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DYT1 Early-Onset Isolated Dystonia

Synonyms: Early-Onset Torsion Dystonia, Oppenheim's Dystonia

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Summary

Clinical characteristics

DYT1 early-onset isolated dystonia typically presents in childhood or adolescence and only on occasion in adulthood. Dystonic muscle contractions causing posturing or irregular tremor of a leg or arm are the most common presenting findings. Dystonia is usually first apparent with specific actions such as writing or walking. Over time, the contractions frequently (but not invariably) become evident with less specific actions and spread to other body regions. No other neurologic abnormalities are present. Disease severity varies considerably even within the same family. Isolated writer's cramp may be the only sign.

Diagnosis/testing

The diagnosis of DYT1 dystonia is established in a proband by identification of a heterozygous *TOR1A* pathogenic variant on molecular genetic testing. A *TOR1A* three base-pair deletion, c.907_909delGAG, is identified in most affected individuals.

Management

Treatment of manifestations: Oral medications, either alone or in combination, are usually tried first, including anticholinergics, baclofen, benzodiazepines, and others. Botulinum toxin injections for treatment of focal symptoms can be used in conjunction with oral medications. If oral medications and botulinum toxin injections do not provide sufficient control of symptoms, surgery enabling deep-brain stimulation (DBS) of the globus pallidus interna (GPi) should be considered.

Prevention of secondary complications: Aggressive medical and surgical intervention to prevent contractures of the joints and deformities of the spine.

Surveillance: Follow up with a neurologist specializing in movement disorders several times a year.

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Agents/circumstances to avoid: The extremities affected by dystonia should not be placed in a brace or cast, unless medically necessary, as this can worsen the dystonia.

Genetic counseling

DYT1 dystonia is inherited in an autosomal dominant manner with reduced penetrance. Offspring of an affected individual or of an asymptomatic individual known to have a *TOR1A* pathogenic variant have a 50% chance of inheriting the variant and if inherited a 30% chance of developing clinical findings. Once the *TOR1A* c.907_909delGAG deletion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for DYT1 dystonia are possible.

Diagnosis

Suggestive Findings

DYT1 early-onset isolated dystonia **should be suspected** in individuals with the following:

- Isolated dystonia (defined as involuntary contraction of muscles that causes repetitive, patterned, and often twisting movements or postures) with:
  - No other abnormalities on neurologic examination (except tremor);
  - Normal routine neuroimaging;
  - No history of known cause of acquired dystonia (e.g., exposure to neuroleptic medications; cerebral trauma, infarct, infection).
- Onset of dystonia before age 26 years (Note: Older age of onset may be seen among relatives of affected individuals; family members with later onset tend to have arm dystonia in the form of writer's cramp [Bressman et al 2000].)
- Family history of early-onset dystonia (Note: Lack of a family history of early-onset dystonia does not preclude the diagnosis.)
- Factors that are more specific to DYT1 early-onset isolated dystonia, including:
  - Ashkenazi Jewish ancestry (although DYT1 dystonia can occur in individuals of any ethnicity);
  - Onset in a limb before age 26 years;
  - Two or more affected limbs.

Establishing the Diagnosis

The diagnosis of DYT1 early-onset isolated dystonia **is established** in a proband by identification of a heterozygous pathogenic variant in *TOR1A* on molecular genetic testing (see Table 1).

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

- **Single-gene testing.** Because the c.907_909delGAG variant is the only definitive pathogenic variant in *TOR1A* associated with DYT1 early-onset isolated dystonia identified to date, targeted analysis for this pathogenic variant can be performed first.

  In the absence of the c.907_909delGAG variant, the clinical utility of full sequence analysis is limited. Despite extensive screening, only a few variants in *TOR1A* have been observed in individuals with related phenotypes (reviewed in Dobričić et al [2015]); see Molecular Genetics.

