GENEReviews

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Early-Onset Primary Dystonia (DYT1)

[*Early-Onset Torsion Dystonia, Oppenheim's Dystonia*]

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Summary

Disease characteristics. Early-onset primary dystonia (DYT1) typically presents in childhood or adolescence and only on occasion in adulthood. Dystonic muscle contractions causing posturing of a foot, leg, or arm are the most common presenting findings. Dystonia is usually first apparent with specific actions; e.g., 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, except for postural arm tremor. Disease severity varies considerably even within the same family. Isolated writer's cramp may be the only sign.

Diagnosis/testing. DYT1 is diagnosed by molecular genetic testing of the *TOR1A* gene revealing the three -base pair deletion c.904_906delGAG in most affected individuals.

Management. *Treatment of manifestations:* Oral medications are usually tried first and include anticholinergics, baclofen, and others alone or in combination (levodopa, clonazepam and other benzodiazepines, carbamazepine, and dopamine-depleting agents). If oral medications fail other options include surgery to enable deep-brain stimulation of the globus pallidus interna (GPi), intrathecal baclofen, and botulinum toxin injections directly into dystonic muscles in which symptoms are disabling. Physical therapy and an appropriate exercise program may be of benefit. *Prevention of secondary complications:* aggressive medical and surgical intervention to prevent contractures of the joints and deformities of the spine. *Surveillance:* follow-up several times a year.

Genetic counseling. DYT1 is inherited in an autosomal dominant manner with reduced penetrance. Offspring of an affected individual or an asymptomatic individual known to have a *TOR1A* disease-causing mutation have a 50% chance of inheriting the disease-causing mutation and a 30% to 40% chance of developing clinical findings. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation in the family is known.

Diagnosis

Clinical Diagnosis

Early-onset primary dystonia (DYT1) is a form of primary dystonia; that is, aside from dystonia (involuntary sustained contraction of muscles that causes directional and repetitive movements often resulting in twisting of the involved body region) no abnormalities except tremor are evident on neurologic examination or routine neuroimaging.

Age of onset of dystonia. Onset before age 26 years was the single diagnostic criterion with 100% sensitivity among 180 individuals with primary dystonia, including 89 with DYT1.

Note: (1) Older ages of onset were also seen among relatives; (2) family members with later onset tended to have arm dystonia in the form of writer's cramp; and, (3) specificity for DYT1 increased, particularly in the case of Ashkenazi Jews, using the criterion of onset in a limb before age 24 years, or of having two or more limbs affected [Bressman et al 2000].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *TOR1A*, encoding the protein torsin-1A (torsinA), is the only gene known to be associated with early-onset primary dystonia (DYT1).

Clinical testing

- **Targeted mutation analysis.** Most individuals with DYT1, regardless of ethnic background, have the three-base pair deletion c.904_906delGAG in the *TOR1A* gene [Ozelius et al 1997, Warner & Jarman 1998].
- **Sequence analysis.** Despite extensive screening, only three other variations in *TOR1A* that change the amino acid sequence of torsin-1A have been found; none has been unequivocally associated with disease. Thus, the utility of sequence analysis for diagnosis is limited:
  - An 18-base pair deletion (c.966_983del18) was identified in a family with individuals with dystonia and myoclonus who were subsequently found to have a mutation in *SGCE*, the gene that causes myoclonus-dystonia, casting doubt on the role of the 18-base pair deletion in causing symptoms [Leung et al 2001].
  - A four-base pair deletion (c.934_937delAGAG) was found in an unaffected control blood donor who was not examined neurologically [Kabakci et al 2004].
  - A disease-modifying variant p.Asp216His encodes aspartic acid in 88% and histidine in 12% of alleles in control populations [Ozelius et al 1997] and modifies DYT1 penetrance [Kock et al 2006b, Risch et al 2007]. Thus, sequence analysis or testing for this variant could potentially be used to refine risk estimates for asymptomatic individuals with the c.904_906delGAG deletion.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Targeted mutation analysis	*TOR1A* c.904_906delGAG	>99%	Clinical Testing
Sequence analysis	*TOR1A* sequence variants	Unknown	

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Establishing the diagnosis in a proband. Detection of the *TOR1A* c.904_906delGAG deletion in a proband is diagnostic of DYT1.

