# GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia

Synonyms: Autosomal Dominant Dopa-Responsive Dystonia, Autosomal Dominant Segawa Syndrome, DYT5a, Hereditary Progressive Dystonia with Marked Diurnal Fluctuation

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## Summary

### Clinical characteristics

GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD) is characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of oral administration of levodopa. This disorder typically presents with gait disturbance caused by foot dystonia, later development of parkinsonism, and diurnal fluctuation of symptoms (aggravation of symptoms toward the evening and alleviation of symptoms in the morning after sleep). Initial symptoms are often gait difficulties attributable to flexion-inversion (equinovarus posture) of the foot. Occasionally, initial symptoms are arm dystonia, postural tremor of the hand, or slowness of movements. Brisk deep-tendon reflexes in the legs, ankle clonus, and/or the striatal toe (dystonic extension of the big toe) are present in many affected individuals. In general, gradual progression to generalized dystonia is observed. Intellectual, cerebellar, sensory, and autonomic disturbances generally do not occur.

### Diagnosis/testing

The diagnosis of GTPCH1-deficient DRD is established in a proband by identification of a heterozygous pathogenic variant in *GCH1* by molecular genetic testing. In individuals with a suspected diagnosis of GTPCH1-deficient DRD and no identifiable *GCH1* pathogenic variants, biochemical testing may be necessary.

### Management

*Treatment of manifestations:* Initial suggested dose of levodopa/decarboxylase inhibitor (DCI):

- Children age <6 years: 1-10 mg/kg levodopa/DCI daily, administered in multiple doses
- Children age ≥6 years: 25-50 mg levodopa/DCI 1-3x daily

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- Adults: 50 mg levodopa/DCI 1-3x daily

For all, dose should be changed slowly and by small increments as needed. Motor benefit occurs immediately or within a few days of starting levodopa; full benefit occurs within several days to a few months. Maximum benefit (complete or near-complete responsiveness of symptoms) is generally achieved by <300-400 mg/day of levodopa/DCI. Although dyskinesias may appear at the beginning of levodopa therapy, they subside following dose reduction and do not reappear when the dose is gradually increased. Typically, adverse motor effects of chronic levodopa therapy (motor response fluctuations and dopa-induced dyskinesias) do not occur.

*Prevention of secondary complications:* Early diagnosis and therapy (with low doses of levodopa) may prevent transient dyskinesias at initiation of levodopa treatment.

*Surveillance*: Examination by a movement disorder specialist at least several times yearly is recommended.

*Agents/circumstances to avoid:* Discontinuation of levodopa treatment.

*Evaluation of relatives at risk:* It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment. Molecular genetic testing cannot be used to predict the occurrence of symptoms, age of onset, severity and type of symptoms, or rate of disease progression in family members who are heterozygous for a *GCH1* pathogenic variant.

*Pregnancy management:* Levodopa therapy is continued during pregnancy without adverse effect in most.

## Genetic counseling

GTPCH1-deficient DRD is inherited in an autosomal dominant manner. Affected individuals often have an affected parent with typical GTPCH1-deficient DRD or adult-onset parkinsonism caused by a *GCH1* pathogenic variant. A proband with GTPCH1-deficient DRD may have the disorder as the result of a *de novo* pathogenic variant. Every child of an individual with autosomal dominant GTPCH1-deficient DRD has a 50% chance of inheriting the pathogenic variant. However, because of sex-related incomplete penetrance (i.e., higher penetrance in women than in men), it is not possible to predict whether offspring with a *GCH1* pathogenic variant will develop symptoms.

# Diagnosis

## Suggestive Findings

GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD) **should be suspected** in individuals with the following characteristics [Nygaard et al 1993a, Segawa & Nomura 1993, Furukawa 2004, Trender-Gerhard et al 2009, Furukawa et al 2013, Wijemanne & Jankovic 2015]:

- Onset typically in childhood following normal early motor development
- Onset of dystonia in a limb, typically foot dystonia (equinovarus posture) resulting in gait disturbance
- Later development of parkinsonism (tremor is mainly postural)
- Presence of brisk deep-tendon reflexes in the legs, ankle clonus, and/or striatal toe (dystonic extension of the big toe, which may be misinterpreted as a Babinski response) in many individuals
- In general, normal intellectual and cognitive function and absence of cerebellar, sensory, and autonomic disturbances
- Diurnal fluctuation (aggravation of symptoms toward the evening and alleviation of symptoms in the morning after sleep). The degree of diurnal fluctuation is variable.
- Gradual progression to generalized dystonia, typically more pronounced dystonia in the legs throughout the disease course

- Frequent attenuation in the magnitude of diurnal fluctuation with age and disease progression
- A dramatic and sustained response (complete or near-complete responsiveness of symptoms) to relatively low doses of orally administered levodopa. Maximum benefit is generally achieved by less than 300-400 mg/day of levodopa with a decarboxylase inhibitor (DCI) or 20-30 mg/kg/day of levodopa without a DCI.
- Typically, absence of adverse motor effects of long-term levodopa therapy (wearing-off and on-off phenomena and dopa-induced dyskinesias) under optimal doses of levodopa
- Female predominance among clinically affected individuals

## Establishing the Diagnosis

The diagnosis of GTPCH1-deficient DRD **is established** in a proband by identification of a heterozygous pathogenic variant in *GCH1* by molecular genetic testing (see Table 1).

In individuals with a suspected diagnosis of GTPCH1-deficient DRD and no identifiable *GCH1* pathogenic variants, biochemical testing may be necessary.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of GTPCH1-deficient DRD is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical features in whom the diagnosis of GTPCH1-deficient DRD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

When the phenotypic and laboratory findings suggest the diagnosis of GTPCH1-deficient DRD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *GCH1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

  Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *GCH1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

## Option 2

When the diagnosis of GTPCH1-deficient DRD is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 GTPCH1-Deficient DRD

| Gene [1] | Test Method | Proportion of Probands with a Pathogenic Variant [2] Detectable by This Method |
|---|---|---|
| *GCH1* | Sequence analysis [3] | ~87% [4] |
| | Gene-targeted deletion/duplication analysis [5] | ~13% [4] |

*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.* Hagenah et al [2005], Zirn et al [2008], Clot et al [2009], Liu et al [2010], Wu-Chou et al [2010], Dobričić et al [2017], Yoshino et al [2018]. Variant detection rate by deletion/duplication analysis ranged from 0% [Yoshino et al 2018] to 38% [Wu-Chou et al 2010].
*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

## Biochemical Testing

If molecular testing does not identify a pathogenic variant, biochemical testing should be performed.

**CSF pterins.** The enzyme GTPCH1 catalyzes the first step in the biosynthesis of tetrahydrobiopterin ($BH_4$), which is the cofactor for tyrosine hydroxylase, tryptophan hydroxylase, and phenylalanine hydroxylase. Concentrations of total biopterin (BP, most of which exists as $BH_4$) and total neopterin (NP, the byproducts of the GTPCH1 reaction) in cerebrospinal fluid (CSF) are reduced in individuals with GTPCH1 deficiencies. A finding of reduced concentrations of both BP and NP in CSF is useful for the diagnosis of GTPCH1-deficient DRD [Furukawa & Kish 1999].

**GTPCH1 activity.** If CSF sampling is not available, evaluation of GTPCH1 activity in phytohemagglutinin-stimulated mononuclear blood cells or cytokine-stimulated fibroblasts may be useful [Ichinose et al 1994, Ichinose et al 1995, Bonafé et al 2001, Van Hove et al 2006].

# Clinical Characteristics

## Clinical Description

GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD), the major form of DRD, is a clinical syndrome characterized by childhood-onset dystonia and a dramatic and sustained response (complete

or near-complete responsiveness of symptoms) to relatively low doses of levodopa. The perinatal and postnatal periods are normal, as is early motor development.

**Symptoms and signs.** Initial symptoms in most individuals with childhood-onset GTPCH1-deficient DRD are gait difficulties attributable to dystonia in the legs, typically flexion-inversion (equinovarus posture) of the foot. Affected individuals have a tendency to fall. A relatively small number of individuals have onset with arm dystonia, postural tremor of the hand, or slowness of movements. Standing position with equinovarus posture of the feet can induce increased lumbar lordosis.

