



## DYT-GNAL

Synonyms: DYT25, GNAL-Related Dystonia

Angela B Deuschländer, MD<sup>1</sup> and Zbigniew K Wszolek, MD<sup>2</sup>

Created: January 3, 2019.

## Summary

### Clinical characteristics

DYT-GNAL caused by a heterozygous *GNAL* pathogenic variant has been reported in more than 60 individuals to date. It is characterized by adult-onset isolated dystonia (i.e., no neurologic abnormalities other than tremor are evident on neurologic examination). The dystonia is most commonly focal and segmental, and rarely generalized. Dystonia is typically cervical in onset and commonly progresses to the cranial region (oromandibular/jaw, larynx, eyelids) and/or to one arm. Tremor reported in DYT-GNAL may be dystonic (i.e., occurring in a body part that shows at least minimal signs of dystonia) and may precede or follow the onset of dystonia. Intra- and interfamilial variability is considerable.

DYT-GNAL caused by biallelic *GNAL* pathogenic variants, reported to date in two sibs from a consanguineous family, is characterized by mild intellectual disability and childhood-onset hypertonia that progresses to generalized dystonia.

### Diagnosis/testing

The diagnosis of DYT-GNAL is established in a proband with either isolated dystonia and a heterozygous *GNAL* pathogenic variant identified by molecular genetic testing or a more complex phenotype (intellectual disability, hypertonia, and generalized dystonia) and biallelic *GNAL* pathogenic variants.

### Management

*Treatment of manifestations:* While oral medication is usually the initial treatment of dystonia, experience in DYT-GNAL specifically is limited. Botulinum toxin intramuscular injections have improved cervical dystonia and dystonia affecting other sites in some patients with DYT-GNAL – as well as dystonia in selected muscles in patients with generalized dystonia. Deep-brain stimulation of the globus pallidus internus has been effective in a few patients with DYT-GNAL. Physical therapy may help prevent joint contractures and spine deformities. Treatment of depression and anxiety, commonly associated with cervical dystonia, is per standard practice.

---

**Author Affiliations:** 1 Departments of Neurology, Neuroscience, and Clinical Genomics, Mayo Clinic, Jacksonville, Florida; Email: [deutschlander.angela@mayo.edu](mailto:deutschlander.angela@mayo.edu). 2 Department of Neurology, Mayo Clinic, Jacksonville, Florida; Email: [wszolek.zbigniew@mayo.edu](mailto:wszolek.zbigniew@mayo.edu).

*Surveillance:* Follow up with a neurologist specializing in movement disorders several times a year is recommended to monitor for worsening of dystonia, development of new manifestations, and treatment effectiveness and side effects.

*Agents/circumstances to avoid:* Dystonia of limbs can worsen if affected limbs are casted or braced. Similarly, neck collars should be avoided in persons with cervical dystonia.

## Genetic counseling

DYT-GNAL is typically inherited in an autosomal dominant manner (to date, 1 family with autosomal recessive inheritance of DYT-GNAL has been reported).

Most individuals with autosomal dominant DYT-GNAL have an affected parent; the proportion of DYT-GNAL caused by a *de novo* pathogenic variant is unknown. Each child of an individual with DYT-GNAL has a 50% chance of inheriting the *GNAL* pathogenic variant; reduced penetrance and large intrafamilial clinical variability have been reported. Once the *GNAL* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

## Diagnosis

No formal diagnostic criteria have been established for DYT-GNAL.

## Suggestive Findings

DYT-GNAL **should be considered** in individuals with the following clinical findings, neuroimaging findings, and family history.

## Clinical Findings

**Dystonia** is defined as involuntary contractions of muscles that lead to abnormal movements and abnormal postures. Dystonic movements are typically repetitive, patterned, and often twisting.

DYT-GNAL is characterized by the following:

- Isolated; no neurologic abnormalities other than tremor evident on neurologic examination
- Age at onset typically in adulthood; rarely in childhood [Fuchs et al 2013, LeDoux et al 2016, Masuho et al 2016]
- Most commonly focal and segmental; rarely generalized [Fuchs et al 2013, Miao et al 2013, Vemula et al 2013, Masuho et al 2016]; and rarely laryngeal dystonia only [Putzel et al 2016]
- Onset typically in the cervical region and commonly progressing to the cranial region (oromandibular/jaw, larynx, blepharospasm) and/or to one arm

## Neuroimaging Studies

Brain magnetic resonance imaging and computed tomography results are normal, showing no structural intracranial lesions that could be considered a cause of acquired dystonia.

## Family History

Consistent with autosomal dominant inheritance (i.e., includes both familial cases and simplex cases [a single occurrence in a family]). The one exception is autosomal recessive inheritance reported in two Turkish sibs [Masuho et al 2016].

## Establishing the Diagnosis

The diagnosis of DYT-GNAL is **established** in a proband with isolated dystonia and a heterozygous *GNAL* pathogenic variant identified by molecular genetic testing (see Table 1).

A single report found a homozygous *GNAL* pathogenic variant, associated with a more complex and more severe phenotype (intellectual disability, hypertonia, and generalized dystonia) with age at onset in infancy [Masuho et al 2016].

## Molecular Genetic Testing

Because the phenotype of DYT-GNAL is indistinguishable from many other inherited disorders with dystonia, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**. Note: Single-gene testing (sequence analysis of *GNAL*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A dystonia multigene panel** that includes *GNAL* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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) Multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **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 DYT-GNAL

Gene <sup>1</sup>	Method	Proportion of Proband with a Pathogenic Variant <sup>2</sup> Detectable by Method
GNAL	Sequence analysis <sup>3</sup>	32/32 <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	None reported to date <sup>6</sup>

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. Fuchs et al [2013], Miao et al [2013], Vemula et al [2013], Dobričić et al [2014], Dufke et al [2014], Kumar et al [2014], Saunders-Pullman et al [2014], Zech et al [2014], Ziegen et al [2014], Zech et al [2015], Carecchio et al [2016], Dos Santos et al [2016], LeDoux et al [2016], Masuho et al [2016], Putzel et al [2016]

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.