  Sequence analysis may be followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found; however, since DYT1 early-onset isolated dystonia occurs through a dominant-negative mechanism and large intragenic deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

- **A multigene panel** that includes *TOR1A* and other genes of interest (see Differential Diagnosis) may also be considered after targeted c.907_909delGAG testing. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *TOR1A*) fails to confirm a diagnosis in an individual with features of DYT1 early-onset isolated dystonia. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation). For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in DYT1 Early-Onset Isolated Dystonia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TOR1A	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

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. Most individuals with DYT1, regardless of ethnic background, have the three base-pair deletion c.907_909delGAG (sometimes referred to as 904_906delGAG) in *TOR1A* [Ozelius et al 1997, Warner & Jarman 1998].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Dystonia is the involuntary sustained or intermittent contraction of muscles that causes movements often resulting in twisting and posturing of the involved body region. An updated definition and classification for dystonia can be found in Albanese et al [2013].

DYT1 dystonia is a form of early-onset isolated dystonia; it is considered an isolated dystonia because it is not associated with other neurologic or systemic abnormalities.

Age of onset. The average age of onset of DYT1 dystonia is approximately 12 years; the median age is between nine and 11 years. Onset ranging from age four to 64 years has been reported [Opal et al 2002, Bressman 2004], with the vast majority beginning before age 26 years.

Life span is not thought to be shortened.

Presentation. DYT1 dystonia usually starts in a leg (average age 9 years) or an arm (average age 15 years). Initially, dystonia is apparent with specific actions; typically, there is a change in gait (foot inversion or eversion, abnormal flexion of the knee or hip) or problems writing. The small minority of individuals who do not have initial limb involvement have onset in trunk, cervical, or cranial muscles.

Once they appear, dystonic movements usually persist through life.

Pain is not a prominent finding except in cervical dystonia, which is uncommon in DYT1 dystonia.

Approximately 20% of DYT1 dystonia is restricted to a single body region, usually as writer's cramp. Unusual phenotypic expression of DYT1 dystonia includes isolated blepharospasm [Tuffery-Giraud et al 2001] and fluctuating unilateral myoclonic dystonia [Gatto et al 2003]. When a group of affected Korean individuals were compared to the typical northern European affected individuals, Korean individuals more commonly had segmental dystonia with more frequent axial onset of symptoms [Lee et al 2012].

Progression. In most (not all) individuals who have onset in a leg, dystonia progresses over months to years. The contractions become less action-specific and may become present at rest. The dystonia can also spread to other body regions, frequently progressing over a period of months to years to "generalized dystonia" involving other limbs and the trunk. In individuals with onset in an arm, progression is more variable and dystonia generalizes in only approximately 50%. Individuals with onset in the neck or cranial muscles also have variable progression. Overall, 60% to 70% of individuals have progression to generalized or multifocal dystonia involving at least a leg and arm, and often axial muscles. Spread to craniocervical muscles can also occur but is much less common.

Depressive illness. An increased rate of recurrent major depression has been reported in individuals with a *TOR1A* pathogenic variant with or without dystonia [Heiman et al 2004].

Neuroimaging

- Brain CT and routine MRI are normal.
- For additional information about PET scan studies and diffusion tensor imaging (DTI) studies in DYT1 dystonia, click here.

Neuropathology. Very few brains of individuals with DYT1 dystonia have been examined. One study found that nigral dopaminergic neurons appeared larger [Rostasy et al 2003]; another study of four brains found perinuclear inclusion bodies in the midbrain reticular formation and periaqueductal gray matter [McNaught et al 2004]. A recent study on seven brains from individuals with the *TOR1A* c.907_909delGAG pathogenic variant (5 unaffected individuals and 2 affected individuals) did not identify any perinuclear inclusions or other abnormalities [Paudel et al 2014].

Genotype-Phenotype Correlations

No genotype-phenotype correlations exist.

Penetrance

The penetrance of the c.907_909delGAG *TOR1A* pathogenic variant is approximately 30%. Thus, on average, 30% of individuals who inherit the disease-causing allele develop DYT1 dystonia and 70% do not.