A variable degree of rigidity and slowness of movements are recognized in the affected limbs. Tremor is usually postural, especially in the early course of illness. Rapid fatiguing of effort with repetitive motor tasks (e.g., finger tapping or foot tapping) is often observed.

Some clinical findings suggestive of pyramidal signs in the lower extremities (brisk deep-tendon reflexes, spasticity, ankle clonus, and/or intermittent extensor plantar responses) are detected in many affected individuals. However, normal efferent cortical spinal activity with magneto-electrical stimulation of the motor cortex suggests a non-pyramidal basis for these findings. In fact, after starting levodopa therapy, severe hyperreflexia and spasticity resolve and an extensor plantar response often disappears in individuals with GTPCH1-deficient DRD. Dystonic extension of the big toe (the striatal toe) may be misinterpreted as an extensor plantar response.

In general, intellectual and cognitive function is normal and there is no evidence of cerebellar, sensory, and autonomic disturbances in individuals with GTPCH1-deficient DRD.

**Diurnal fluctuation** (aggravation of symptoms toward the evening and alleviation of symptoms in the morning after sleep) is characteristic [Segawa et al 1976]. The degree of fluctuation is variable, with some individuals being normal in the morning and others being only less severely affected in the morning compared to later in the day. Some individuals demonstrate only exercise-induced exacerbation or manifestation of dystonia. Diurnal fluctuation often attenuates with age and disease progression.

**Progression of symptoms.** In general, gradual progression to generalized dystonia occurs in individuals with childhood-onset GTPCH1-deficient DRD. Typically, dystonia remains more pronounced in the legs throughout the disease course.

Symptoms in individuals with adolescent onset are usually milder than in those with childhood onset and disease progression is slower. Individuals with adolescent-onset GTPCH1-deficient DRD seldom develop severe generalized dystonia. Such individuals may become more symptomatic in mid-adulthood because of development of overt parkinsonism.

**Response to levodopa.** All individuals with GTPCH1-deficient DRD demonstrate a dramatic and sustained complete or near-complete response of symptoms to relatively low doses of levodopa [Nygaard et al 1991, Segawa & Nomura 1993, Furukawa et al 2005] (see Treatment of Manifestations). Even individuals who have been untreated for more than 50 years (e.g., persons initially diagnosed with cerebral palsy) can show a remarkable response to levodopa.

At the initiation of levodopa therapy, some individuals with GTPCH1-deficient DRD develop dyskinesias, which subside following dose reduction and do not reappear when the dose is slowly increased later; note that these transient dyskinesias are different from those with motor response fluctuations observed in persons with early-onset parkinsonism and Parkinson disease during chronic levodopa therapy. Under optimal doses, individuals with typical GTPCH1-deficient DRD on long-term levodopa treatment do not develop either motor response fluctuations or dopa-induced dyskinesias.

**Female predominance.** A predominance of clinically affected females is observed, with reported female-to-male ratios ranging from 1.3:1 to 8.3:1 [Furukawa et al 1998b, Segawa et al 2003, Trender-Gerhard et al 2009, Furukawa et al 2013, Wijemanne & Jankovic 2015, Dobričić et al 2017]. See Penetrance.

**Phenotypic variability and spectrum.** Wide intra- and interfamilial variations in expressivity have been reported in GTPCH1-deficient DRD [Bandmann et al 1998, Steinberger et al 1998, Furukawa et al 2000, Grimes et al 2002, Postuma et al 2003, Trender-Gerhard et al 2009].

The clinical phenotypic spectrum has been extended to include adult-onset "benign" parkinsonism, various types of focal dystonia, DRD-simulating cerebral palsy or spastic paraplegia, and spontaneous remission of dystonia and/or parkinsonism (sometimes with a relapse in the later course of illness) [Furukawa et al 2013].

**Adult-onset parkinsonism.** There are two types of adult-onset parkinsonism in families with GTPCH1-deficient DRD [Furukawa & Kish 2015].

- Individuals with adult-onset "benign" parkinsonism manifest no dystonia prior to the onset of parkinsonism in mid- or late adulthood. These individuals respond markedly to low doses of levodopa and, when treated with optimal doses of levodopa, remain functionally normal for a long period of time without developing motor response fluctuations or dopa-induced dyskinesias. PET and SPECT studies using presynaptic dopaminergic markers have demonstrated normal results in "benign" parkinsonism [Nygaard et al 1992, O'Sullivan et al 2001, De La Fuente-Fernández et al 2003, Kang et al 2004, Furukawa et al 2013, Lewthwaite et al 2015, Terbeek et al 2015, Lin et al 2018].
- "Neurodegenerative" parkinsonism, including Parkinson disease associated with *GCH1* pathogenic variants, can be found in families with GTPCH1-deficient DRD; in contrast to findings in "benign" parkinsonism, individuals with "neurodegenerative" parkinsonism or dystonia-parkinsonism associated with *GCH1* pathogenic variants were found to have abnormal $^{18}$F-fluorodopa PET or dopamine transporter (DAT) SPECT imaging [Kikuchi et al 2004, Hjermind et al 2006, Eggers et al 2012, Ceravolo et al 2013, Mencacci et al 2014, Lewthwaite et al 2015, Terbeek et al 2015, Lin et al 2018].

**Myoclonus-dystonia.** Leuzzi et al [2002] reported an individual who demonstrated delayed attainment of early motor milestones and involuntary jerky movements that were responsive to levodopa; myoclonus-dystonia as a phenotype of GTPCH1-deficient DRD was found only in this individual [Furukawa & Rajput 2002, Luciano et al 2009, Wijemanne & Jankovic 2015].

**Non-motor symptoms.** In individuals with GTPCH1-deficient DRD, there are conflicting reports on the frequency of non-motor symptoms. Antelmi et al [2015] analyzed published data on non-motor symptoms in GTPCH1-deficient DRD and stated that overt non-motor symptoms would suggest a diagnosis of DRD plus diseases (other neurotransmitter disorders that may sometimes mimic DRD) rather than of GTPCH1-deficient DRD.

- In rare instances, anxiety, depression, obsessive-compulsive disorder, and/or sleep disturbances have been reported [Hahn et al 2001, Van Hove et al 2006, Trender-Gerhard et al 2009].
- Six of the 23 individuals with GTPCH1-deficient DRD described by Tadic et al [2012] reported one or more non-motor symptoms including depression, anxiety, and migraine. However, a more recent study by the same researchers did not confirm an increased frequency of non-motor symptoms in individuals with *GCH1*-associated DRD [Brüggemann et al 2014].
- Timmers et al [2017] found a higher lifetime prevalence of psychiatric disorders and daytime sleepiness in adults but not in children with GTPCH1-deficient DRD.

**Neuroimaging.** Brain CT and MRI are normal.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies using presynaptic dopaminergic markers have demonstrated normal results in the striatum of DRD and "benign"

parkinsonism due to *GCH1* pathogenic variants [Jeon et al 1998, Kishore et al 1998, O'Sullivan et al 2001, De La Fuente-Fernández et al 2003, Kang et al 2004, Furukawa et al 2013, Lewthwaite et al 2015, Terbeek et al 2015, Lin et al 2018]. These PET and SPECT findings are supported by normal striatal levels of dopa decarboxylase, dopamine transporter, and vesicular monoamine transporter at autopsy of individuals with GTPCH1-deficient DRD, indicating that striatal dopamine nerve terminals are preserved in this disorder [Furukawa et al 1999, Furukawa et al 2002]. Using [$^{11}$C]-raclopride PET, elevated D2-receptor binding in the striatum has been found in GTPCH1-deficient DRD [Kishore et al 1998].

Network analysis of [$^{18}$F]-fluorodeoxyglucose PET images has shown that GTPCH1-deficient DRD is associated with a specific metabolic topography, which is characterized by increases in the dorsal midbrain, cerebellar vermis, and supplementary motor area and by decreases in the putamen as well as lateral premotor and motor cortical regions [Asanuma et al 2005].