6. Kumar et al [2014] used quantitative PCR of GNAL exon 9 to test for whole-gene deletions/duplications in 318 patients with dystonia; no deletions or duplications were found. No further data on detection rates of gene-targeted deletion/duplication analyses are available.

## Clinical Characteristics

### Clinical Description

DYT-GNAL is a mostly adult-onset isolated dystonia (in which no additional neurologic abnormalities other than tremor are evident on neurologic examination). The dystonia is most commonly focal and segmental, and rarely generalized. Dystonia is typically cervical in onset and commonly progresses to the cranial region (oromandibular/jaw, larynx, eyelids) and/or to one arm. DYT-GNAL tremor may be dystonic (i.e., occurring in a body part that shows at least minimal signs of dystonia) and may precede or follow the onset of dystonia).

Since its original description [Fuchs et al 2013, Vemula et al 2013], DYT-GNAL has been reported in:

- 62 individuals with a heterozygous *GNAL* pathogenic variant [Miao et al 2013, Dobričić et al 2014, Dufke et al 2014, Kumar et al 2014, Saunders-Pullman et al 2014, Zech et al 2014, Ziegen et al 2014, Zech et al 2015, Carecchio et al 2016, Dos Santos et al 2016, LeDoux et al 2016, Putzel et al 2016];
- Two sibs (from a consanguineous union) homozygous for a *GNAL* pathogenic variant [Masuho et al 2016].

### Heterozygous DYT-GNAL

**Age of onset.** In the 28 individuals first described by Fuchs et al [2013], mean age at disease onset was 31.3 years ( $\pm$  12.4 years); range: 7-54 years. Mean age at disease onset for an additional 29 individuals was 42.5 years ( $\pm$  13.2 years); range: 8-68 years.

**Initial body region involved.** DYT-GNAL most frequently starts as focal dystonia involving the neck (cervical dystonia, torticollis) with or without head tremor. Initial presentation can also occur in the oromandibular region or in the larynx (spasmodic dysphonia).

Data available on 56 individuals revealed the following regarding the first body region affected by dystonia:

- Cervical region: 78%
- Larynx: 9%
- Oromandibular region/jaw/tongue: 7%

- Leg: two individuals
- Face: one individual

Other initial manifestations were dystonic arm tremor (2 individuals) and isolated head tremor (1 individual).

**Type of dystonia.** Dystonia may remain focal (e.g., cervical dystonia is the only manifestation) or become segmental (e.g., cervical dystonia spreads to the cranial region or an upper limb). The trunk and the legs are rarely affected. Generalized dystonia is far less common.

In a study of 28 individuals, dystonia remained focal in 12 and became segmental in 13 or generalized in three [Fuchs et al 2013]. The phenotypic variability within families was wide.

In 62 individuals the sites involved during the disease course included the following:

- Cervical dystonia: 84%
- Oromandibular dystonia including dystonia of the jaw and tongue: 29%
- Upper facial dystonia including blepharospasm: 22.6%
- Dystonia of the arm or isolated dystonic tremor of the arm: 29%
- Laryngeal dystonia: 21%
- Truncal dystonia: 16%
- Dystonia in a leg: 8%

Tremor was also frequently reported, most commonly as dystonic head and/or arm tremor.

Speech involvement was reported in 44% of 28 patients [Fuchs et al 2013].

**Dystonic tremor.** In a family with four affected individuals in whom the most disabling manifestation was tremor, age at onset in two family members was 36 and 58 years [Carecchio et al 2016]. EMG performed in two of the four showed the tremor to be dystonic. Other findings included focal speech-induced dystonia (likely due to intermittent oromandibular dystonia), isolated dystonic tremor of the right arm only, and jerky cervical dystonia with laryngeal involvement and arm tremor.

**Hyposmia.** In one family with five affected individuals who were alive and available for a neurologic examination, two had hand-forearm dystonia and three had anosmia or microsmia [Vemula et al 2013]. It is possible that microsmia is more common than reported to date, since the olfactory dysfunction identified in this family was not self-reported but required specialized testing.

**Psychiatric comorbidities.** While there are insufficient data on psychiatric manifestations in DYT-GNAL, it is known that psychiatric comorbidities, mainly depression and anxiety, are common in individuals with (cervical) dystonia. Of note, some medications may cause psychiatric side effects (see Management, Treatment of Manifestations).

**Intrafamilial phenotypic variability** includes age at disease onset, initial body region involved, type of dystonia (focal versus segmental versus generalized), sites involved during the course of the disease, disease severity, and rate of progression [Fuchs et al 2013, Carecchio et al 2016]. In one family the following was observed in five living affected individuals who were examined: age at onset 45 to 63 years; generalized dystonia involving the arms, legs, and neck (1 individual), focal dystonia (torticollis) without progression (1 individual), and segmental dystonia (3 individuals); laryngeal involvement (3 individuals); and blepharospasm (1 individual) [Vemula et al 2013]. Of note, no information was available on the three other deceased individuals who were likely affected.