The clinical variability of DYT1 dystonia is great; an affected individual may be more or less severely affected than the parent from whom the disease-causing allele was inherited. Clinical heterogeneity within a single family is exemplified by the report of a family with one individual with writer's cramp and another with severe dystonic storm [Opal et al 2002].

Nomenclature

A naming system that combines the "DYT" designation (to indicate the main clinical feature) and the name of the (confirmed) gene or chromosome locus has been proposed [Marras et al 2012] and now recommended as new nomenclature for genetic movement disorders [Marras et al 2016]. The new designation for DYT1 isolated dystonia using this system is DYT-TOR1A.

Terms used for DYT1 isolated dystonia in the past include the following:

- Dystonia muscularum deformans
- Primary torsion dystonia (PTD)

Prevalence

DYT1 dystonia is a common form of early-onset isolated dystonia [Ozelius et al 1997].

DYT1 dystonia is estimated to account for approximately 16% to 53% of early-onset dystonia in non-Jews and approximately 80% to 90% in Ashkenazi Jews [reviewed in Ozelius & Bressman 2011]. Because a minority of isolated dystonia is early onset, the rate of DYT1 dystonia as a percentage of all isolated dystonia is low (i.e., adult-onset focal dystonia is far more common) [Grundmann et al 2003, Elia et al 2006, Lin et al 2006].

The prevalence of early-onset dystonia in Ashkenazi Jews is estimated at 1:3000-1:9000; because of the reduced penetrance (i.e., 30%), the carrier frequency for the *TOR1A* pathogenic variant is estimated to be 1:1000-1:3000 [Risch et al 1995]. Among non-Jews, the prevalence is lower.

The increased prevalence in Ashkenazim is the result of a founder variant that appeared approximately 350 years ago [Risch et al 1995].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *TOR1A*.

Differential Diagnosis

In studies of individuals with different forms of dystonia (see Dystonia Overview) and unclassified movement disorders, a high proportion of those individuals with the typical phenotype (early-onset isolated dystonia starting in limb and then generalizing) have the *TOR1A* c.907_909delGAG deletion [Kamm et al 1999, Klein et al 1999, Ozelius & Bressman 2011].

Dopa-responsive dystonia (*GCH1*), DYT6 (*THAP1*) dystonia, and DYT25 (*GNAL*) dystonia [Fuchs et al 2013] can cause clinical phenotypes similar to that of DYT1 dystonia.

Other, as-yet unidentified genetic forms of autosomal dominant early-onset dystonia also exist [Valente et al 2001, Fasano et al 2006].

Early-onset isolated dystonia can also be inherited in an autosomal recessive manner. Biallelic pathogenic variants in *HPCA* have been identified in individuals with this form of dystonia [Charlesworth et al 2015].

The following findings tend to exclude a diagnosis of DYT1 dystonia [Bressman et al 1997, Bressman & Greene 2000, Albanese et al 2006]:

- Onset in adulthood (especially age >40 years)
- **Isolated** focal or segmental cervical-cranial dystonia, including:
  - Spasmodic torticollis (cervical dystonia)
  - Spasmodic dysphonia (laryngeal dystonia resulting in either broken and strangled or breathy speech)
  - Blepharospasm (involuntary eye closure), which may also include contractions of other facial muscles
  - Oromandibular dystonia (the jaw is held open or shut)
- Dramatic improvement with levodopa therapy suggests the diagnosis of dopa-responsive dystonia (DRD). DRD is an early-onset form of dystonia caused primarily by heterozygous mutation of *GCH1*. Individuals with DRD have near-resolution of symptoms with low-dose levodopa. Another cause of early-onset dystonia that responds to levodopa is juvenile-onset Parkinson disease caused by biallelic pathogenic variants in *PRKN* (*PARK2*) (see Parkin Type of Early-Onset Parkinson Disease).
- Abnormal brain CT examination or MRI examination
- Additional abnormalities on neurologic examination. Findings other than dystonia are indicative of a combined rather than isolated dystonia. Combined dystonia can be due to a genetic or acquired etiology (see Dystonia Overview).
- A history that suggests an acquired cause of dystonia, such as exposure to neuroleptics or other dopamine-blocking drugs (tardive dystonia), perinatal ischemia/injury, stroke, cerebral trauma, or encephalitis
- Presence of inconsistent weakness, non-physiologic sensory findings, or incongruous movements that suggest a psychogenic basis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with DYT1 early-onset isolated dystonia, the following evaluations are recommended:

