GeneReviews

GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Myoclonus-Dystonia

[*Dystonia 11, Hereditary Essential Myoclonus, Myoclonic Dystonia*]

Deborah Raymond, MS
Department of Neurology
Beth Israel Medical Center
draymond@bethisraelny.org

Laurie Ozelius, PhD
Department of Molecular Genetics
Albert Einstein College of Medicine
ozelius@aecom.yu.edu

Initial Posting: May 21, 2003.
Last Update: December 19, 2005.

Summary

Disease characteristics. Myoclonus-dystonia (M-D) is a movement disorder characterized by a combination of rapid, brief muscle contractions (myoclonus) and/or sustained twisting and repetitive movements that result in abnormal postures (dystonia). The myoclonic jerks typical of M-D most often affect the neck, trunk, and upper limbs with less common involvement of the legs. Approximately 50% of affected individuals have additional focal or segmental dystonia, presenting as cervical dystonia and/or writer's cramp. The most prominent non-motor features have been psychiatric problems including depression, anxiety, obsessive-compulsive disorder (OCD), personality disorders, addiction, and panic attacks. Symptom onset is usually in childhood or early adolescence but ranges from six months to 38 years. Most affected adults report a dramatic reduction in myoclonus in response to alcohol ingestion. The disease is compatible with an active life of normal span.

Diagnosis/testing. The diagnosis of myoclonus-dystonia is based on clinical findings, family history, absence of other neurologic deficits, and normal neuroimaging studies. Mutations in the *SGCE* gene are associated with familial M-D. Although mutations in two other genes, *DRD2* and *DYT1*, have been associated with M-D, the significance of the mutations is unknown. Sequence analysis of select exons of the *SGCE* gene is clinically available.

Management. Benzodiazepines (particularly clonazepam) used to treat myoclonus-dystonia improve both myoclonus and tremor. Anti-epileptic drugs, including valproate and topiramate, may improve myoclonus. Anti-cholinergic medication may improve dystonia and botulinum toxin injection may be especially helpful for cervical dystonia. Improvement with L-5-hydroxytryptophan as well as L-dopa has been reported. Stereotactic thalamotomy can improve myoclonus but has caused dysarthria and hemiparesis. Deep brain stimulation has improved both myoclonus and dystonia in several individuals. Symptoms of M-D usually resolve with ingestion of alcohol, but the risk of addiction recommends against its use in the long term.

Genetic counseling. Myoclonus-dystonia is inherited in an autosomal dominant manner. A proband with M-D may have the disorder as the result of a *de novo* gene mutation, the proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with M-D has a 50% chance of inheriting the mutation. Almost all children who inherit the mutation from their fathers develop symptoms. About 15% of children who inherit the mutation from their mothers develop symptoms. Prenatal testing is available.

GeneReviews GeneReviews GeneReviews GeneReviews

Diagnosis

Clinical Diagnosis

The following diagnostic criteria have been proposed by Klein (2002) based on families with proven linkage to DYT11 or with *SGCE* mutations. These criteria have been modified from Mahloudji & Pikielny (1967) and Gasser (1998):

- Onset of myoclonus, usually in the first or second decade of life; dystonic features are also observed in more than half of affected individuals in addition to myoclonus; rarely, dystonia may be the only manifestation of the disorder.
- Males and females about equally affected
- A relatively benign course, often variable but compatible with an active life of normal span in most cases
- Autosomal dominant mode of inheritance with variable severity and incomplete penetrance, which is dependent on the parental origin of the disease allele; affected individuals usually inherit the disease from their fathers.
- Absence of dementia, gross ataxia, and other neurologic deficits
- Normal somatosensory evoked potentials (SSEP)
- Normal neuroimaging studies (CT or MRI) (Degenerative changes may be seen as a result of chronic alcohol use.)

Optional diagnostic criteria:

- Alleviation of symptoms (particularly of the myoclonus and to a lesser degree of the dystonia) with alcohol use
- Various psychiatric symptoms

Note: Normal EEG was a diagnostic criterion; however, two reports have associated mutation-positive familial M-D with epilepsy and/or EEG abnormalities [Foncke et al 2003, O'Riordan et al 2004]. Therefore, EEG changes and epilepsy should no longer be considered exclusion criteria.

Testing

In general, all laboratory tests are normal in individuals with M-D. Abnormal liver function tests may be the result of chronic alcohol use.

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.