## Biallelic DYT-GNAL

To date the only individuals known to have biallelic DYT-GNAL are two sibs from a consanguineous Turkish family reported by Masuho et al [2016], whose phenotype was more severe than that of heterozygous DYT-

GNAL. The initial finding was increased muscle tone at age one year that progressed to generalized dystonia with involvement of the head, neck, trunk, and limbs. Action-induced spasms were observed. Both sibs had mild intellectual disability.

## Genotype-Phenotype Correlations

No genotype-phenotype correlations are known for either heterozygous or biallelic *GNAL* pathogenic variants.

## Penetrance

The penetrance for heterozygous DYT-GNAL is currently unknown. The following asymptomatic heterozygotes for a *GNAL* pathogenic variant have been reported:

- 14 unaffected heterozygotes (mean age: 29 years, age range: 9-51 years) identified in three of four families [Vemula et al 2013]
- One unaffected heterozygote who was a parent of two offspring with DYT-GNAL ages 50 and 59 years [Fuchs et al 2013]
- One unaffected heterozygote who was the mother of a 40-year-old with laryngeal dystonia [Putzel et al 2016]

## Nomenclature

Following the new naming system for the genetic dystonias in which the causative gene has been confirmed, the prefix "DYT" is followed by the gene symbol [Marras et al 2016]. Thus, the new designation for DYT25 isolated dystonia is DYT-GNAL.

## Prevalence

DYT-GNAL is rare. To date 64 individuals (including two homozygotes) with DYT-GNAL have been reported.

Studies in families of northern European descent with primary torsion dystonia of mixed European origin [Fuchs et al 2013] and in Swiss-German Amish-Mennonite families with primary dystonia [Saunders-Pullman et al 2014] found DYT-GNAL-causing variants in affected family members in 15% and 7.5%, respectively.

In contrast, in studies including mostly simplex cases (i.e., a single occurrence in a family) with mostly isolated dystonia, the prevalence was about 0.5% (0-1.1%) [Miao et al 2013, Vemula et al 2013, Charlesworth et al 2014, Dobričić et al 2014, Dufke et al 2014, Zech et al 2014, Ziegen et al 2014, Ma et al 2015, Zech et al 2015, Dos Santos et al 2016, LeDoux et al 2016].

A study on 57 patients with isolated laryngeal dystonia found a slightly higher prevalence of 1.8% [Putzel et al 2016].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with either germline heterozygous or biallelic *GNAL* pathogenic variants.

## Differential Diagnosis

See [Hereditary Dystonia Overview](#).

**Table 2.** Autosomal Dominant Disorders to Consider in the Differential Diagnosis of DYT-GNAL

Disorder	Gene	Clinical Features of Disorder That Overlap w/DYT-GNAL	Further Details of This Disorder			
			Age at onset of dystonia	Site of dystonia at onset	Dystonia type	Other
DYT-THAP1	THAP1	Craniocervical dystonia &/or laryngeal involvement may be presenting feature(s).	<ul style="list-style-type: none"> <li>• Median: 13 yrs (range: 2-49 yrs)<sup>1</sup></li> <li>• Median: 13 yrs (range 2-62 yrs)<sup>2</sup></li> <li>• Mean: 48 yrs (range: 8-69 yrs)<sup>3</sup></li> </ul>	Cervical & laryngeal; upper limb	Craniocervical involvement common	Penetrance of ~60%
DYT-TOR1A	TOR1A	Isolated blepharospasm or craniocervical dystonia in some	<ul style="list-style-type: none"> <li>• Mean: 14 yrs (range 4-44 yrs)<sup>4</sup></li> <li>• Early onset, typically childhood; late onset in some</li> </ul>	Typically in 1 limb	<ul style="list-style-type: none"> <li>• 60% to 70% progress to generalized (or multifocal) dystonia.<sup>5</sup></li> <li>• ~20% have focal dystonia, most frequently writer's cramp.</li> </ul>	<ul style="list-style-type: none"> <li>• Ashkenazi Jewish ancestry common<sup>4</sup></li> <li>• Reduced penetrance of ~30%</li> <li>• More rapid progression</li> <li>• Face &amp; neck typically spared</li> </ul>
DYT-SGCE (see Myoclonus-Dystonia)	SGCE	<ul style="list-style-type: none"> <li>• Cervical dystonia<sup>6</sup></li> <li>• Myoclonic jerks typical of DYT-SGCE have been described in DYT-GNAL.<sup>7</sup></li> </ul>	1st or 2nd decade	Neck, proximal arm, trunk	Myoclonic jerks of mostly proximal muscles, typically cervical dystonia & writer's cramp	<ul style="list-style-type: none"> <li>• Action-induced, alcohol-responsive myoclonic jerks</li> <li>• Psychiatric features common (incl alcohol dependence)</li> </ul>
DYT-ANO3	ANO3	<ul style="list-style-type: none"> <li>• Adult-onset craniocervical dystonia</li> <li>• Laryngeal dystonia</li> <li>• Upper-limb dystonia (incl arm tremor)</li> </ul>	Early childhood to 6th decade (typically adult onset)	Mostly craniocervical	Segmental/multifocal (craniocervical dystonia, head tremor, upper-limb dystonia, dystonic arm tremor, laryngeal dystonia)	Most have dystonic tremor.