- Thorough history, including family history
- General physical examination
- Neurologic examination. The standard scale used to measure the clinical extent of dystonia is the Burke-Fahn-Marsden rating scale.
- If evidence of psychiatric problems (especially depression) exist, consideration of psychiatric assessment
- Consultation with a clinical geneticist and/or genetic counselor
- Consideration of occupational and/or physical therapy evaluation

Treatment of Manifestations

Treatment is aimed at relieving symptoms [Albanese et al 2011, Lubarr & Bressman 2011, Bertucco & Sanger 2015, Dressler et al 2016, Shanker & Bressman 2016].

Oral medications are usually tried first:

- Anticholinergics (e.g., trihexyphenidyl)
  - Trihexyphenidyl can be titrated to high doses (in the range of 100 mg/day) in children, who tend to tolerate high doses better than adults.

    - Anticholinergic side effects, particularly cognitive effects, must be monitored closely. Pyridostigmine can be used to counter anticholinergic side effects, but does not improve cognitive side effects.
- Baclofen (Lioresal®)
- Benzodiazepines
- Other medications including levodopa, antiepileptics, and dopamine-depleting agents; these have been used to treat dystonia with variable effects.

Botulinum toxin injections directly into dystonic muscles are generally the treatment of choice for adult-onset focal dystonias. For individuals with more widespread dystonia in whom specific muscle groups produce disabling symptoms, such injections may also be helpful and are often used in combination with oral medications.

If medications fail

- Surgery to enable **deep-brain stimulation (DBS) of the globus pallidus interna (GPi)** has been shown to be an effective treatment for medically refractory isolated generalized dystonia in randomized controlled studies [Vidailhet et al 2005, Kupsch et al 2006, Vidailhet et al 2007], including in individuals with DYT1 early-onset dystonia [reviewed in Fox & Alterman 2015].
    - GPi DBS has become a well-established and important treatment option for individuals with medically refractory DYT1 early-onset dystonia. Overall, individuals with DYT1 early-onset dystonia tend to have good outcomes after GPi DBS, with some showing dramatic improvement.
    - Some, though not all, studies have found that the presence of a *TOR1A* pathogenic variant is a positive predictive factor of good outcome of GPi DBS surgery [Isaias et al 2008, Andrews et al 2010, Borggraefe et al 2010, Air et al 2011].
    - Shorter disease duration has been correlated with improved outcomes, highlighting the importance of early referral for DBS in children with severe, medically refractory DYT1 dystonia. [Markun et al 2012, Lumsden et al 2013]. Conversely, referral for DBS should not be made prematurely (i.e., prior to sufficient medication trials).
    - Clinical effect has been found to be well sustained at follow up of up to 13 years [Alcindor et al 2010, Cif et al 2010, Panov et al 2013, Krause et al 2016].

  Note: Intrathecal baclofen therapy has been used for treatment of generalized dystonia of various etiologies in the past [van Hilten et al 2000, Walker et al 2000, Albright et al 2001], however, GPi DBS surgery has become the preferred surgical treatment for severe, medically refractory DYT1 early-onset dystonia because of the good treatment outcomes.

- Physical therapy and an appropriate exercise program may be of benefit.

Prevention of Secondary Complications

Aggressive medical and surgical intervention including regular follow up for adjustment of medicines and timely referral for GPi DBS surgery when indicated is appropriate in order to prevent long-term orthopedic complications such as joint contractures or spine deformities. However, little systematic data support or negate the use of this approach.

Surveillance

Follow up several times a year with a neurologist specializing in movement disorders is recommended (especially if there is progression) to prevent secondary complications, although little information regarding the benefit of this approach is available.