**Neuropathology.** Neuropathologic studies demonstrated a normal population of cells with reduced melanin and no evidence of Lewy body formation in the substantia nigra of four individuals with GTPCH1-deficient DRD and one asymptomatic individual with a *GCH1* pathogenic variant [Rajput et al 1994, Furukawa et al 1999, Furukawa et al 2002, Grötzsch et al 2002, Wider et al 2008, Segawa et al 2013].

**Neurochemistry.** Neurochemical data are available for GTPCH1-deficient DRD [Rajput et al 1994, Furukawa et al 1999, Furukawa et al 2002, Furukawa et al 2016].

At autopsy, biopterin (BP) and neopterin (NP) levels in the putamen were substantially lower in two affected individuals (mean: -84% and -62%) than in age-matched normal controls. The caudal portion of the putamen was the striatal subdivision most affected by dopamine loss (-88%). Striatal levels of dopa decarboxylase protein, dopamine transporter, and vesicular monoamine transporter were normal, but tyrosine hydroxylase (TH) protein levels were markedly decreased in the putamen (> -97%). These biochemical findings suggest that striatal dopamine reduction in GTPCH1-deficient DRD is caused by both decreased TH activity resulting from a low cofactor (BH$_4$) level and actual loss of TH protein without nerve terminal loss. This TH protein reduction in the striatum may be caused by diminished regulatory effect of BH$_4$ on the steady-state level of TH molecules [Furukawa et al 1999, Sumi-Ichinose et al 2001, Furukawa et al 2002, Sumi-Ichinose et al 2005].

In an asymptomatic individual with a *GCH1* pathogenic variant, decreases in BP and NP levels in the putamen (-82% and -57%) paralleled those in the two symptomatic individuals who were autopsied [Furukawa et al 2002]. However, TH protein and dopamine levels in the caudal putamen (-52% and -44%) were not as severely affected as in the symptomatic individuals. Consistent with other postmortem brain data suggesting that greater than 60%-80% striatal dopamine loss is necessary for overt motor symptoms to occur [Furukawa 2003, Furukawa 2004], the maximal 44% dopamine reduction in the striatum of the asymptomatic individual with the *GCH1* pathogenic variant was not sufficient to produce any symptoms of GTPCH1-deficient DRD. Striatal levels of serotonin markers (serotonin, TPH protein, serotonin transporter protein [Kish et al 2008]) were normal in GTPCH1-deficient DRD [Furukawa et al 2016].

## Genotype-Phenotype Correlations

No correlations between specific clinical features and types of pathogenic variants in *GCH1* have been established in individuals with GTPCH1-deficient DRD.

## Penetrance

Penetrance in individuals with GTPCH1-deficient DRD has been reported to be higher in females than in males: 87% vs 38% [Furukawa et al 1998b], 100% vs 55% [Steinberger et al 1998], and 87% vs 35% [Segawa et al 2003].

## Nomenclature

The term "DRD" is now used to delineate the following disease entities:

- GTPCH1-deficient DRD (DYT-GCH1, DYT5a; the major form of DRD)
- TH-deficient DRD (DYT-TH, DYT5b; the mild form of TH deficiency [Furukawa et al 2004b])
- SR-deficient DRD (DYT-SPR; the very mild form of SR deficiency [Arrabal et al 2011])

## Prevalence

Dopa-responsive dystonia (DRD) is observed worldwide, and prevalence of DRD (of any cause) in both England and Japan has been estimated at 0.5 per million [Nygaard et al 1993b].

Dobričić et al [2017] found that prevalence of GTPCH1-deficient DRD in Serbia was 2.96 per million (21 symptomatic individuals with *GCH1* pathogenic variants per 7.1 million individuals). There was no evidence for a common founder; however, haplotype analysis indicated that some of the affected individuals had common ancestors.

# Genetically Related (Allelic) Disorders

**Autosomal recessive GTPCH1 deficiency** (tetrahydrobiopterin [BH4]-deficient hyperphenylalaninemia; OMIM 233910). Individuals with autosomal recessive GTPCH1 deficiency usually develop $BH_4$-dependent hyperphenylalaninemia (HPA) in the first six months of life [Niederwieser et al 1984, Ichinose et al 1995, Furukawa 2004]. In these individuals, GTPCH1 enzyme activity is not detectable in liver biopsy specimens. Autosomal recessive GTPCH1 deficiency presents with severe neurologic dysfunction, including convulsions, intellectual disability, swallowing difficulties, developmental motor delay, truncal hypotonia, limb hypertonia, and involuntary movements. In contrast to dominantly inherited GTPCH1-deficient DRD, administration of levodopa, 5-hydroxytryptophan, and $BH_4$ is necessary for recessively inherited GTPCH1-deficient HPA.

**Dystonia with motor delay.** A phenotype of GTPCH1 deficiency (dystonia with motor delay) that is clinically and biochemically intermediate between GTPCH1-deficient DRD (mild) and GTPCH1-deficient HPA (severe) has been found in compound heterozygotes and (rarely) homozygotes for *GCH1* pathogenic variants [Furukawa et al 1998a, Furukawa et al 2003, Nardocci et al 2003, Furukawa et al 2004a, Horvath et al 2008, Trender-Gerhard et al 2009, Bodzioch et al 2011, Opladen et al 2011, Flotats-Bastardas et al 2018]. This phenotype is characterized by developmental motor delay, limb dystonia/hypertonia (with truncal hypotonia) that progresses to generalized dystonia, and absence of overt HPA in infancy. Intriguingly, such compound heterozygotes can be identified even in families with dominantly inherited GTPCH1-deficient DRD [Furukawa et al 1998a, Furukawa et al 2003, Bodzioch et al 2011].

**Contiguous gene deletion syndrome.** Lohmann et al [2017] found chromosome rearrangements, including a large deletion encompassing *GCH1* and adjacent genes, in a family with seemingly non-Mendelian inheritance of DRD associated with digital and eye abnormalities.

# Differential Diagnosis

A dramatic and sustained response to low doses of levodopa in dopa-responsive dystonia (DRD) distinguishes this disorder from cerebral palsy, spastic paraplegia, and all other forms of dystonia, including early-onset primary dystonia (DYT1). (For a differential diagnosis of dystonia, see Dystonia Overview.)

The major differential diagnoses of GTPCH1-deficient DRD are summarized in Table 2 and include TH-deficient DRD, SR-deficient DRD (rare), and early-onset Parkinson disease.

**Table 2.** Disorders to Consider in the Differential Diagnosis of GTPCH1-Deficient DRD

| DiffDx Disorder | Gene(s) | MOI | Clinical Features of DiffDx Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/GTPCH1-Deficient DRD | Distinguishing from GTPCH1-Deficient DRD |
| Tyrosine hydroxylase-deficient DRD (DYT5b; DYT-TH) | TH [1] | AR | • Persons w/mild form of TH deficiency can develop DRD.<br>• Complete responsiveness of symptoms to levodopa<br>• Onset of symptoms generally age 12 mos - 6 yrs<br>• Initial symptoms typically lower-limb dystonia &/or difficulty walking<br>• No delay in psychomotor development | Nl concentrations of BP & NP in CSF [2] |
| Sepiapterin reductase-deficient DRD (DYT-SPR) [3] | SPR | AR [4] | • 1 family reported w/strikingly mild sepiapterin reductase deficiency phenotype (DRD w/o motor & cognitive delay) [5,6]<br>• Sepiapterin reductase deficiency w/mild findings may mimic GTPCH1-deficient DRD.<br>• Remarkable response to levodopa<br>• Diurnal fluctuation of symptoms | • ↑ concentration of BP is assoc w/nl concentration of NP in CSF. [2]<br>• Manifestations of DYT-SPR typically begin earlier than those in GTPCH1-deficient DRD. |

