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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. • Complete responsiveness of symptoms to levodopa • Onset of symptoms generally age 12 mos - 6 yrs • Initial symptoms typically lower-limb dystonia &/or difficulty walking • 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] • Sepiapterin reductase deficiency w/mild findings may mimic GTPCH1-deficient DRD. • Remarkable response to levodopa • Diurnal fluctuation of symptoms	• ↑ concentration of BP is assoc w/nl concentration of NP in CSF. [2] • 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): ◦ Children <6 yrs: 1-10 mg/kg levodopa/DCI daily, administered in multiple doses [3] ◦ Children ≥6 years: 25-50 mg levodopa/DCI 1-3x/day ◦ Adults: 50 mg levodopa/DCI 1-3x/day • Changing the dose slowly & by small increments is recommended. • 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. • 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. **Note:** Such transient dyskinesias are different from those observed in Parkinson disease during chronic levodopa therapy. • 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 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
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Fax: 312-803-0138
  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.

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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
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