1. Bressman et al [2009]; patients with familial dystonia

2. Blanchard et al [2011]; review

3. Xiao et al [2010]; cohort consisted mainly of individuals with late-onset focal dystonia (n = 1,210).

4. Bressman et al [2000]

5. See [DYT1 Early-Onset Isolated Dystonia](#).

6. Cervical dystonia may be the only presentation in DYT-SGCE.

7. Carecchio et al [2016]

*CIZ1*-related dystonia was described in a large family of northern European descent with adult-onset cervical dystonia and an otherwise normal neurologic examination [Xiao et al 2012]. Although Dufke et al [2015] also

reported *CIZ1* variants in individuals with or without a family history of predominantly cervical dystonia, the significance of these variants remains unknown. Thus, *CIZ1* pathogenic variants as a cause for adult-onset cervical dystonia are currently unconfirmed.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with DYT-GNAL, 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 DYT-GNAL

Organ System	Evaluation	Comment
Neurologic	Complete neurologic exam performed by neurologist specializing in movement disorders	Attention to blepharospasm, oromandibular dystonia, dystonia of jaw/tongue, (jerky) cervical dystonia, dystonia of arms/legs, truncal dystonia, tremor (head or extremities), laryngeal dystonia, hyposmia
	Eval using a dystonia rating scale	Rating scale such as: <ul style="list-style-type: none"> <li>Burke-Fahn-Marsden dystonia rating scale (BFMDRS)</li> <li>Unified Dystonia Rating Scale (UDRS)</li> <li>Global Dystonia Rating Scale (GDS)</li> </ul> For cervical dystonia: Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) & Comprehensive Cervical Dystonia Rating Scale (CCDRS)
	Eval by physical therapist	Attention to craniocervical dystonia, dystonia of extremities & trunk; geste antagoniste <sup>1</sup>
ENT	<ul style="list-style-type: none"> <li>Eval for botulinum toxin injections into laryngeal muscles by otorhinolaryngologist</li> <li>Eval by speech therapist</li> </ul>	For those w/laryngeal dystonia
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

1. Voluntary maneuver that temporarily reduces the severity of dystonic postures or movements

## Treatment of Manifestations

### Dystonia

All treatment options are symptomatic.

**Oral medication.** A trial with oral medication is usually first. Very few reports on the effect of oral medication specifically in DYT-GNAL are available.

- Oral drugs currently used to treat dystonia:
  - Anticholinergics (trihexyphenidyl is most widely used; bztropine). These need to be monitored especially for cognitive side effects.
  - Baclofen
  - Benzodiazepines (diazepam, clonazepam, lorazepam)
- Additional drugs that may be considered:
  - Levodopa. Note: Levodopa/carbidopa was not beneficial in patients with DYT-GNAL [Bressman et al 1994, Carecchio et al 2016].



- Antiepileptics; e.g., gabapentin [Esposito et al 2014, Sarva et al 2019]
- Dopamine-depleting agents, most importantly tetrabenazine, which requires monitoring for psychiatric side effects (depressive episodes). Note: Tetrabenazine provided no benefit in one patient with DYT-GNAL [Carecchio et al 2016].
- Propranolol, cyclobenzaprine, trabenazine, and ethopropazine reported in a recent study [Sarva et al 2019]

**Botulinum toxin** intramuscular injections, repeated in intervals of about three months, have improved cervical dystonia in some patients with DYT-GNAL [Dobričić et al 2014, Carecchio et al 2016, Dos Santos et al 2016] as well as dystonia affecting other sites (e.g., blepharospasm, oromandibular dystonia, focal dystonia of a limb) including selected muscles in individuals with generalized dystonia.

**Deep-brain stimulation of the globus pallidus internus** has been effective in treatment of isolated dystonia in the following instances:

- Two patients with DYT-GNAL cervical dystonia accompanied by severe head tremor had a very good response [Carecchio et al 2016].
- One patient with DYT-GNAL cervical and truncal dystonia showed a good response [Ziegen et al 2014].
- In three patients, cervical dystonia improved significantly, while cranial dystonia (including dysarthria) and limb dystonia did not improve or worsened [Sarva et al 2019].

Follow up includes more frequent visits in the first weeks and months after surgery in order to determine the best stimulation parameters.

**Physical therapy** may help prevent joint contractures and spine deformities.

## Psychiatric Comorbidities

Depression and anxiety are treated as per standard practice. Of note, dopamine-depleting agents, anticholinergics, and other drugs may cause or worsen psychiatric and cognitive features.

## Surveillance

Follow up with a neurologist specializing in movement disorders several times a year is recommended to monitor for the following:

- Worsening of dystonia
- Development of new manifestations
- Medication side effects
- Issues related to DBS treatment including side effects such as hypokinesia and battery life

Regular monitoring for psychiatric and cognitive features is indicated; medication adjustments and consultation with a psychiatrist may be necessary.

## Agents/Circumstances to Avoid

Dystonia of limbs can worsen if affected limbs are casted or braced. Similarly, neck collars should be avoided in persons with cervical dystonia.

## Evaluation of Relatives at Risk

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

## Pregnancy Management

Controlled human studies on the safety of baclofen use during pregnancy have not been completed. Several case reports of baclofen use in the first trimester of pregnancy with normal fetal outcome have been published. Third-trimester exposure may lead to abnormalities in neonatal adaptation.

The use of diazepam during the first trimester of pregnancy may be associated with an increased risk of cleft palate; thus, in situations where use of a benzodiazepine during pregnancy is required, other medications (e.g., lorazepam or clonazepam) may be preferable. Third-trimester use of a benzodiazepine may lead to neonatal complications, such as decreased tone and/or sedation.

Botulinum toxin injections are typically avoided during pregnancy and breastfeeding. However, in several case reports of women who received botulinum toxin A injections in the first trimester of pregnancy, infants were born at full term with no complications.

Data are insufficient to determine if the use of trihexyphenidyl during pregnancy has an effect on the developing fetus.

See [MotherToBaby](#) for further information on medication use during pregnancy.