*Table 2. continued from previous page.*

| DiffDx Disorder | Gene(s) | MOI | Clinical Features of DiffDx Disorder | |
| --- | --- | --- | --- | --- |
| | | | Overlapping w/GTPCH1-Deficient DRD | Distinguishing from GTPCH1-Deficient DRD |
| Early-onset Parkinson disease (See Parkin Type of Early-Onset Parkinson Disease, *PINK1* Type of Young-Onset Parkinson Disease, and Parkinson Disease Overview.) | *PINK1* [7] *PRKN* [8] | AR | • In the early course, the clinical differentiation between early-onset Parkinson disease w/dystonia & GTPCH1-deficient DRD is difficult. • Persons w/early-onset Parkinson disease (esp those w/onset age <20 yrs) often develop gait disturbance (attributable to foot dystonia) as the initial symptom. [9] | • ↓ concentration of BP is assoc w/nl concentration of NP in CSF of Parkinson disease (incl parkin type of early-onset Parkinson disease). [2] • PINK1 type of early-onset Parkinson disease often presents w/ abnl behavior &/or psychiatric manifestations. • The most reliable clinical distinction between early-onset Parkinson disease (especially parkin-type) & GTPCH1-deficient DRD is the subsequent occurrence of adverse motor effects of chronic levodopa therapy (wearing-off & on-off phenomena & dopa-induced dyskinesias) in early-onset Parkinson disease. |

AD = autosomal dominant; AR = autosomal recessive; BP = total biopterin; CSF = cerebrospinal fluid; DiffDx = differential diagnosis; DRD = dopa-responsive dystonia; MOI = mode of inheritance; nl = normal; NP = total neopterin; XL = X-linked

*1.* Analyses of both *GCH1* and *TH* demonstrated pathogenic variants in 86% of families with DRD or dystonia with motor delay [Furukawa 2004].

*2.* Both total biopterin (BP) and total neopterin (NP) are reduced in GTPCH1-deficient DRD [Furukawa et al 1996b].

*3.* Sepiapterin reductase deficiency is a rare cause of dopa-responsive dystonia.

*4.* Shalash et al [2017] reported a rare heterozygous *SPR* variant as a cause of dominantly inherited SR-deficient DRD with incomplete penetrance and a common heterozygous dihydrofolate reductase (*DHFR*) variant as a potential modifier, affecting the penetrance of the pathogenic *SPR* variant; the presence of another individual with DRD caused by autosomal dominant SR deficiency was suggested previously [Steinberger et al 2004].

*5.* Arrabal et al [2011]

*6.* Sepiapterin reductase deficiency is usually associated with more severe symptoms [Dill et al 2012, Friedman et al 2012, Friedman 2016].

*7.* Pathogenic variants in *PINK1* account for 1%-7% of individuals with early-onset Parkinson disease. See Parkinson Disease Overview.

*8.* Pathogenic variants in *PRKN* account for up to 50% of individuals with early-onset Parkinson disease. See Parkinson Disease Overview.

*9.* Furukawa et al [1996a]

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 3.** Recommended Evaluations Following Initial Diagnosis in Individuals with GTPCH1-Deficient DRD

| Organ System | Evaluation | Comment |
| --- | --- | --- |
| **Neurologic** | Baseline neurologic exam | Important to assess severity of symptoms prior to starting levodopa administration |
| **Other** | Consultation w/clinical geneticist &/or genetic counselor | |

## Treatment of Manifestations

**Table 4.** Treatment of Manifestations in Individuals with GTPCH1-Deficient DRD

| Manifestation | Treatment | Considerations/Other |
|---|---|---|
| **Dystonia/ parkinsonism** | Levodopa/DCI | • Initial suggested dose [1,2,3] (a levodopa trial):<br>　○ Children <6 yrs: 1-10 mg/kg levodopa/DCI daily, administered in multiple doses [3]<br>　○ Children ≥6 years: 25-50 mg levodopa/DCI 1-3x/day<br>　○ Adults: 50 mg levodopa/DCI 1-3x/day<br>• Changing the dose slowly & by small increments is recommended.<br>• Motor benefit can be recognized immediately or w/in a few days of starting levodopa therapy; full benefit occurs w/in several days to a few months.<br>• Maximum benefit (complete or near-complete responsiveness of symptoms) is generally achieved by <300-400 mg/day of levodopa/DCI. |
| **Transient dyskinesias assoc w/initiation of treatment w/levodopa/DCI** | Reduction of dose of levodopa/DCI | • Transient dyskinesias do not reappear w/later gradual increment in dose.<br>**Note:** Such transient dyskinesias are different from those observed in Parkinson disease during chronic levodopa therapy.<br>• Typically, adverse motor effects of chronic levodopa therapy (motor response fluctuations and dopa-induced dyskinesias) do not occur. |

DCI = decarboxylase inhibitor
*1.* Nygaard et al [1991]
*2.* Furukawa et al [2013]
*3.* Wijemanne & Jankovic [2015]

## Prevention of Secondary Complications

Early diagnosis and therapy (with low doses of levodopa) may prevent transient dyskinesias at initiation of levodopa treatment.

## Surveillance

Examination by a movement disorder specialist at least several times yearly is recommended.

## Agents/Circumstances to Avoid

Discontinuation of levodopa treatment usually results in return of symptoms.

## Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment.

Note: Molecular genetic testing cannot be used to predict the occurrence of symptoms (see Penetrance), age of onset, severity and type of symptoms, or rate of disease progression in family members found to be heterozygous for a *GCH1* pathogenic variant.

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

## Pregnancy Management

In 20 pregnancies reported in 12 affected individuals, levodopa was continued without adverse effect in most. Two women experienced remission resulting in a reduction or cessation of therapy. Two women reported mild deterioration of dystonia; an increase in dose was required in one. No fetal abnormalities were identified [Trender-Gerhard et al 2009].

See MotherToBaby for further information on medication use during pregnancy.

## Therapies Under Investigation

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for 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

GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD) is inherited in an autosomal dominant manner.

## Risk to Family Members

**Parents of a proband**

- Many individuals diagnosed with GTPCH1-deficient DRD have a parent with GTPCH1-deficient DRD or adult-onset parkinsonism caused by a *GCH1* pathogenic variant.
- Some individuals diagnosed with GTPCH1-deficient DRD have the disorder as the result of a *de novo GCH1* pathogenic variant [Furukawa et al 1998b, Wu-Chou et al 2010, Lohmann et al 2017]. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo GCH1* pathogenic variant (i.e., the proband is the only individual in the family known to have GTPCH-deficient DRD).
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of a proband inheriting a pathogenic variant from a parent with germline mosaicism have been reported.
- The family history of some individuals diagnosed with GTPCH1-deficient DRD may appear to be negative because of failure to recognize the disorder in family members, sex-related incomplete penetrance (i.e., higher penetrance in women than in men), phenotypic variability, early death of the parent before the onset of symptoms, or late onset of the disease in the heterozygous parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and molecular genetic testing has been performed on the parents of the proband.

**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 heterozygous for the *GCH1* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Because of sex-related incomplete penetrance, a sib who inherits a *GCH1* pathogenic variant may be asymptomatic.
- If the parents have been tested for the *GCH1* pathogenic variant identified in the proband and the *GCH1* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs of inheriting the variant 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 *GCH1* pathogenic variant but are clinically unaffected, sibs are still at increased risk for GTPCH1-deficient DRD because of the possibility of reduced penetrance in a parent, late onset of symptoms in a parent, or the theoretic possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with GTPCH1-deficient DRD has a 50% chance of inheriting the *GCH1* pathogenic variant. However, because of sex-related incomplete penetrance, it cannot be predicted whether offspring with a *GCH1* pathogenic variant will develop symptoms.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *GCH1* pathogenic variant, his or her family members may be at risk.