Note: Because the c.904_906delGAG deletion is the only definitive DYT1 disease-causing mutation identified to date, sequence analysis is unlikely to provide additional diagnostic information in an individual who does not have the deletion.

Guidelines published by Bressman et al (2000) recommend genetic counseling and testing for persons who have (1) primary torsion dystonia (PTD) with onset before age 26 years and/or (2) a family history of early-onset dystonia.

Testing of at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *TOR1A*.

Clinical Description

Natural History

Dystonia is the involuntary sustained contraction of muscles that causes directional and repetitive movements often resulting in twisting of the involved body region. Early-onset primary dystonia (DYT1) is considered a primary dystonia because it is not associated with other neurologic abnormalities.

DYT1 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 the neck or a cranial muscle.

In most (not all) individuals who have onset in a leg, dystonia progresses over several years. The contractions become less action-specific and may even be present at rest. Also, the dystonia spreads 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 aapproximately 50%. Those individuals with onset in the neck or cranial muscles 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.

The cranial muscles are involved in 11% to 18% of individuals [Muller et al 1998, Valente et al 1998, Bressman 2004]. Approximately 20% of DYT1 is restricted to a single body region, usually as writer's cramp. In one family, the only manifestation was early-onset brachial dystonia [Gasser et al 1998]. Dystonia that is restricted to an arm or the neck occurs in a minority of individuals with adult onset. Unusual phenotypic expression of DYT1 includes isolated blepharospasm [Tuffery-Giraud et al 2001] and fluctuating unilateral myoclonic dystonia [Gatto et al 2003].

Once they appear, dystonic movements usually persist through life.

Pain is not a prominent finding except in torticollis, which is rare in DYT1.

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

The average age of onset of DYT1 is approximately 12 years; the median age is between nine and 11 years. Onset ranges at least from age four to 64 years [Opal et al 2002, Bressman 2004], with the vast majority beginning before age 26 years. Life span is not thought to be shortened.

Neuroimaging. Brain CT and routine MRI are normal.

Fluorodeoxyglucose (FDG) PET scan studies of individuals with a *TOR1A* mutation with and without dystonia show increased metabolism in the lentiform nucleus, cerebellum, and supplementary motor cortex. Individuals with a *TOR1A* mutation and dystonia have additional movement-related hypermetabolism in the cerebellum, midbrain, and thalamus [Eidelberg et al 1998, Carbon et al 2004b].

Studies combining PET scanning and psychomotor testing in individuals with a *TOR1A* mutation without dystonia show subtle sequence-learning abnormalities in motor performance and recruitment of brain networks [Carbon et al 2002, Ghilardi et al 2002, Carbon et al 2008]. This PET evidence suggests the presence of abnormal brain processing in individuals with a *TOR1A* mutation regardless of the presence or absence of dystonia.

Other imaging abnormalities detected in individuals with a *TOR1A* mutation include decreased striatal D2 receptor binding [Asanuma et al 2005] and microstructural changes involving the subgyral white matter of the sensorimotor cortex [Carbon et al 2004a, Carbon et al 2004b], as well as pons in the region of the left superior cerebellar peduncle [Carbon et al 2008].

Neuropathology. Very few brains of individuals with DYT1 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].

Genotype-Phenotype Correlations

Although the phenotype is highly variable, all affected individuals have the c.904_906delGAG deletion in the coding sequence of the gene. Thus, no genotype-phenotype correlations exist.

Penetrance

The penetrance for a disease-causing mutation of the *TOR1A* gene is approximately 30% overall. Thus, on average, 30% of individuals who inherit the disease-causing allele develop DYT1 and 70% do not.

Individuals who have an uncommon disease-modifying His216 variant (p.Asp216His) in trans configuration with the c.904_906delGAG deletion are largely protected from expression of the disease; disease penetrance is only 3% with the His216 variant, whereas it is 35% if the Asp216 variant occurs in trans configuration with the c.904_906delGAG deletion [Risch et al 2007]. In the study by Risch et al (2007), two of 119 symptomatic individuals with the c.904_906delGAG deletion had the His216 allele in trans configuration compared to 24 of 113 asymptomatic individuals. (All other chromosomes studied had the Asp216 variant.)