Individuals treated with GPi DBS surgery require regular follow up, more frequent in the first year after surgery, for programming of the stimulation parameters and monitoring of battery life.

Agents/Circumstances to Avoid

The extremities affected by dystonia should not be placed in a brace or cast, unless medically necessary, as this can worsen the dystonia.

Evaluation of Relatives at Risk

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

Pregnancy Management

Data on the use of the oral medications typically used for treatment of dystonia during pregnancy are limited. Isolated case reports of treatment with trihexyphenidyl or carbidopa/levodopa for various conditions (including certain forms of dystonia) during pregnancy have not found adverse effects on either the affected mother or the fetus [Watanabe et al 2009, Mendhekar & Andrade 2011, Robottom & Reich 2011, Serikawa et al 2011, Watanabe & Matsubara 2012, Dostal et al 2013].

No adverse fetal or maternal outcomes were reported in two series of women, including four women with DYT1 dystonia, who were treated with DBS implantation prior to pregnancy. [Scelzo et al 2015, Ziman et al 2016].

Therapies Under Investigation

RNA interference (RNAi) has been used in cell culture systems overexpressing the mutated torsin protein to block aggregate formation and restore normal distribution of wild type torsin-1A (torsinA) [Kock et al 2006], suggesting a possible future role for RNAi in DYT1 therapy.

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

Genetic Counseling

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

Mode of Inheritance

DYT1 early-onset isolated dystonia (DYT1 dystonia) is inherited in an autosomal dominant manner with reduced penetrance and broad clinical variability.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with DYT1 dystonia inherited a *TOR1A* c.907_909delGAG deletion from a parent who may or may not have clinical features of the disorder (~70% of individuals who have the deletion are asymptomatic).

- In rare cases, a proband with DYT1 dystonia may have the disorder as the result of a *de novo* GAG deletion in *TOR1A*; three cases have been reported [Klein et al 1998, Hjermind et al 2002, De Carvalho Aguiar et al 2010].
- It is appropriate to offer molecular genetic testing to both parents of an affected individual to determine if either has the c.907_909delGAG deletion in *TOR1A*.
- Although most individuals diagnosed with DYT1 dystonia have a parent who has the c.907_909delGAG deletion in *TOR1A*, the family history may appear to be negative because of reduced penetrance (many parents are asymptomatic) or failure to recognize the disorder in family members with mild clinical features (i.e., writer's cramp only).

Sibs of a proband

- The risk to the sibs of an affected person depends on the genetic status of the proband's parents.
- If a parent has the c.907_909delGAG deletion in *TOR1A*, the risk to sibs of inheriting the deletion is 50%. The penetrance for the deletion is approximately 30%. Thus, on average, 30% of individuals who inherit the c.907_909delGAG deletion in *TOR1A* develop dystonia and 70% do not develop dystonia. The clinical variability is great, and an affected individual may be more or less severely affected than the parent who transmitted the deletion (see Penetrance).
- If the c.907_909delGAG deletion in *TOR1A* is not detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism. No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband

- Each child of an individual with DYT1 dystonia has a 50% chance of inheriting the c.907_909delGAG deletion in *TOR1A*. However, the risk that a child will be affected is less than 50% because of reduced penetrance. On average, 70% of individuals who inherit the c.907_909delGAG deletion in *TOR1A* do not develop dystonia (see Penetrance).
- Intrafamilial clinical variability is great, and an affected child may be more severely or less severely affected than the parent who transmitted the deletion.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a c.907_909delGAG deletion in *TOR1A*, his or her family members are 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, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or 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.

Testing of at-risk asymptomatic adult relatives of individuals with DYT1 dystonia is possible once the molecular diagnosis has been confirmed in an affected family member. Such testing should be performed in the context of formal genetic counseling. Note: Asymptomatic adults rarely develop symptoms, particularly after age

26 years, and those with mild symptoms are unlikely to progress significantly if at all. Thus, while there is a reduced age-related risk for adults, the term "predictive testing" may not be appropriate for DYT1 dystonia.

