [Willemsen et al 2010, Yeung et al 2011, Pons et al 2013]. Nevertheless, it is possible that even at the lowest initial dosage recommended (i.e., 0.5 mg/kg/day), some individuals with the very severe form of TH deficiency (see Table 2) will develop intolerable dyskinesias [Zafeiriou et al 2009, Pons et al 2013].

When tolerated, the dose of levodopa can be increased gradually. However, with the exception of those with mild TH-deficient DRD (see Table 2), it is often difficult to increase levodopa doses smoothly in affected individuals due to the risk of developing severe dyskinesias. In such individuals, combined administration of levodopa and selegiline (a monoamine oxidase B inhibitor, which inhibits dopamine degradation) has been recommended [Dionisi-Vici et al 2000, Häussler et al 2001, Willemsen et al 2010, Yeung et al 2011, Leuzzi et al 2017].

As reported in compound heterozygotes for *GCH1* pathogenic variants [Furukawa et al 2004a], amantadine (an *N*-methyl-D-aspartate receptor antagonist) can suppress dopa-induced dyskinesias, which develop at initiation of levodopa therapy, in some individuals with TH deficiency [Pons et al 2013].

Mild form (TH-deficient DRD). Individuals demonstrate complete responsiveness of symptoms to levodopa treatment. Such an excellent response without any motor adverse effects of chronic levodopa therapy for more than 30 years has been confirmed in some individuals with TH-deficient DRD [Swaans et al 2000, Schiller et al 2004].

Severe form (TH-deficient infantile parkinsonism with motor delay). Individuals show a marked response to levodopa. However, in contrast to TH-deficient DRD, the responsiveness is generally not complete and/or it takes several months or even years before full effects of treatment become established. Some individuals with the severe form of TH deficiency are hypersensitive to levodopa and are prone to intolerable dyskinesias at initiation of levodopa therapy; this hypersensitivity necessitates use of very low initial doses of levodopa [Grattan-Smith et al 2002, Yeung et al 2006, Clot et al 2009, Doummar et al 2009, Yeung et al 2011].

Very severe form (TH-deficient progressive infantile encephalopathy). Individuals are extremely sensitive to levodopa. Accordingly, treatment with levodopa is often limited by severe dyskinesias. Some individuals with the very severe form of TH deficiency develop intolerable dyskinesias even at doses of 0.2 to 1.5 mg/kg/day levodopa and no or only minimal improvement is observed [de Lonlay et al 2000, Hoffmann et al 2003, Zafeiriou et al 2009].

Prevention of Primary Manifestations

As described in Treatment of Manifestations, appropriate levodopa therapy can reverse symptoms and signs of TH-deficient DRD; thus, levodopa treatment from early infancy may not be required to prevent disease manifestations in this mild form of TH deficiency.

Levodopa therapy from early infancy may prevent manifestations of some symptoms and signs in TH-deficient infantile parkinsonism with motor delay; however, no levodopa trials in the early postnatal period of infants with this type of TH deficiency and biallelic *TH* pathogenic variants have been reported.

Prevention of Secondary Complications

Additional side effects associated with peak-dose levodopa include gastroesophageal reflux, vomiting, or significant suppression of appetite leading to poor growth. Although these problems may be most evident in the first few weeks of onset of levodopa treatment, close monitoring of symptoms and ongoing adjustment of levodopa dosing in conjunction with appropriate supportive intervention as needed help in management.

Surveillance

Examination by a movement disorder specialist in pediatric or adult neurology at least several times yearly is recommended.

Agents/Circumstances to Avoid

The prokinetic agent Reglan®, commonly used for treatment of bowel dysmotility, is contraindicated in individuals with TH deficiency because of its antidopaminergic activity. Use of Reglan® or related antidopaminergic agents, including some antipsychotic medications, could result in a dystonic crisis.

Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from prompt initiation of treatment.

Evaluations include:

- Clinical examination to identify mild dystonic and/or parkinsonian symptoms or unexplained gait disorders;
- Molecular genetic testing if the *TH* pathogenic variants have been identified in the family.

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

Tyrosine hydroxylase (TH) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a proband are obligate heterozygotes (i.e., carriers of one *TH* pathogenic variant).
- Heterozygotes (carriers) are generally asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are generally asymptomatic.

Offspring of a proband. Unless an individual with TH deficiency has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *TH*.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *TH* 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, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It may be 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 *TH* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Prenatal diagnosis of TH deficiency has been reported [Møller et al 2005].

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.

- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org
- **Dystonia Society**
  89 Albert Embankment
  3rd Floor
  London SE1 7TP
  United Kingdom
  Phone: 0845 458 6211; 0845 458 6322 (Helpline)
  Fax: 0845 458 6311

Email: support@dystonia.org.uk
www.dystonia.org.uk

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. Tyrosine Hydroxylase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TH	11p15.5	Tyrosine 3-monooxygenase	TH database	TH	TH

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 Tyrosine Hydroxylase Deficiency (View All in OMIM)

191290	TYROSINE HYDROXYLASE; TH
605407	SEGAWA SYNDROME, AUTOSOMAL RECESSIVE

Molecular Pathogenesis

Tyrosine hydroxylase (TH) (tyrosine 3-monooxygenase) catalyzes the initial and rate-limiting step in the synthesis of catecholamine, including dopamine, adrenaline (epinephrine), and noradrenaline (norepinephrine).

Complete disruption of TH function in mice results in severe catecholamine deficiency and perinatal lethality. Mice heterozygous for *Th* pathogenic variants exhibit defects in neuropsychological function and impaired motor control and operant learning. In humans, homozygous or compound heterozygous pathogenic variants can result in reduced TH enzyme function.

Gene structure. Human *TH* consists of 14 exons spanning approximately 8.5 kb [Grima et al 1987, Kaneda et al 1987]. Four types of mRNA are produced through alternative splicing from a single primary transcript (several additional types of mRNA are known) [Furukawa 2004, Kobayashi & Nagatsu 2005]. Type 1 mRNA and type 4 mRNA contain the coding regions of 1491 and 1584 base pairs, encoding 497 and 528 amino acid residues, respectively. Type 1 mRNA encodes TH isoform b and type 4 mRNA encodes TH isoform a. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Approximately 60 *TH* pathogenic variants (including single-nucleotide variants in the cAMP response element of the *TH* promoter) have been reported in individuals with TH deficiency [Knappskog et al 1995, Lüdecke et al 1995, Lüdecke et al 1996, Bräutigam et al 1998, Surtees & Clayton 1998, van den Heuvel et al 1998, Bräutigam et al 1999, Wevers et al 1999, de Lonlay et al 2000, de Rijk-Van Andel et al 2000, Dionisi-Vici et al 2000, Janssen et al 2000, Swaans et al 2000, Furukawa et al 2001, Häussler et al 2001, Grattan-Smith et al 2002, Hoffmann et al 2003, Schiller et al 2004, Diepold et al 2005, Møller et al 2005, Yeung et al 2006, Giovanniello et al 2007, Ribasés et al 2007, Verbeek et al 2007, Wu et al 2008, Clot et al 2009, Doummar et al 2009, Zafeiriou et al 2009, Pons et al 2010, Willemsen et al 2010, Haugarvoll & Bindoff 2011, Najmabadi et al 2011, Ormazabal et al 2011, Yeung et al 2011, Chi et al 2012, Giovanniello et al 2012, Stamelou et al 2012, Szentiványi et al 2012, Pons et al 2013, Sun et al 2014, Ortez et al 2015, Tristán-Noguero et al 2016, Leuzzi et al 2017, Yan et al 2017, Zhang et al 2017]. Founder effects have been described for the c.698G>A pathogenic variant in the Dutch population [van den Heuvel et al 1998] and for the c.707T>C pathogenic variant in the Greek population [Pons et al 2010].

Table 3. Selected *TH* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.698G>A [1]	p.Arg233His	NM_199292.2 NP_954986.2
c.707T>C [2]	p.Leu236Pro	
	p.Arg328Trp	
	p.Thr399Met	

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.
1. Founder variant in Dutch population [van den Heuvel et al 1998]
2. Founder variant in Greek population [Pons et al 2010]

Normal gene product. The normal product is the TH (EC 1.14.16.2) protein. The enzyme TH, a BH_4-dependent monooxygenase, catalyzes the rate-limiting step (the formation of dopa from tyrosine) in the biosynthesis of catecholamines (dopamine, noradrenaline, adrenaline). The native TH enzyme is a tetramer of four identical subunits [Goodwill et al 1997].

Abnormal gene product. Because *TH* null variants are lethal in *Th*(-/-) knockout mice [Zhou et al 1995], it appears that both homozygotes and compound heterozygotes for *TH* pathogenic variants have some residual enzyme activity.

- In one family with TH-deficient DRD and homozygosity for a *TH* missense variant, the mutated enzyme had approximately 15% of specific activity compared with the wild type in an in vitro coupled transcription-translation assay system [Knappskog et al 1995, Lüdecke et al 1995].
- In an individual with TH-deficient infantile parkinsonism with motor delay and a homozygous *TH* pathogenic variant, the mutated enzyme revealed 0.3%-16% of wild-type enzyme activity in three complementary expression systems [Lüdecke et al 1996].

Chapter Notes

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- 11 May 2017 (sw) Comprehensive update posted live
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