The clinical variability of DYT1 is great; an affected individual may be more or less severely affected than the parent from whom the disease-causing allele was inherited.

Anticipation

There is no evidence for anticipation.

Nomenclature

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

- Dystonia muscularum deformans
- Primary torsion dystonia (PTD)

Prevalence

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

DYT1 is estimated to account for approximately 16% to 53% of early-onset dystonia in non-Jews and approximately 80% to 90% in Ashkenazi Jews [Bressman et al 1994, Risch et al 1995, Valente et al 1998, Ikeuchi et al 1999, Slominsky et al 1999, Brassat et al 2000, Bressman et al 2000, Zorzi et al 2002]. Because a minority of primary dystonia is early-onset, the rate of DYT1 as a percentage of all primary dystonia is low [Grundmann et al 2003, Elia et al 2006, Lin et al 2006].

The disease frequency in Ashkenazi Jews is estimated at 1:3000-1:9000; the prevalence of those having a *TOR1A* mutation is 1:1000-1:3000 [Risch et al 1995]. Among non-Jews, the prevalence is lower.

In one study from southeastern France that genotyped newborns, the heterozygote incidence was 1:12,000 [Frédéric et al 2007]; this is consistent with the approximately fivefold increased frequency of early-onset dystonia in Ashkenazim compared to non-Jews proposed in studies prior to gene identification [Zeman & Dyken 1967].

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

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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 dystonia starting in limb and then generalizing) have the *TOR1A* c.904_906delGAG deletion [Kamm et al 1999, Klein et al 1999, de Carvalho Aguiar & Ozelius 2002]. However, there are clearly other, rarer genetic causes of early-onset primary dystonia

(DTY1) that have yet to be identified [Bressman et al 1994, Valente et al 2001, Fasano et al 2006, Saunders-Pullman et al 2007].

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

- Onset in adulthood (especially after age 40 years)
- Focal or segmental cervical-cranial dystonia, including the following:
  - 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)

    Note: Blepharospasm and oromandibular dystonia occurring together are called Meige or Brueghel syndrome.
- Dramatic improvement with levodopa therapy, suggesting dopa-responsive dystonia (DRD). DRD is an early-onset form of dystonia caused primarily by heterozygous mutations in *GTP*, the gene encoding cyclohydrolase 1. 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 mutations in *PARK2*, the gene encoding parkin (See Parkin Type of Juvenile Parkinson Disease).
- Abnormal brain CT examination or MRI examination
- Additional abnormalities on neurologic examination. Findings other than dystonia suggest that dystonia is not primary but caused by another disorder that may be inherited, complex, or acquired in etiology. Parkinsonism is a frequent associated finding. Inherited causes of dystonia include: Wilson disease, Huntington disease, spinocerebellar ataxias (see Ataxia Overview), rapid-onset dystonia parkinsonism, and panthothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome), among others.
- A history that suggests an acquired cause of dystonia such as exposure to neuroleptics and other dopamine-blocking drugs (tardive dystonia), perinatal ischemia/injury, head or peripheral trauma, encephalitis, toxins, or stroke
- Presence of inconsistent weakness, non-physiologic sensory findings, or incongruous movements that suggest a psychogenic basis. However, it is also important to note that often dystonia is improperly diagnosed as "psychogenic," causing considerable distress in affected individuals.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with early-onset primary dystonia (DYT1), the following evaluations are recommended:

- Thorough history, including family history
- Physical examination

- Neurologic examination. A useful tool to measure the clinical extent of dystonia is the Burke-Fahn-Marsden rating scale.
- If evidence of psychiatric problems (especially depression) exists, consideration of psychiatric assessment

Treatment of Manifestations

Treatment is aimed at relieving symptoms [Adler 2000, Bressman & Greene 2000, Coubes et al 2000, Gross & Lozano 2000, Scott 2000, Goetz & Horn 2001].