## Therapies Under Investigation

The following clinical trials (identified by NCT number) on DBS in "primary dystonia" are listed in [ClinicalTrials.gov](#). (The term "primary dystonia" currently is mainly used for genetic or idiopathic forms of isolated dystonia without a consistent pathologic/structural change.) Note that none is specifically recruiting patients with DYT-GNAL:

- [NCT02542839](#) evaluates repetitive transcranial magnetic stimulation (rTMS) delivered over each cerebellar hemisphere in addition to treatment with botulinum toxin injections in patients with primary cervical dystonia.

Other rTMS studies conducted or recruiting:

- [NCT02073630](#) in patients with primary dystonia
- [NCT03369613](#) in patients with cervical dystonia
- [NCT03247868](#) evaluates the influence of motor learning techniques in patients with primary cervical dystonia.

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## 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

DYT-GNAL is typically inherited in an autosomal dominant manner.

Autosomal recessive inheritance of DYT-GNAL has been reported to date only once [Masuho et al 2016] (see Clinical Description, Biallelic DYT-GNAL). For a discussion of autosomal recessive inheritance, see [Hereditary Dystonia Overview](#).

## Risk to Family Members – Autosomal Dominant Inheritance

### Parents of a proband

- About 65% of individuals diagnosed with DYT-GNAL have a parent with dystonia (significant clinical variability is observed within families).
- Some individuals diagnosed with DYT-GNAL have the disorder as the result of a *de novo* GNAL pathogenic variant [Dobričić et al 2014]. Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the pathogenic variant occurred *de novo* in the proband or was transmitted by a heterozygous, asymptomatic parent, the proportion of DYT-GNAL 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* GNAL pathogenic variant.
- If the GNAL 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 instance of a proband inheriting a pathogenic variant from a parent with germline mosaicism has been reported.
- The family history of some affected individuals may appear to be negative for DYT-GNAL because of failure to recognize the disorder in family members. Because features of DYT-GNAL may not develop in individuals who are heterozygous for the GNAL pathogenic variant due to reduced penetrance or death before the onset of manifestations, molecular genetic testing is required to clarify the genetic status of parents of a proband.

**Sibs of a proband.** The risk to the sibs of a proband with heterozygous DYT-GNAL depends on the genetic status of the proband's parents.

- If the parents have been tested for the GNAL pathogenic variant identified in the proband and:
  - A parent of the proband has the GNAL pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Sibs who inherit the pathogenic variant will likely develop dystonia; however, adults heterozygous for a GNAL pathogenic variant have been reported to be unaffected [Fuchs et al 2013, Vemula et al 2013, Putzel et al 2016]. There is large phenotypic variability within families (see Clinical Description, **Intrafamilial phenotypic variability**).
  - The GNAL pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the GNAL pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for DYT-GNAL because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.
- Of note, several families with unaffected parents and multiple affected sibs of a proband have been reported [Fuchs et al 2013, Vemula et al 2013, Carecchio et al 2016, Masuho et al 2016].

### Offspring of a proband

- Each child of an individual with DYT-GNAL has a 50% chance of inheriting the GNAL pathogenic variant. However, the risk that a child will be affected is less than 50% because of reduced penetrance (see Penetrance).

- Because of significant intrafamilial phenotypic variability, an affected child may be more severely or less severely affected than the parent who transmitted the pathogenic variant.

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

## Related Genetic Counseling Issues

**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, 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** is the storage of DNA (typically extracted from white blood cells) for possible future use. 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 of affected individuals.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *GNAL* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Note: Because of reduced penetrance and variable expressivity, the results of prenatal testing may not be useful in accurately predicting the onset or severity of DYT-GNAL.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Dystonia Coalition**

*The Dystonia Coalition is a collaboration of medical researchers and patient advocacy groups that is working to advance the pace of clinical and translational research in the dystonias to find better treatments.*

[www.rarediseasesnetwork.org/cms/dystonia](http://www.rarediseasesnetwork.org/cms/dystonia)

- **Dystonia Europe**

Belgium

**Phone:** 46 739 98 49 61

**Email:** [sec@dystonia-europe.org](mailto:sec@dystonia-europe.org)

[www.dystonia-europe.org](http://www.dystonia-europe.org)

- **Dystonia Medical Research Foundation**  
**Phone:** 312-755-0198; 800-377-DYST (3978)  
**Fax:** 312-803-0138  
**Email:** [dystonia@dystonia-foundation.org](mailto:dystonia@dystonia-foundation.org)  
[dystonia-foundation.org](http://dystonia-foundation.org)
- **Dystonia Society**  
 89 Albert Embankment  
 3rd Floor  
 London SE1 7TP  
 United Kingdom  
**Phone:** 0845 458 6211; 0845 458 6322 (Helpline)  
**Fax:** 0845 458 6311  
**Email:** [support@dystonia.org.uk](mailto:support@dystonia.org.uk)  
[www.dystonia.org.uk](http://www.dystonia.org.uk)
- **Medline Plus**  
[Dystonia](#)
- **German Dystonia Registry**  
 Germany  
[www.dystract.cio-marburg.de](http://www.dystract.cio-marburg.de)
- **Global Dystonia Registry**  
[www.globaldystoniaregistry.org](http://www.globaldystoniaregistry.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.** DYT-GNAL: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
<i>GNAL</i>	18p11.21	Guanine nucleotide-binding protein G(olf) subunit alpha	GNAL	GNAL

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 DYT-GNAL ([View All in OMIM](#))

139312	GUANINE NUCLEOTIDE-BINDING PROTEIN, ALPHA-ACTIVATING ACTIVITY POLYPEPTIDE, OLFACTORY TYPE; GNAL
615073	DYSTONIA 25; DYT25