## 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.

**Considerations in families with an apparent *de novo* pathogenic variant.** When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

**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 or at risk.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

## Prenatal Testing and Preimplantation Genetic Testing

Once the *GCH1* pathogenic variant has been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic diagnosis for GTPCH1-deficient DRD are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider 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 UK**
  United Kingdom
  **Email:** info@dystonia.org.uk
  dystonia.org.uk

- **Dystonia Medical Research Foundation**
  **Phone:** 312-755-0198; 800-377-DYST (3978)
  **Email:** dystonia@dystonia-foundation.org
  dystonia-foundation.org

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.*

**Table A.** GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|------|------------------|---------|--------------------------|------|---------|
| GCH1 | 14q22.2 | GTP cyclohydrolase 1 | BIOMDBdb : Database of Mutations Causing BH4 Deficiencies and other PND (GCH1) GCH1 database | GCH1 | GCH1 |

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 GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia (View All in OMIM)

| | |
|--------|--------------------------------|
| 128230 | DYSTONIA, DOPA-RESPONSIVE; DRD |
| 600225 | GTP CYCLOHYDROLASE I; GCH1 |

**Gene structure.** *GCH1* is composed of six exons spanning approximately 30 kilobases [Ichinose et al 1995]. There are three cDNA transcript variants with different 3'-ends as a result of alternative splicing; only type 1 cDNA (having the longest coding region) gives rise to the active enzyme. A full-length cDNA clone encoding human GTPCH1 type 1 NM_000161.2 from a pheochromocytoma consists of 2,941 base pairs including a poly(A) tail. For a detailed summary of gene and protein information, see Table A, **Gene**.

**Pathogenic variants.** More than 250 pathogenic variants have been reported in individuals with GTPCH1 deficiencies. See Table A.

**Normal gene product.** *GCH1* encodes GTPCH1 (GTP cyclohydrolase I; EC 3.5.4.16), a 250-amino acid enzyme (NP_000152.1). The enzyme GTPCH1 catalyzes the first step in the biosynthesis of tetrahydrobiopterin ($BH_4$), the essential cofactor for tyrosine hydroxylase (TH), tryptophan hydroxylase (TPH), and phenylalanine hydroxylase (PAH).

**Abnormal gene product.** GTPCH1-deficient DRD is caused by a dominantly inherited pathogenic variant in *GCH1*, resulting in decreased GTPCH1 activity and reduced $BH_4$ biosynthesis. However, this reduction in $BH_4$ biosynthesis does not result in hyperphenylalaninemia and individuals with GTPCH1-deficient DRD seldom

develop overt symptoms relating to a deficit in serotonin [Antelmi et al 2015, Furukawa et al 2016]. The different susceptibility to $BH_4$ depletion among the aromatic amino acid hydroxylases may be explained by differences in Km values of these hydroxylases for $BH_4$, different *GCH1* expression levels in various tissues and neurons, and differences in the degree of regulatory effects of $BH_4$ on stability/expression of TH, TPH, and PAH [Furukawa & Kish 1999].

Human and animal data indicate that striatal dopamine reduction in GTPCH1-deficient DRD is caused not only by decreased TH activity resulting from low biopterin content but also by actual loss of TH protein without nerve terminal loss [Furukawa et al 1999, Sumi-Ichinose et al 2001, Rose et al 2017]. In contrast, serotonin and TPH protein levels were normal in the striatum of GTPCH1-deficient DRD [Furukawa et al 2016].

The same degrees of biopterin reduction associated with the different degrees of TH protein and dopamine reduction in the putamen of symptomatic and asymptomatic individuals with GTPCH1-deficient DRD suggest that there are additional genetic and/or environmental factors modulating the regulatory effect of $BH_4$ on TH stability and that the extent of striatal TH protein loss may be critical in determining clinical outcome [Furukawa et al 2002]. More than 50% reduction in brain biopterin levels in GTPCH1-deficient DRD and results of experimental investigations [Hirano et al 1998, Hirano & Ueno 1999, Hwu et al 2000] suggest a dominant-negative effect in this autosomal dominant disorder. In some instances (e.g., a complete *GCH1* deletion on one allele), an additional abnormality in transcriptional control factors of *GCH1* (including endogenous molecules that can stimulate *GCH1* expression) could be involved in GTPCH1-deficient DRD.

# References

## Literature Cited

Antelmi E, Stamelou M, Liguori R, Bhatia KP. Nonmotor symptoms in dopa-responsive dystonia. Mov Disord Clin Pract. 2015;2:347–56. PubMed PMID: 30363518.

Arrabal L, Teresa L, Sánchez-Alcudia R, Castro M, Medrano C, Gutiérrez-Solana L, Roldán S, Ormazábal A, Pérez-Cerdá C, Merinero B, Pérez B, Artuch R, Ugarte M, Desviat LR. Genotype-phenotype correlations in sepiapterin reductase deficiency. A splicing defect accounts for a new phenotypic variant. Neurogenetics. 2011;12:183–91. PubMed PMID: 21431957.

Asanuma K, Ma Y, Huang C, Carbon-Correll M, Edwards C, Raymond D, Bressman SB, Moeller JR, Eidelberg D. The metabolic pathology of dopa-responsive dystonia. Ann Neurol. 2005;57:596–600. PubMed PMID: 15786454.

Bandmann O, Valente EM, Holmans P, Surtees RA, Walters JH, Wevers RA, Marsden CD, Wood NW. Dopa-responsive dystonia: a clinical and molecular genetic study. Ann Neurol. 1998;44:649–56. PubMed PMID: 9778264.

Bodzioch M, Lapicka-Bodzioch K, Rudzinska M, Pietrzyk JJ, Bik-Multanowski M, Szczudlik A. Severe dystonic encephalopathy without hyperphenylalaninemia associated with an 18-bp deletion within the proximal GCH1 promoter. Mov Disord. 2011;26:337–40. PubMed PMID: 20842687.

Bonafé L, Thöny B, Leimbacher W, Kierat L, Blau N. Diagnosis of dopa-responsive dystonia and other tetrahydrobiopterin disorders by the study of biopterin metabolism in fibroblasts. Clin Chem. 2001;47:477–85. PubMed PMID: 11238300.

Brüggemann N, Stiller S, Tadic V, Kasten M, Münchau A, Graf J, Klein C, Hagenah J. Non-motor phenotype of dopa-responsive dystonia and quality of life assessment. Parkinsonism Relat Disord. 2014;20:428–31. PubMed PMID: 24444533.

Ceravolo R, Nicoletti V, Garavaglia B, Reale C, Kiferle L, Bonuccelli U. Expanding the clinical phenotype of *DYT5* mutations: is multiple system atrophy a possible one? Neurology. 2013;81:301–2. PubMed PMID: 23771491.

Clot F, Grabli D, Cazeneuve C, Roze E, Castelnau P, Chabrol B, Landrieu P, Nguyen K, Ponsot G, Abada M, Doummar D, Damier P, Gil R, Thobois S, Ward AJ, Hutchinson M, Toutain A, Picard F, Camuzat A, Fedirko E, Sân C, Bouteiller D, LeGuern E, Durr A, Vidailhet M, Brice A. Exhaustive analysis of BH4 and dopamine biosynthesis genes in patients with Dopa-responsive dystonia. Brain. 2009;132:1753–63. PubMed PMID: 19491146.

De La Fuente-Fernández R, Furtada S, Guttman M, Furukawa Y, Lee CS, Calne DB, Ruth TJ, Stoessl AJ. VMAT2 binding is elevated in dopa-responsive dystonia: visualizing empty vesicles by PET. Synapse. 2003;49:20–8. PubMed PMID: 12710012.

Dill P, Wagner M, Somerville A, Thöny B, Blau N, Weber P. Paroxysmal stiffening, upward gaze, and hypotonia: hallmarks of sepiapterin reductase deficiency. Neurology. 2012;78:e29–32. PubMed PMID: 22291068.

Dobričić V, Tomić A, Branković V, Kresojević N, Janković M, Westenberger A, Rašić VM, Klein C, Novaković I, Svetel M, Kostić VS. GCH1 mutations are common in Serbian patients with dystonia-parkinsonism: challenging previously reported prevalence rates of DOPA-responsive dystonia. Parkinsonism Relat Disord. 2017;45:81–4. PubMed PMID: 28958832.