Testing of asymptomatic individuals younger than age 18 years at risk for DYT1 dystonia is not considered appropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.

Testing is appropriate to consider in symptomatic individuals in a family with an established diagnosis of DYT1 dystonia regardless of age.

See also the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, 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 pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *TOR1A* c.907_909delGAG deletion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing (PGT) for DYT1 dystonia are possible. The presence of the *TOR1A* deletion detected by prenatal testing or PGT does not predict whether individuals will be symptomatic, or, if they are, what the age of onset or severity of the disorder will be.

Resources

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

- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org
- **Dystonia UK**
  United Kingdom
  Email: info@dystonia.org.uk
  dystonia.org.uk
- **Norton & Elaine Sarnoff Center for Jewish Genetics**
  Phone: 312-357-4718
  Email: jewishgenetics@juf.org
  www.juf.org/cjg
- **Global Dystonia Registry**
  Dystonia Medical Research Foundation
  Email: Coordinator@globaldystoniaregistry.org
  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. DYT1 Early-Onset Isolated Dystonia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TOR1A	9q34.11	Torsin-1A	TOR1A database	TOR1A	TOR1A

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 DYT1 Early-Onset Isolated Dystonia (View All in OMIM)

128100	DYSTONIA 1, TORSION, AUTOSOMAL DOMINANT; DYT1
605204	TORSIN 1A; TOR1A

Gene structure. *TOR1A* comprises five exons. Exon 5 includes a GAGGAG sequence that is highly conserved.

Pathogenic variants. The majority of affected individuals have a 3-bp deletion c.907_909delGAG involving the highly conserved GAGGAG sequence in exon 5 [Ozelius et al 1997] (for more information, see Table A and Table 2). Other variants have been reported; however, none has been unequivocally associated with disease (Table 2).

Three additional in-frame deletions have been reported:

- An 18-bp deletion (c.966_983del18) identified in a family with individuals with dystonia and myoclonus who were subsequently found to have a pathogenic variant in *SGCE*, the gene that causes myoclonus-dystonia, casting doubt on the role of the 18-bp deletion in causing symptoms [Leung et al 2001]
- A 4-bp deletion (c.934_937delAGAG), found in an unaffected control blood donor who was not examined neurologically [Kabakci et al 2004], an individual with a complex movement disorder including myoclonus, dystonia, and mild signs of Parkinson disease [Ritz et al 2009]
- A 6-bp deletion (c.40_45delGCGCCG) in a female with cervical dystonia with onset at age 31 followed by dystonic head and hand tremor later in life [Vulinovic et al 2014]

In addition, five other novel changes, each identified in a single affected individual and most reported in the ExAC database (see Table 2), have been reported:

- A c.863G>A (p.Arg288Gln) variant in an individual with facial palsy and severe fixed dystonia starting in infancy [Zirn et al 2008]
- A c.613T>A (p.Phe205Ile) variant in a male with orobulbar dystonia beginning in his forties [Calakos et al 2010]
- A c.361G>A (p.Glu121Lys) variant in an individual with segmental dystonia including cervical dystonia and spasmodic dysphonia [Vulinovic et al 2014]
- A c.581A>T (p.Asp194Val) variant in an individual age 23 years with cervical dystonia, tremor in both hands and slight spasmodic dysphonia. In addition, this individual has a *THAP1* (*DYT6*) variant (c.539T>C; p.Leu180Ser). Each is inherited from one of the parents [Cheng et al 2014].
- A c.385G>A (p.Val129Ile) variant in a Serbian woman age 38 years with adult onset cervical dystonia [Dobričić et al 2015]

Interestingly, individuals with a disease-modifying p.Asp216His variant in *trans* configuration with the c.907_909delGAG deletion (i.e., the variants are on different alleles) are largely protected from expression of the disease: disease penetrance is approximately 3% with the p.His216 variant and 35% with the p.Asp216 variant

[Risch et al 2007]. Although information regarding these disease-modifying variants may be of interest, associations can rarely be used to direct patient care, and thus clinical genetic testing for these variants is not recommended.