**Gene structure.** *GNAL* spans more than 80 kb [Vuoristo et al 2000, Vemula et al 2013]. Alternative splicing results in multiple transcript variants encoding different isoforms (1-3). Transcript variant 1 ([NM\\_182978.3](#)) is the longest and encodes the longest protein, isoform 1 ([NP\\_892023.1](#), 458 amino acids). Isoform 2 ([NP\\_001135811.1](#), 381 amino acids) is encoded by transcript variant 3 ([NM\\_001142339.2](#)); it is the major

transcript, and it differs in the 5'UTR compared to variant 1. Isoforms 1 and 2 differ in exon 1. Transcript variant 5 (NM\_001261444.1) lacks a large portion of the 5' coding region and encodes a shorter protein, isoform 3 (NP\_001248373.1, 174 amino acids), which is not found in the brain. For a detailed summary of gene, transcript, and protein information, see Table A, **Gene**.

**Benign variants.** An intronic splice site variant was found in a Chinese female with cervical dystonia (c.932-7T>G) [Miao et al 2013]; the variant was originally considered likely pathogenic, since *in silico* analyses showed that this variant may affect the splice efficiency with exon 11 skipping. Although intronic variants that do not affect conserved splice sites are generally considered non-pathogenic, this variant is considered likely benign as Dufke et al [2014] found the variant in 19/137 patients, corresponding to the frequency given in public databases. LeDoux et al [2016] found the variant in 74 patients and classified it as benign (American College of Medical Genetics and Genomics [ACMG] standards published in Richards et al [2008]).

**Variants of unknown significance.** Ma et al [2015] reported one missense variant of unknown significance.

**Pathogenic variants.** Currently, 30 different pathogenic variants causing DYT-GNAL have been described, including three missense variants reported as "likely pathogenic" [Richards et al 2008, LeDoux et al 2016]. Pathogenic variants are missense (n = 15), nonsense (n = 5), and frameshift (n = 4) [Fuchs et al 2013, Miao et al 2013, Vemula et al 2013, Dobričić et al 2014, Dufke et al 2014, Kumar et al 2014, Saunders-Pullman et al 2014, Zech et al 2014, Ziegen et al 2014, Zech et al 2015, Carecchio et al 2016, Dos Santos et al 2016, LeDoux et al 2016, Masuho et al 2016, Putzel et al 2016].

In addition, one splice site variant [Fuchs et al 2013, Zech et al 2015], one in-frame deletion [Fuchs et al 2013], and one start codon disruption [Vemula et al 2013] were reported.

Twenty-eight pathogenic variants were found only in a single family. Two pathogenic variants were reported in two independent studies: c.274-5T>C [Fuchs et al 2013, Zech et al 2015] and c.733C>T [Vemula et al 2013, Dufke et al 2014].

**Table 4.** GNAL Variants Discussed in This GeneReview

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
<b>Likely benign</b>	c.932-7T>G		
<b>Pathogenic</b>	c.274-5T>C		NM_001142339.2 NP_001135811.1
	c.733C>T	p.Arg245Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

**Normal gene product.** Guanosine triphosphate (GTP) binding proteins (G proteins) are heterotrimers composed of three subunits: the  $\alpha$ -,  $\beta$ -, and  $\gamma$ -subunits [McCudden et al 2005]. G proteins are categorized into four subfamilies according to their  $\alpha$ -subunits (Gas, Gai/o, Gaq, and Ga12). Ga(olf) is regarded as a member of the Gas family.

GNAL encodes the stimulatory G-alpha subunit Ga(olf) of the G protein. Ga(olf) contains guanine nucleotide binding sites. It couples dopamine type 1 receptors of the direct pathway and adenosine A2A receptors of the indirect pathway to the activation of adenylate cyclase type 5 and to histone H3 phosphorylation. Stimulation of the D1 receptor by dopamine leads to the dissociation of Ga(olf) from the heterotrimer. Ga(olf) is assumed to harbor a Ras-like domain that mediates guanosine triphosphate (GTP) binding. It catalyzes the exchange of guanosine diphosphate to GTP.

Gα(olf) was first identified in the olfactory epithelium as a G protein subunit that mediates odorant signaling. It was later found to be widely expressed in the brain, especially in motor regions that have been linked to dystonia pathogenesis. Gα(olf) is expressed at high levels in the striatum (striatal medium spiny neurons, MSNs), postsynaptically in dopaminergic neurons and/or cholinergic interneurons (reviewed by Fuchs et al [2013]). It was also found to be highly expressed in cerebellar Purkinje cells, where it co-localizes with corticotropin-releasing hormone receptors; further brain regions with high Gα(olf) expression include the olfactory bulb, thalamus, and substantia nigra [Vemula et al 2013].

**Abnormal gene product.** The efficiency of the formation of the G protein heterotrimer and the coupling to D1 dopamine receptors was shown to be impaired in vitro by *GNAL* pathogenic variants [Fuchs et al 2013]. Thus, a loss-of-function mechanism of the altered Gα(olf) protein is assumed to cause DYT-GNAL. Missense variants that lead to amino acid changes near a GTP binding site may result in the disturbance or disruption of binding GTP [Dobričić et al 2014]. Impaired dopaminergic and cholinergic transmission is assumed to result from *GNAL* loss-of-function variants. Loss of Gα(olf) function may further disturb the G<sub>1</sub>-S cell cycle control [Vemula et al 2013].

*GNAL* null mice were reported to be anosmic [Belluscio et al 1998].