Eggers C, Volk AE, Kahraman D, Fink GR, Leube B, Schmidt M, Timmermann L. Are dopa-responsive dystonia and Parkinson's disease related disorders? A case report. Parkinsonism Relat Disord. 2012;18:666–8. PubMed PMID: 22030322.

Flotats-Bastardas M, Hebert E, Raspall-Chaure M, Munell F, Macaya A, Lohmann K. Novel GCH1 compound heterozygosity mutation in infancy-onset generalized dystonia. Neuropediatrics. 2018;49:296–7. PubMed PMID: 29471552.

Friedman J, Roze E, Abdenur JE, Chang R, Gasperini S, Saletti V, Wali GM, Eiroa H, Neville B, Felice A, Parascandalo R, Zafeiriou DI, Arrabal-Fernandez L, Dill P, Eichler FS, Echenne B, Gutierrez-Solana LG, Hoffmann GF, Hyland K, Kusmierska K, Tijssen MA, Lutz T, Mazzuca M, Penzien J, Poll-The BT, Sykut-Cegielska J, Szymanska K, Thöny B, Blau N. Sepiapterin reductase deficiency: a treatable mimic of cerebral palsy. Ann Neurol. 2012;71:520–30. PubMed PMID: 22522443.

Friedman JR. What is not in the name? Dopa-responsive dystonia may respond to more than L-dopa. Pediatr Neurol. 2016;59:76–80. PubMed PMID: 27080360.

Furukawa Y. Genetics and biochemistry of dopa-responsive dystonia: significance of striatal tyrosine hydroxylase protein loss. Adv Neurol. 2003;91:401–10. PubMed PMID: 12442699.

Furukawa Y. Update on dopa-responsive dystonia: locus heterogeneity and biochemical features. Adv Neurol. 2004;94:127–38. PubMed PMID: 14509665.

Furukawa Y, Filiano JJ, Kish SJ. Amantadine for levodopa-induced choreic dyskinesia in compound heterozygotes for GCH1 mutations. Mov Disord. 2004a;19:1256–8. PubMed PMID: 15389992.

Furukawa Y, Guttman M, Kish SJ. Dopa-responsive dystonia. In: Frucht SJ, Fahn S, eds. *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment.* Totowa, NJ: Humana Press; 2005:209-29

Furukawa Y, Guttman M, Nakamura S, Kish SJ. Dopa-responsive dystonia. In: Frucht SJ, ed. *Movement Disorder Emergencies: Diagnosis and Treatment.* 2 ed. New York, NY: Springer (Humana Press); 2013:319-40

Furukawa Y, Guttman M, Sparagana SP, Trugman JM, Hyland K, Wyatt P, Lang AE, Rouleau GA, Shimadzu M, Kish SJ. Dopa-responsive dystonia due to a large deletion in the GTP cyclohydrolase I gene. Ann Neurol. 2000;47:517–20. PubMed PMID: 10762165.

Furukawa Y, Guttman M, Wong H, Farrell SA, Furtado S, Kish SJ. Serum prolactin in symptomatic and asymptomatic dopa-responsive dystonia due to a GCH1 mutation. Neurology. 2003;61:269–70. PubMed PMID: 12874420.

Furukawa Y, Kapatos G, Haycock JW, Worsley J, Wong H, Kish SJ, Nygaard TG. Brain biopterin and tyrosine hydroxylase in asymptomatic dopa-responsive dystonia. Ann Neurol. 2002;51:637–41. PubMed PMID: 12112113.

Furukawa Y, Kish SJ. Dopa-responsive dystonia: recent advances and remaining issues to be addressed. Mov Disord. 1999;14:709–15. PubMed PMID: 10495030.

Furukawa Y, Kish SJ. Parkinsonism in GTP cyclohydrolase I-deficient DOPA-responsive dystonia. Brain. 2015;138:e351. PubMed PMID: 25416181.

Furukawa Y, Kish SJ, Bebin EM, Jacobson RD, Fryburg JS, Wilson WG, Shimadzu M, Hyland K, Trugman JM. Dystonia with motor delay in compound heterozygotes for GTP- cyclohydrolase I gene mutations. Ann Neurol. 1998a;44:10–16. PubMed PMID: 9667588.

Furukawa Y, Kish SJ, Fahn S. Dopa-responsive dystonia due to mild tyrosine hydroxylase deficiency. Ann Neurol. 2004b;55:147–8. PubMed PMID: 14705130.

Furukawa Y, Lang AE, Trugman JM, Bird TD, Hunter A, Sadeh M, Tagawa T, St George-Hyslop PH, Guttman M, Morris LW, Hornykiewicz O, Shimadzu M, Kish SJ. Gender-related penetrance and de novo GTP-cyclohydrolase I gene mutations in dopa-responsive dystonia. Neurology. 1998b;50:1015–20. PubMed PMID: 9566388.

Furukawa Y, Mizuno Y, Narabayashi H. Early-onset parkinsonism with dystonia. Clinical and biochemical differences from hereditary progressive dystonia or DOPA-responsive dystonia. Adv Neurol. 1996a;69:327–37. PubMed PMID: 8615147.

Furukawa Y, Nygaard TG, Gutlich M, Rajput AH, Pifl C, DiStefano L, Chang LJ, Price K, Shimadzu M, Hornykiewicz O, Haycock JW, Kish SJ. Striatal biopterin and tyrosine hydroxylase protein reduction in dopa-responsive dystonia. Neurology. 1999;53:1032–41. PubMed PMID: 10496263.

Furukawa Y, Rajput AH. Inherited myoclonus-dystonia: how many causative genes and clinical phenotypes? Neurology. 2002;59:1130–1. PubMed PMID: 12391338.

Furukawa Y, Rajput AH, Tong J, Tomizawa Y, Hornykiewicz O, Kish SJ. A marked contrast between serotonergic and dopaminergic changes in dopa-responsive dystonia. Neurology. 2016;87:1060–1. PubMed PMID: 27488599.

Furukawa Y, Shimadzu M, Rajput AH, Shimizu Y, Tagawa T, Mori H, Yokochi M, Narabayashi H, Hornykiewicz O, Mizuno Y, Kish SJ. GTP-cyclohydrolase I gene mutations in hereditary progressive amd dopa-responsive dystonia. Ann Neurol. 1996b;39:609–17. PubMed PMID: 8619546.

Grimes DA, Barclay CL, Duff J, Furukawa Y, Lang AE. Phenocopies in a large GCH1 mutation positive family with dopa responsive dystonia: confusing the picture? J Neurol Neurosurg Psychiatry. 2002;72:801–4. PubMed PMID: 12023430.

Grötzsch H, Pizzolato GP, Ghika J, Schorderet D, Vingerhoets FJ, Landis T, Burkhard PR. Neuropathology of a case of dopa-responsive dystonia associated with a new genetic locus, DYT14. Neurology. 2002;58:1839–42. PubMed PMID: 12084887.

Hagenah J, Saunders-Pullman R, Hedrich K, Kabakci K, Habermann K, Wiegers K, Mohrmann K, Lohnau T, Raymond D, Vieregge P, Nygaard T, Ozelius LJ, Bressman SB, Klein C. High mutation rate in dopa-responsive dystonia: detection with comprehensive GCHI screening. Neurology. 2005;64:908–11. PubMed PMID: 15753436.

Hahn H, Trant MR, Brownstein MJ, Harper RA, Milstien S, Butler IJ. Neurologic and psychiatric manifestations in a family with a mutation in exon 2 of the guanosine triphosphate-cyclohydrolase gene. Arch Neurol. 2001;58:749–55. PubMed PMID: 11346370.

Hirano M, Ueno S. Mutant GTP cyclohydrolase I in autosomal dominant dystonia and recessive hyperphenylalaninemia. Neurology. 1999;52:182–4. PubMed PMID: 9921872.

Hirano M, Yanagihara T, Ueno S. Dominant negative effect of GTP cyclohydrolase I mutations in dopa-responsive hereditary progressive dystonia. Ann Neurol. 1998;44:365–71. PubMed PMID: 9749603.