Table 2. *TOR1A* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Disease modifier	c.646G>C	p.Asp216His	NM_000113.2 NP_000104.1
Uncertain clinical significance	c.40_45delGCGCCG [1]	p.Ala14_Pro15del	
	c.361G>A [1]	p.Glu121Lys	
	c.385G>A [1]	p.Val129Ile	
	c.581A>T	p.Asp194Val	
	c.613T>A [1]	p.Phe205Ile	
	c.863G>A [1]	p.Arg288Gln	
	c.934_937delAGAG	p.Arg312PhefsTer14	
	c.966_983del18 [1]	p.Phe323_Tyr328del	
Pathogenic	c.907_909delGAG [1]	p.Glu303del	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. In ExAC database

Normal gene product. The protein torsin-1A comprises 332 amino acids. It has an ATP-binding domain and a putative N-terminal leader sequence. It is a member of a superfamily of ATPases, with particular homology to heat shock proteins, and is ubiquitous, with particularly intense expression in the substantia nigra, dopamine neurons, cerebellar Purkinje cells, thalamus, globus pallidus, hippocampal formation, and cerebral cortex [Augood et al 1998, Augood et al 2003]. Torsin-1A is expressed in at least four brain regions beginning between age four and eight weeks [Siegert et al 2005].

Torsin-1A shuttles between the endoplasmic reticulum (ER) and the nuclear envelope (NE) [Goodchild & Dauer 2004, Naismith et al 2004, Hewett et al 2006]. In the ER, it plays a role in endoplasmic reticulum-associated degradation (ERAD) making cells less sensitive to ER stress [Nery et al 2011]. Torsin-1A also localizes to neurite varicosities and vesicles, and along neuronal processes and may play a role in dopamine release and metabolism as well as tyrosine hydroxylase activity [Ledoux et al 2013, Rose et al 2015]. Torsin-1A has recently been found in large ribonucleoprotein granules, where it is thought to play a role in delivering messenger RNAs to synapses [Jokhi et al 2013]. In addition, torsin-1A is involved in cytoskeletal dynamics that may be important for neurite extensions during brain development [Kamm et al 2004, Hewett et al 2006, Hewett et al 2007, Nery et al 2008, Naismith et al 2009].

Abnormal gene product. The common c.907_909delGAG deletion results in the loss of one of two of glutamic acid residues in a conserved region of the torsin-1A protein. In cell cultures, overexpressed mutated torsin-1A forms spheroid inclusions usually flanking the nucleus and deriving from ER or nuclear membrane. The significance of these inclusions is unclear because they have not been found in postmortem brain samples of individuals with DYT1 [Bragg et al 2004].

Knock-in, knockout, and knockdown mouse models, a drosophila knockout model, as well as cellular studies support a loss-of-function mechanism in DYT1 dystonia resulting from a dominant-negative effect [Caldwell et al 2013, Richter & Richter 2014, Rose et al 2015]. Both knock-in and knockout mice homozygous for the c.907_909delGAG deletion die at birth with seemingly normal morphology, but showing post-migratory

neurons with abnormal nuclear membranes [Goodchild et al 2005]. Mutated torsin-1A appears to destabilize the wild-type protein, causing premature degradation not only through the macroautophagy pathway but also by the proteasome [Giles et al 2008, Giles et al 2009].

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Chapter Notes

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Revision History

- 17 November 2016 (sw) Comprehensive update posted live
- 2 January 2014 (me) Comprehensive update posted live
- 23 November 2010 (cd) Revision: corrected mutation nomenclature: c.904_906delGAG → c.907_909delGAG
- 1 July 2008 (me) Comprehensive update posted live
- 31 August 2006 (cd) Revision: *TOR1A* mutations other than 3-bp deletion may cause DYT1; clinical testing available for such mutations
- 5 April 2005 (me) Comprehensive update posted live
- 21 January 2003 (me) Comprehensive update posted live
- 14 April 1999 (pb) Review posted live
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