Oral medications are usually tried first:

- Anticholinergics (moderately effective for ~40%-50% of individuals)
- Baclofen (Lioresal®)
- Other medications tried alone or in combination: levodopa, clonazepam and other benzodiazepines, carbamazepine, and dopamine depleting agents (reserpine, tetrabenazine)

If oral medications fail:

- Surgery to enable deep-brain stimulation of the globus pallidus interna (GPi) is a treatment option that has been effective in randomized controlled studies [Vidailhet et al 2005, Kupsch et al 2006, Vidailhet et al 2007], particularly for intractable generalized primary dystonia, including DYT1 dystonia [Cif et al 2003, Kupsch et al 2003, Coubes et al 2004, Krause et al 2004].
- Intrathecal baclofen may be considered, though efficacy rates for primary dystonia have not been well established [van Hilten et al 2000, Walker et al 2000, Albright et al 2001].

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 be helpful.

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 orthopedic surgery when necessary, has been advocated to prevent contractures of the joints and deformities of the spine. 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 data regarding the benefit of this approach are available.

Testing of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Early-onset primary dystonia (DYT1) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with DYT1 have a parent who has the mutant *TOR1A* allele.
- Approximately 70% of individuals who have the disease-causing allele are asymptomatic.
- It is appropriate to offer molecular genetic testing to both parents of an affected individual to determine if either has the c.904_906delGAG deletion in the *TOR1A* gene.
- A proband with DYT1 may also have the disorder as the result of a *de novo* gene mutation. While *de novo* mutations are probably rare [Ozelius, unpublished], two cases have been reported [Klein et al 1998, Hjermind et al 2002].

Note: Although most individuals diagnosed with DYT1 have a parent who has the c.904_906delGAG deletion in the *TOR1A* gene, many parents are unaffected because the penetrance is low (~30%). The family history may also appear to be negative because of failure to recognize the disorder, particularly in family members affected with 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 parent.
- If a parent has the c.904_906delGAG deletion in the *TOR1A* gene, the risk to sibs of inheriting the mutation is 50%. The penetrance for a disease-causing mutation of the

TOR1A gene is approximately 30%. Thus, on average, 30% of individuals who inherit the mutant allele develop DYT1; and 70% do not develop DYT1. The clinical variability is great, and an affected individual may be more or less severely affected than the parent who transmitted the disease-causing allele. One study indicated that a sib who has the His216 disease-modifying variant (p.Asp216His) in trans configuration with the c.904_906delGAG deletion is unlikely to develop dystonia (see Penetrance).

- When molecular genetic testing does not reveal the c.904_906delGAG deletion in the *TOR1A* gene in either parent, the risk to the sibs of a proband appears to be low. No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband

- A proband with the c.904_906delGAG deletion in the *TOR1A* gene has a 50% risk of transmitting it to each offspring whether the proband is symptomatic or not.
- The penetrance for the disease-causing mutation of the *TOR1A* gene is 30%. Thus, on average, 30% of offspring who inherit the mutant allele develop DYT1; and 70% do not. One study indicated that a sib who has the His216 disease-modifying variant (p.Asp216His) in trans configuration with the c.904_906delGAG deletion is unlikely to develop dystonia (see Penetrance).
- The clinical variability is great, and an affected child may be more severely or less severely affected than the parent who transmitted the disease-causing allele.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is found to have a gene mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations, including alternate paternity or undisclosed adoption, could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

It 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 adults for DYT1 is available using the same techniques described in Molecular Genetic Testing. It is appropriate to offer molecular genetic testing to asymptomatic at-risk adult relatives for genetic counseling purposes.

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.

Testing of asymptomatic at-risk adult family members usually involves pretest interviews in which the motives for requesting the test, the individual's knowledge of DYT1, the possible impact of positive and negative test results for the individual and for family members, and neurologic status are assessed. An in-depth discussion of reduced age-related penetrance and

variable symptom severity (also age-related) is a critical part of genetic counseling. Affected individuals should also be apprised of possible problems that they may encounter as a result of genetic testing with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. The primary reasons for testing asymptomatic at-risk adults are to facilitate decision making regarding reproduction and to better assess the risk to children. Another motivation for testing may be simply a "need to know." After proper counseling, a positive *TOR1A* c.904_906delGAG deletion test result in an adult is unlikely to affect financial decisions or career planning. When testing at-risk individuals for DYT1, an affected family member should be tested first to confirm the molecular diagnosis in the family.