Molecular Genetic Testing—Genes. Mutations in the *SGCE* gene (locus DYT11), which encodes the protein epsilon-sarcoglycan, are identified in many individuals with familial M-D tested to date [Zimprich et al 2001, Asmus et al 2002, Klein 2002, Muller et al 2002, Marechal et al 2003, Hjermind et al 2003, Hedrich et al 2004, Schule et al 2004, Tezenas du Montcel et al 2005, Valente et al 2005].

GeneReviews GeneReviews GeneReviews GeneReviews

Note: The recent identification of exonic deletions in two families with M-D without identifiable *SGCE* mutations suggests that some percentage of individuals with M-D and as-yet-uncharacterized mutations have this type of mutation [Asmus et al 2005].

Mutations in two other genes have been associated with M-D:

- *DRD2*. It is unclear if the *DRD2* missense mutation found in a single family is disease-causing or a rare polymorphism [Klein et al 1999].
- *DYT1*, the gene associated with early-onset primary dystonia (DYT1):
  - An 18-bp deletion in the *DYT1* gene was found in one other family [Leung et al 2001]. However, mutations in *SGCE* were subsequently identified in the two families [Klein et al 2002] and the significance of this combination of mutations is unknown.
  - More recently a male with alcohol-responsive M-D was found to have the typical three-base pair deletion in *DYT1* and no mutation in *SGCE* [Tezenas du Montcel et al 2005]. His mother was Ashkenazi Jewish but only had writer's cramp.

Other loci. Simplex and familial cases without identifiable SGCE mutations have been reported [Han et al 2003, Valente et al 2003, Grundmann et al 2004, Hedrich et al 2004, Schule et al 2004, Tezenas du Montcel et al 2005, Valente et al 2005], suggesting locus heterogeneity. A large Canadian family with clinically similar M-D does not have a mutation in the *SGCE* gene but rather shows linkage to markers on chromosome 18p (locus DYT15) [Grimes et al 2002]. Two other families also show possible linkage to this chromosome region [Schule et al 2004]. The overall contribution of this locus to M-D cannot be determined until the gene is identified.

Molecular genetic testing: Clinical uses

- Confirmation of diagnosis
- Presymptomatic diagnosis
- Prenatal testing

Molecular genetic testing: Clinical methods

- **Sequence analysis.** To date, the vast majority (~95%) of mutations in the *SGCE* gene have been found in exons 1-7; the remaining approximately 5% have been found in exon 9.
- **Deletion/duplication analysis.** Identification of exonic deletions of *SGCE* identified in two families suggests that quantitative PCR will be needed for complete mutation detection [Asmus et al 2005].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Myoclonus-Dystonia

Test Method	Mutations Detected	Mutation Detection Rate [1]		Test Availability
		Familial [1]	Simplex [2, 3, 4]	
Sequencing of select exons	*SGCE* sequence alterations in exons 1-7, 9	~30-50%	~10-15%	Clinical Testing
Deletion/duplication analysis	*SGCE* exonic deletions	Unknown [5]		

1. The mutation detection rate among familial cases ranges from 0% to 100% with the high range biased by linkage studies; on average, the overall rate based on the literature is close to 50% (see Table 2 for references).

GeneReviews GeneReviews GeneReviews GeneReviews

2. The mutation detection rate among individuals with no family history of M-D ranges averages about 12-13% overall [Asmus et al 2002,Han et al 2003,Valente et al 2003,Grundmann et al 2004,Hedrich et al 2004,Schule et al 2004,Tezenas du Montcel et al 2005,Valente et al 2005].
3. Of the 39 mutations in 55 probands reported in the literature to date, ten occurred in individuals who do not have a reported family history of M-D; one is a confirmed *de novo* mutation [see Table 2).
4. In two probands who appeared to represent simplex cases (i.e., a single affected individual in a family), the mutation was subsequently identified in the fathers [Muller et al 2002,Hedrich et al 2004,Kock et al 2004].
5. The identification of exonic deletions in two families with M-D suggests that the overall mutation rate will be higher when quantitative PCR is used [Asmus et al 2005].

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

Genetically Related Disorders

No other phenotype is associated with mutations in *SGCE*.

A 32-month-old child with an interstitial deletion of chromosome 7q21 including *SGCE* had myoclonus, microcephaly, short stature, distinctive facial features, and language delay [DeBerardinis et al 2003].