## References

### Literature Cited

- Belluscio L, Gold GH, Nemes A, Axel R. Mice deficient in G(olf) are anosmic. *Neuron*. 1998;20:69–81. PubMed PMID: 9459443.
- Blanchard A, Ea V, Roubertie A, Martin M, Coquart C, Claustres M, Bérout C, Collod-Bérout G. DYT6 dystonia: review of the literature and creation of the UMD Locus-Specific Database (LSDB) for mutations in the THAP1 gene. *Hum Mutat*. 2011;32:1213–24. PubMed PMID: 21793105.
- Bressman SB, Heiman GA, Nygaard TG, Ozelius LJ, Hunt AL, Brin MF, Gordon MF, Moskowitz CB, de Leon D, Burke RE, Fahn S, Risch NJ, Breakefield XO, Kramer PL. A study of idiopathic torsion dystonia in a non-Jewish family: evidence for genetic heterogeneity. *Neurology*. 1994;44:283–7. PubMed PMID: 8309575.
- Bressman SB, Raymond D, Fuchs T, Heiman GA, Ozelius LJ, Saunders-Pullman R. Mutations in THAP1 (DYT6) in early-onset dystonia: a genetic screening study. *Lancet Neurol*. 2009;8:441–6. PubMed PMID: 19345147.
- Bressman SB, Sabatti C, Raymond D, de Leon D, Klein C, Kramer PL, Brin MF, Fahn S, Breakefield X, Ozelius LJ, Risch NJ. The DYT1 phenotype and guidelines for diagnostic testing. *Neurology*. 2000;54:1746–52. PubMed PMID: 10802779.
- Carecchio M, Panteghini C, Reale C, Barzaghi C, Monti V, Romito L, Sasanelli F, Garavaglia B. Novel *GNAL* mutation with intra-familial clinical heterogeneity: expanding the phenotype. *Parkinsonism Relat Disord*. 2016;23:66–71. PubMed PMID: 26725140.
- Charlesworth G, Bhatia KP, Wood NW. No pathogenic *GNAL* mutations in 192 sporadic and familial cases of cervical dystonia. *Mov Disord*. 2014;29:154–5. PubMed PMID: 24222099.
- Dobričić V, Kresojević N, Westenberger A, Svetel M, Tomić A, Ralić V, Petrović I, Lukić MJ, Lohmann K, Novaković I, Klein C, Kostić VS. De novo mutation in the *GNAL* gene causing seemingly sporadic dystonia in a Serbian patient. *Mov Disord*. 2014;29:1190–3. PubMed PMID: 24729450.
- Dos Santos CO, Masuho I, da Silva-Júnior FP, Barbosa ER, Silva SM, Borges V, Ferraz HB, Rocha MS, Limongi JC, Martemyanov KA, de Carvalho Aguiar P. Screening of *GNAL* variants in Brazilian patients with isolated dystonia reveals a novel mutation with partial loss of function. *J Neurol*. 2016;263:665–8. PubMed PMID: 26810727.

- Dufke C, Hauser AK, Sturm M, Fluhr S, Wächter T, Leube B, Auburger G, Ott T, Bauer P, Gasser T, Grundmann K. Mutations in *CIZ1* are not a major cause for dystonia in Germany. *Mov Disord*. 2015;30:740–3. PubMed PMID: 25778706.
- Dufke C, Sturm M, Schroeder C, Moll S, Ott T, Riess O, Bauer P, Grundmann K. Screening of mutations in *GNAL* in sporadic dystonia patients. *Mov Disord*. 2014;29:1193–6. PubMed PMID: 24408567.
- Esposito F, Addor MC, Humm AM, Vingerhoets F, Wider C. *GNAL* deletion as a probable cause of dystonia in a patient with the 18p- syndrome. *Parkinsonism Relat Disord*. 2014;20:351–2. PubMed PMID: 24405754.
- Fuchs T, Saunders-Pullman R, Masuho I, Luciano MS, Raymond D, Factor S, Lang AE, Liang TW, Trosch RM, White S, Ainehsazan E, Hervé D, Sharma N, Ehrlich ME, Martemyanov KA, Bressman SB, Ozelius LJ. Mutations in *GNAL* cause primary torsion dystonia. *Nat Genet*. 2013;45:88–92. PubMed PMID: 23222958.
- Kumar KR, Lohmann K, Masuho I, Miyamoto R, Ferbert A, Lohnau T, Kasten M, Hagenah J, Brüggemann N, Graf J, Münchau A, Kostic VS, Sue CM, Domingo AR, Rosales RL, Lee LV, Freimann K, Westenberger A, Mukai Y, Kawarai T, Kaji R, Klein C, Martemyanov KA, Schmidt A. Mutations in *GNAL*: a novel cause of craniocervical dystonia. *JAMA Neurol*. 2014;71:490–4. PubMed PMID: 24535567.
- LeDoux MS, Vemula SR, Xiao J, Thompson MM, Perlmutter JS, Wright LJ, Jinnah HA, Rosen AR, Hedera P, Comella CL, Weissbach A, Junker J, Jankovic J, Barbano RL, Reich SG, Rodriguez RL, Berman BD, Chouinard S, Severt L, Agarwal P, Stover NP. Clinical and genetic features of cervical dystonia in a large multicenter cohort. *Neurol Genet*. 2016;2:e69. PubMed PMID: 27123488.
- Ma LY, Wang L, Yang YM, Wan XH. Mutations in *GNAL* gene in 214 cases with isolated dystonia. *Parkinsonism Relat Disord*. 2015;21:1367–8. PubMed PMID: 26365774.
- Marras C, Lang A, van de Warrenburg BP, Sue CM, Tabrizi SJ, Bertram L, Mercimek-Mahmutoglu S, Ebrahimi-Fakhari D, Warner TT, Durr A, Assmann B, Lohmann K, Kostic V, Klein C. Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society task force. *Mov Disord*. 2016;31:436–57. PubMed PMID: 27079681.
- Masuho I, Fang M, Geng C, Zhang J, Jiang H, Özgül RK, Yilmaz DY, Yalnızoğlu D, Yüksel D, Yarrow A, Myers A, Burn SC, Crotwell PL, Padilla-Lopez S, Dursun A, Martemyanov KA, Kruer MC. Homozygous *GNAL* mutation associated with familial childhood-onset generalized dystonia. *Neurol Genet*. 2016;2:e78. PubMed PMID: 27222887.
- McCudden CR, Hains MD, Kimple RJ, Siderovski DP, Willard FS. G-protein signaling: back to the future. *Cell Mol Life Sci*. 2005;62:551–77. PubMed PMID: 15747061.
- Miao J, Wan XH, Sun Y, Feng JC, Cheng FB. Mutation screening of *GNAL* gene in patients with primary dystonia from Northeast China. *Parkinsonism Relat Disord*. 2013;19:910–2. PubMed PMID: 23759320.
- Putzel GG, Fuchs T, Battistella G, Rubien-Thomas E, Frucht SJ, Blitzer A, Ozelius LJ, Simonyan K. *GNAL* mutation in isolated laryngeal dystonia. *Mov Disord*. 2016;31:750–5. PubMed PMID: 27093447.
- 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.
- Richards CS, Bale S, Bellissimo DB, Das S, Grody WW, Hegde MR, Lyon E, Ward BE, et al. ACMG recommendations for standards for interpretation and reporting of sequence variations: revisions 2007. *Genet Med*. 2008;10:294–300. PubMed PMID: 18414213.
- Sarva H, Trosch R, Kiss ZHT, Furtado S, Luciano MS, Glickman A, Raymond D, Ozelius LJ, Bressman SB, Saunders-Pullman R. Deep brain stimulation in isolated dystonia with a *GNAL* mutation. *Mov Disord*. 2019;34:301–3. PubMed PMID: 30536916.