Testing of at-risk individuals during childhood. Consensus holds that individuals younger than age 18 years who are at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications. Furthermore, no preventive treatment for DYT1 is available. Children who are symptomatic usually benefit from having a specific diagnosis established. See also the resolution of the National Society of Genetic Counselors on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents (pdf; see Genetic Testing).

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal testing for pregnancies at 50% risk for DYT1 is possible by analysis of DNA extracted from fetal cells obtained through chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation or amniocentesis usually performed at approximately 15-18 weeks' gestation. The disease-causing allele must be identified in the family before prenatal testing can be performed. The presence of the *TOR1A* mutation detected by prenatal testing does not predict whether individuals will be symptomatic, or if they are, the age of onset or progression of the disorder.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) for the c.904_906delGAG deletion in *TOR1A* has also been reported [Rechitsky et al 2004]. PGD may be available for families in which the disease-causing mutation has been identified. The presence of the *TOR1A* mutation detected by PGD does not predict whether individuals will be symptomatic, or, if they are, what the age of onset or progression of the disorder will be. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Early-Onset Primary Dystonia (DYT1)

Gene Symbol	Chromosomal Locus	Protein Name
TOR1A	9q34	Torsin-1A

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Early-Onset Primary Dystonia (DYT1)

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

Table C. Genomic Databases for Early-Onset Primary Dystonia (DYT1)

Gene Symbol	Entrez Gene	HGMD
TOR1A	1861 (MIM No. 605204)	TOR1A

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The normal gene comprises five exons. Exon 5 includes a GAGGAG sequence that is highly conserved.

Pathologic allelic variants: The majority of affected individuals have a 3-bp deletion c.904_906delGAG involving the highly conserved GAGGAG sequence in exon 5 [Ozelius et al 1997]. (For more information, see Genomic Databases table.) (see Table 2).

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

Class of Variant Allele	DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
Disease Modifier	c.646G>C	p.Asp216His	NM_000113.2 NP_000104.1
Pathologic	c.904_906delGAG	p.Glu302del	
	c.934_937delAGAG [1]	p.Arg312PhefsX14	
	c.966_983del18	p.Phe323_Tyr328del	

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

1. Mutation identified in an unaffected control blood donor who was not examined neurologically [Kabakci et al 2004]; see Molecular Genetic Testing.

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]. In vitro and in vivo studies have localized torsin-1A primarily to the lumen of the endoplasmic reticulum (ER) but also to neurite varicosities and vesicles, and along neuronal processes [Ferrari-Toninelli et al 2004]. In addition, torsin-1A has been shown to interact with the kinesin light chain 1 (KLC1) [Kamm et al 2004] and with vimentin (VIM) [Hewett et al 2006], as well as to regulate the cellular trafficking of the dopamine transporter and other membrane-bound proteins [Torres et al 2004]. These and other findings suggest a chaperone function for torsin-1A [Bragg et al 2004].

Abnormal gene product: The common c.904_906delGAG deletion results in the loss of one of a pair of glutamic acid residues in a conserved region of the torsin-1A protein. In cell cultures, over-expressed mutant 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 DYT1 brain samples [Bragg et al 2004].

Knock-in, knockout, and knockdown mouse models as well as cellular studies support a loss of function mechanism in DYT1, which is presumed to result from a dominant-negative effect [Goodchild & Dauer 2004, Goodchild et al 2005]. Both knock-in and knockout mice homozygous for the c.904_906delGAG deletion die at birth with seemingly normal morphology, but showing postmigratory neurons with abnormal nuclear membranes [Goodchild et al 2005]. RNA interference (RNAi) has been used in cell culture systems overexpressing the mutant torsin protein to block aggregate formation and restore normal distribution of wild type torsin-1A (torsinA) [Kock et al 2006a], suggesting a possible future role for RNAi in DYT1 therapy.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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WE MOVE (Worldwide Education and Awareness for Movement Disorders)
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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents (pdf; see Genetic Testing)

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Chapter Notes

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Revision History

- 2 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 to live Web site
- 21 January 2003 (me) Comprehensive update posted to live Web site
- 14 April 1999 (pb) Review posted to live Web site
- 2 December 1998 (ddl) Original submission