Hjermind LE, Johannsen LG, Blau N, Wevers RA, Lucking C-B, Hertz JM, Friberg L, Regeur L, Nielsen JE, Sørensen SA. Dopa-responsive dystonia and early-onset Parkinson's disease in a patient with GTP cyclohydrolase I deficiency? Mov Disord. 2006;21:679–82. PubMed PMID: 16267845.

Horvath GA, Stockler-Ipsiroglu SG, Salvarinova-Zivkovic R, Lillquist YP, Connolly M, Hyland K, Blau N, Rupar T, Waters PJ. Autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia: evidence of a phenotypic continuum between dominant and recessive forms. Mol Genet Metab. 2008;94:127–31. PubMed PMID: 18276179.

Hwu W-L, Chiou YW, Lai SY, Lee YM. Dopa-responsive dystonia is induced by a dominant-negative mechanism. Ann Neurol. 2000;48:609–13. PubMed PMID: 11026444.

Ichinose H, Ohye T, Matsuda Y, Hori T, Blau N, Burlina A, Rouse B, Matalon R, Fujita K, Nagatsu T. Characterization of mouse and human GTP cyclohydrolase I genes. Mutations in patients with GTP cyclohydrolase I deficiency. J Biol Chem. 1995;270:10062–71. PubMed PMID: 7730309.

Ichinose H, Ohye T, Takahashi E, Seki N, Hori T, Segawa M, Nomura Y, Endo K, Tanaka H, Tsuji S, Fujita K, Nagatsu T. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet. 1994;8:236–42. PubMed PMID: 7874165.

Jeon BS, Jeong JM, Park SS, Kim JM, Chang YS, Song HC, Kim KM, Yoon KY, Lee MC, Lee SB. Dopamine transporter density measured by [123I]beta-CIT single-photon emission computed tomography is normal in dopa-responsive dystonia. Ann Neurol. 1998;43:792–800. PubMed PMID: 9629849.

Kang J-H, Kang S-Y, Kang H-K, Koh Y-S, Im J-H, Lee MC. A novel missense mutation of the GTP cyclohydrolase I gene in a Korean family with hereditary progressive dystonia/dopa-responsive dystonia. Brain Dev. 2004;26:287–91. PubMed PMID: 15165667.

Kikuchi A, Takeda A, Fujihara K, Kimpara T, Shiga Y, Tanji H, Nagai M, Ichinose H, Urano F, Okamura N, Arai H, Itoyama Y. Arg(184)His mutant GTP cyclohydrolase I, causing recessive hyperphenylalaninemia, is responsible for dopa-responsive dystonia with parkinsonism: a case report. Mov Disord. 2004;19:590–3. PubMed PMID: 15133828.

Kish SJ, Tong J, Hornykiewicz O, Rajput A, Chang L-J, Guttman M, Furukawa Y. Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease. Brain. 2008;131:120–31. PubMed PMID: 17956909.

Kishore A, Nygaard TG, de la Fuente-Fernandez R, Naini AB, Schulzer M, Mak E, Ruth TJ, Calne DB, Snow BJ, Stoessl AJ. Striatal D2 receptors in symptomatic and asymptomatic carriers of dopa-responsive dystonia measured with [11C]-raclopride and positron-emission tomography. Neurology. 1998;50:1028–32. PubMed PMID: 9566390.

Leuzzi V, Carducci C, Carducci C, Cardona F, Artiola C, Antonozzi I. Autosomal dominant GTP-CH deficiency presenting as a dopa-responsive myoclonus-dystonia syndrome. Neurology. 2002;59:1241–3. PubMed PMID: 12391354.

Lewthwaite AJ, Lambert TD, Rolfe EB, Olgiati S, Quadri M, Simons EJ, Morrison KE, Bonifati V, Nicholl DJ. Novel GCH1 variant in Dopa-responsive dystonia and Parkinson's disease. Parkinsonism Relat Disord. 2015;21:394–7. PubMed PMID: 25634433.

Lin L, Ye J, Zhang H, Han ZF, Zheng ZH. Degree of dopaminergic degeneration measured by 99mTc-TRODAT-1 SPECT/CT imaging. Neural Regen Res. 2018;13:1281–7. PubMed PMID: 30028339.

Liu X, Zhang SS, Fang DF, Ma MY, Guo XY, Yang Y, Shang HF. GCH1 mutation and clinical study of Chinese patients with dopa-responsive dystonia. Mov Disord. 2010;25:447–51. PubMed PMID: 20108370.

Lohmann K, Redin C, Tönnies H, Bressman SB, Subero JIM, Wiegers K, Hinrichs F, Hellenbroich Y, Rakovic A, Raymond D, Ozelius LJ, Schwinger E, Siebert R, Talkowski ME, Saunders-Pullman R, Klein C. Complex and dynamic chromosomal rearrangements in a family with seemingly non-Mendelian inheritance of dopa-responsive dystonia. JAMA Neurol. 2017;74:806–12. PubMed PMID: 28558098.

Luciano MS, Ozelius L, Sims K, Raymond D, Liu L, Saunders-Pullman R. Responsiveness to levodopa in epsilon-sarcoglycan deletions. Mov Disord. 2009;24:425–8. PubMed PMID: 19133653.

Mencacci NE, Isaias IU, Reich MM, Ganos C, Plagnol V, Polke JM, Bras J, Hersheson J, Stamelou M, Pittman AM, Noyce AJ, Mok KY, Opladen T, Kunstmann E, Hodecker S, Münchau A, Volkmann J, Samnick S, Sidle K, Nanji T, Sweeney MG, Houlden H, Batla A, Zecchinelli AL, Pezzoli G, Marotta G, Lees A, Alegria P, Krack P, Cormier-Dequaire F, Lesage S, Brice A, Heutink P, Gasser T, Lubbe SJ, Morris HR, Taba P, Koks S, Majounie E, Raphael Gibbs J, Singleton A, Hardy J, Klebe S, Bhatia KP, Wood NW, et al. Parkinson's disease in GTP cyclohydrolase 1 mutation carriers. Brain. 2014;137:2480–92. PubMed PMID: 24993959.

Nardocci N, Zorzi G, Blau N, Fernandez Alvarez E, Sesta M, Angelini L, Pannacci M, Invernizzi F, Garavaglia B. Neonatal dopa-responsive extrapyramidal syndrome in twins with recessive GTPCH deficiency. Neurology. 2003;60:335–7. PubMed PMID: 12552057.

Niederwieser A, Blau N, Wang M, Joller P, Atares M, Cardesa-Garcia J. GTP cyclohydrolase I deficiency, a new enzyme defect causing hyperphenylalaninemia with neopterin, biopterin, dopamine, and serotonin deficiencies and muscular hypotonia. Eur J Pediatr. 1984;141:208–14. PubMed PMID: 6734669.

Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: long-term treatment response and prognosis. Neurology. 1991;41:174–81. PubMed PMID: 1899474.

Nygaard TG, Snow BJ, Fahn S, Calne DB. Dopa-responsive dystonia: clinical characteristics and definition. In: Segawa M, ed. *Hereditary Progressive Dystonia with Marked Diurnal Fluctuation*. NY: Parthenon Publishing; 1993a:21-35.

Nygaard TG, Takahashi H, Heiman GA, Snow BJ, Fahn S, Calne DB. Long-term treatment response and fluorodopa positron emission tomographic scanning of parkinsonism in a family with dopa-responsive dystonia. Ann Neurol. 1992;32:603–8. PubMed PMID: 1449240.

Nygaard TG, Wilhelmsen KC, Risch NJ, Brown DL, Trugman JM, Gilliam TC, Fahn S, Weeks DE. Linkage mapping of dopa-responsive dystonia (DRD) to chromosome 14q. Nat Genet. 1993b;5:386–91. PubMed PMID: 8298648.

O'Sullivan JD, Costa DC, Gacinovic S, Lees AJ. SPECT imaging of the dopamine transporter in juvenile-onset dystonia. Neurology. 2001;56:266–7. PubMed PMID: 11160970.

Opladen T, Hoffmann G, Hörster F, Hinz AB, Neidhardt K, Klein C, Wolf N. Clinical and biochemical characterization of patients with early infantile onset of autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia. Mov Disord. 2011;26:157–61. PubMed PMID: 20818608.