- Saunders-Pullman R, Fuchs T, San Luciano M, Raymond D, Brashear A, Ortega R, Deik A, Ozelius LJ, Bressman SB. Heterogeneity in primary dystonia: lessons from THAP1, GNAL, and TOR1A in Amish-Mennonites. *Mov Disord.* 2014;29:812–8. PubMed PMID: 24500857.
- Vemula SR, Puschmann A, Xiao J, Zhao Y, Rudzińska M, Frei KP, Truong DD, Wszolek ZK, LeDoux MS. Role of Gα(olf) in familial and sporadic adult-onset primary dystonia. *Hum Mol Genet.* 2013;22:2510–9. PubMed PMID: 23449625.
- Vuoristo JT, Berrettini WH, Overhauser J, Prockop DJ, Ferraro TN, Ala-Kokko L. Sequence and genomic organization of the human G-protein G $\alpha$  gene (GNAL) on chromosome 18p11, a susceptibility region for bipolar disorder and schizophrenia. *Mol Psychiatry.* 2000;5:495–501. PubMed PMID: 11032382.
- Xiao J, Uitti RJ, Zhao Y, Vemula SR, Perlmutter JS, Wszolek ZK, Maraganore DM, Auburger G, Leube B, Lehnhoff K, LeDoux MS. Mutations in CIZ1 cause adult onset primary cervical dystonia. *Ann Neurol.* 2012;71:458–69. PubMed PMID: 22447717.
- Xiao J, Zhao Y, Bastian RW, Perlmutter JS, Racette BA, Tabbal SD, Karimi M, Paniello RC, Wszolek ZK, Uitti RJ, van Gerpen JA, Simon DK, Tarsy D, Hedera P, Truong DD, Frei KP, Dev Batish S, Blitzer A, Pfeiffer RF, Gong S, LeDoux MS. Novel THAP1 sequence variants in primary dystonia. *Neurology.* 2010;74:229. PubMed PMID: 20083799.
- Zech M, Boesch S, Sycha T, Mueller J, Poewe W, Winkelmann J. TOR1A, THAP1, and GNAL mutational screening in Austrian patients with primary isolated dystonia. *Mov Disord.* 2015;30:1853–4. PubMed PMID: 26506956.
- Zech M, Gross N, Jochim A, Castrop F, Kaffe M, Dresel C, Lichtner P, Peters A, Gieger C, Meitinger T, Haslinger B, Winkelmann J. Rare sequence variants in ANO3 and GNAL in a primary torsion dystonia series and controls. *Mov Disord.* 2014;29:143–7. PubMed PMID: 24151159.
- Ziegan J, Wittstock M, Westenberger A, Dobričić V, Wolters A, Benecke R, Klein C, Kamm C. Novel GNAL mutations in two German patients with sporadic dystonia. *Mov Disord.* 2014;29:1833–4. PubMed PMID: 25382112.

## Chapter Notes

### Acknowledgments

AD is supported by the Max Kade Foundation and a gift from Carl Edward Bolch Jr and Susan Bass Bolch. ZKW is partially supported by the NIH/NINDS P50 NS072187, Mayo Clinic Neuroscience Focused Research Team (Cecilia and Dan Carmichael Family Foundation and the James C and Sarah K Kennedy Fund for Neurodegenerative Disease Research at the Mayo Clinic in Florida), the Sol Goldman Charitable Trust, and a gift from Donald G and Jodi P Heeringa.

### Revision History

- 3 January 2019 (bp) Review posted live
- 19 December 2017 (ad) Original submission

## License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No

further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: [admasst@uw.edu](mailto:admasst@uw.edu).