Postuma RB, Furukawa Y, Rogaeva E, St George-Hyslop PH, Farrer MJ, Lang AE. Dopa-responsive dystonia presenting with prominent isolated bilateral resting leg tremor: evidence for a role of parkin? Mov Disord. 2003;18:1070–2.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Rajput AH, Gibb WR, Zhong XH, Shannak KS, Kish S, Chang LG, Hornykiewicz O. Dopa-responsive dystonia: pathological and biochemical observations in a case. Ann Neurol. 1994;35:396–402. PubMed PMID: 7908789.

Rose SJ, Harrast P, Donsante C, Fan X, Joers V, Tansey MG, Jinnah HA, Hess EJ. Parkinsonism without dopamine neuron degeneration in aged L-dopa-responsive dystonia knockin mice. Mov Disord. 2017;32:1694–700. PubMed PMID: 28949038.

Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. Adv Neurol. 1976;14:215–33. PubMed PMID: 945938.

Segawa M, Nomura Y. Hereditary progressive dystonia with marked diurnal fluctuation. In: Segawa M, ed. *Hereditary Progressive Dystonia with Marked Diurnal Fluctuation*. New York: Parthenon Publishing; 1993:3-19.

Segawa M, Nomura Y, Hayashi M. Dopa-responsive dystonia is caused by particular impairment of nigrostriatal dopamine neurons different from those involved in Parkinson disease: evidence observed in studies on Segawa disease. Neuropediatrics. 2013;44:61–6. PubMed PMID: 23468278.

Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol. 2003;54 Suppl 6:S32–45. PubMed PMID: 12891652.

Shalash AS, Rösler TW, Müller SH, Salama M, Deuschl G, Müller U, Opladen T, Petersen BS, Franke A, Hopfner F, Kuhlenbäumer G, Höglinger GU. c. 207C>G mutation in sepiapterin reductase causes autosomal dominant dopa-responsive dystonia. Neurol Genet. 2017;3:e197. PubMed PMID: 29147684.

Steinberger D, Blau N, Goriuonov D, Bitsch J, Zuker M, Hummel S, Müller U. Heterozygous mutation in 5'-untranslated region of sepiapterin reductase gene (SPR) in a patient with dopa-responsive dystonia. Neurogenetics. 2004;5:187–90. PubMed PMID: 15241655.

Steinberger D, Weber Y, Korinthenberg R, Deuschl G, Benecke R, Martinius J, Muller U. High penetrance and pronounced variation in expressivity of GCH1 mutations in five families with dopa-responsive dystonia. Ann Neurol. 1998;43:634–9. PubMed PMID: 9585358.

Sumi-Ichinose C, Urano F, Kuroda R, Ohye T, Kojima M, Tazawa M, Shiraishi H, Hagino Y, Nagatsu T, Nomura T, Ichinose H. Catecholamines and serotonin are differently regulated by tetrahydrobiopterin: a study from 6-pyruvoyltetrahydropterin synthase knockout mice. J Biol Chem. 2001;276:41150–60. PubMed PMID: 11517215.

Sumi-Ichinose C, Urano F, Shimomura A, Sato T, Ikemoto K, Shiraishi H, Senda T, Ichinose H, Nomura T. Genetically rescued tetrahydrobiopterin-depleted mice survive with hyperphenylalaninemia and region-specific monoaminergic abnormalities. J Neurochem. 2005;95:703–14. PubMed PMID: 16135092.

Tadic V, Kasten M, Brüggemann N, Stiller S, Hagenah J, Klein C. Dopa-responsive dystonia revisited: diagnostic delay, residual signs, and nonmotor signs. Arch Neurol. 2012;69:1558–62. PubMed PMID: 22986512.

Terbeek J, Hermans S, Van Laere K, Vandenberghe W. Parkinson's disease in GTP cyclohydrolase 1 mutation carriers. Brain. 2015;138:e350. PubMed PMID: 25433916.

Timmers ER, Kuiper A, Smit M, Bartels AL, Kamphuis DJ, Wolf NI, Poll-The BT, Wassenberg T, Peeters EAJ, de Koning TJ, Tijssen MAJ. Non-motor symptoms and quality of life in dopa-responsive dystonia patients. Parkinsonism Relat Disord. 2017;45:57–62. PubMed PMID: 29066160.

Trender-Gerhard I, Sweeney MG, Schwingenschuh P, Mir P, Edwards MJ, Gerhard A, Polke JM, Hanna MG, Davis MB, Wood NW, Bhatia KP. Autosomal-dominant GTPCH1-deficient DRD: clinical characteristics and long-term outcome of 34 patients. J Neurol Neurosurg Psychiatry. 2009;80:839–45. PubMed PMID: 19332422.

Van Hove JL, Steyaert J, Matthijs G, Legius E, Theys P, Wevers R, Romstad A, Moller LB, Hedrich K, Goriounov D, Blau N, Klein C, Casaer P. Expanded motor and psychiatric phenotype in autosomal dominant Segawa

syndrome due to GTP cyclohydrolase deficiency. J Neurol Neurosurg Psychiatry. 2006;77:18–23. PubMed PMID: 16361586.

Wider C, Melquist S, Hauf M, Solida A, Cobb SA, Kachergus JM, Gass J, Coon KD, Baker M, Cannon A, Stephan DA, Schorderet DF, Ghika J, Burkhard PR, Kapatos G, Hutton M, Farrer MJ, Wszolek ZK, Vingerhoets FJG. Study of a Swiss dopa-responsive dystonia family with a deletion in GCH1: redefining DYT14 as DYT5. Neurology. 2008;70:1377–83. PubMed PMID: 17804835.

Wijemanne S, Jankovic J. Dopa-responsive dystonia - clinical and genetic heterogeneity. Nat Rev Neurol. 2015;11:414–24. PubMed PMID: 26100751.

Wu-Chou YH, Yeh TH, Wang CY, Lin JJ, Huang CC, Chang HC, Lai SC, Chen RS, Weng YH, Huang CL, Lu CS. High frequency of multiexonic deletion of the GCH1 gene in a Taiwanese cohort of dopa-response dystonia. Am J Med Genet B Neuropsychiatr Genet. 2010;153B:903–8. PubMed PMID: 20082337.

Yoshino H, Nishioka K, Li Y, Oji Y, Oyama G, Hatano T, Machida Y, Shimo Y, Hayashida A, Ikeda A, Mogushi K, Shibagaki Y, Hosaka A, Iwanaga H, Fujitake J, Ohi T, Miyazaki D, Sekijima Y, Oki M, Kusaka H, Fujimoto KI, Ugawa Y, Funayama M, Hattori N. GCH1 mutations in dopa-responsive dystonia and Parkinson's disease. J Neurol. 2018;265:1860–70. PubMed PMID: 29948246.

Zirn B, Steinberger D, Troidl C, Brockmann K, von der Hagen M, Feiner C, Henke L, Muller U. Frequency of GCH1 deletions in dopa-responsive dystonia. J Neurol Neurosurg Psychiatry. 2008;79:183–6. PubMed PMID: 17898029.

# Chapter Notes

## Revision History

- 24 January 2019 (ha) Comprehensive update posted live
- 5 March 2015 (me) Comprehensive update posted live
- 3 May 2012 (yf) Revision: information about autosomal recessive sepiapterin reductase (SR)-deficient DRD added
- 6 October 2011 (me) Comprehensive update posted live
- 4 August 2009 (me) Comprehensive update posted live
- 15 February 2007 (me) Comprehensive update posted live. Change in scope of Dopa-Responsive Dystonia chapter: GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia (i.e., this chapter) and Tyrosine Hydroxylase-Deficient Dopa-Responsive Dystonia (Tyrosine Hydroxylase Deficiency)
- 15 June 2004 (me) Comprehensive update posted live
- 5 March 2004 (me) Comprehensive update posted live
- 21 February 2002 (me) Review posted live
- 30 June 2001 (yf) Original submission

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