Clinical Description

Natural History

Myoclonus-dystonia (M-D) is a movement disorder characterized by a combination of rapid, brief muscle contractions (myoclonus) and/or sustained twisting and repetitive movements that result in abnormal postures (dystonia). Symptom onset, usually in childhood or early adolescence, ranges from six months to 38 years [Quinn 1996; Gasser 1998; Klein, Schilling et al 2000; Vidailhet et al 2001, Asmus et al 2002, Valente et al 2005]. Although most affected adults report a dramatic response of myoclonic symptoms to alcohol ingestion [Mahloudji & Pikielny 1967, Kyllerman et al 1990, Quinn 1996], the alleviation of symptoms following alcohol ingestion varies within and between families [Klein, Gurvich et al 2000; Vidailhet et al 2001].

The myoclonic jerks typical of M-D are brief, lightning-like movements most often affecting the neck, trunk, and upper limbs with legs affected less prominently. Myoclonus is usually the presenting symptom. Laryngeal myoclonus has been reported [Hjermind et al 2003].

Approximately half of affected individuals (54%) have focal or segmental dystonia that presents as cervical dystonia and/or writer's cramp [Klein 2002, Asmus et al 2002]. In contrast to primary torsion dystonia [Bressman et al 2000], involvement of lower limbs is rare and usually does not occur at onset. In addition, the dystonia does not tend to worsen or generalize in the course of the disease. Rarely, dystonia is the only manifestation.

The involuntary movements are frequently precipitated or worsened by active movements of the affected body parts. Other factors eliciting or enhancing the movements include stress [Korten et al 1974, Kyllerman et al 1990], sudden noise [Korten et al 1974, Kurlan et al 1988, Asmus et al 2001, Trottenberg et al 2001], caffeine [Nygaard et al 1999], and tactile stimuli [Kurlan et al 1988, Nygaard et al 1999].

M-D is compatible with an active life of normal span [Nygaard et al 1999]. Although spontaneous remission of M-D has been reported [Korten et al 1974, Fahn & Sjaastad 1991], in some cases, M-D may be gradually progressive [Kurlan et al 1988, Quinn 1996, Borges et al 2000, Trottenberg et al 2001] and may lead to considerable functional disability and result in early retirement [Borges et al 2000, Trottenberg et al 2001, Marechal et al 2003, Hjermind

GeneReviews GeneReviews GeneReviews GeneReviews

et al 2003]. Additional neurologic features mainly include postural and other forms of tremor [Korten et al 1974, Kurlan et al 1988, Kyllerman et al 1990, Vidailhet et al 2001].

The most prominent non-motor features have been psychiatric disease reported in some [Klein et al 1999, Nygaard et al 1999, Kyllerman et al 1990] but not all [Asmus et al 2001] families. Reported psychiatric problems include depression, anxiety, and obsessive-compulsive disorder (OCD) [Nygaard et al 1999, Saunders-Pullman, Shriberg et al 2002]; depression, personality disorders, and addiction [Klein et al 1999]; and panic attacks [Scheidtmann et al 2000]. However, systematic study for psychiatric illness was not performed in these families with M-D and it is unknown whether these features segregated with the M-D mutation. Saunders-Pullman, Ozelius et al (2002) studied psychiatric features in detail in three families linked to chromosome 7q and found an association between OCD and M-D. This finding was supported by Doheny et al (2002) and Marechal et al (2003), who reported OCD in combination with M-D in several other families.

Other neurologic signs and symptoms, including dementia and ataxia [Gasser 1998], are rare in M-D. Seizures have been reported in two affected families, but the significance of this finding is still unclear [Foncke et al 2003, O'Riordan et al 2004].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Penetrance

Reduced penetrance on maternal transmission of the disease allele has been observed, suggesting maternal genomic imprinting of the *SGCE* gene [Zimprich et al 2001]. Two studies demonstrated paternal transmission of the *SGCE* mutant allele in affected individuals [Muller et al 2002, Grabowski et al 2003] as well as DNA methylation differences supporting maternal imprinting. However, the apparent suppression of the phenotype by maternal inheritance is incomplete, with fewer than 5% of affected individuals inheriting the mutant allele from their mothers [Zimprich et al 2001, Grabowski et al 2003]. In these instances, the phenotype may be milder. The reasons for reversal of the maternal imprint are unknown.

Anticipation

Anticipation is not observed in M-D.

Nomenclature

Terms used in the past for myoclonus-dystonia include myoclonic dystonia, inherited myoclonus dystonia syndrome, alcohol-responsive myoclonic dystonia, hereditary essential myoclonus and DYT11 dystonia [Quinn et al 1988, Quinn 1996, Lang 1997, Saunders-Pullman, Shriberg et al 2002].

When myoclonic movements were reported in individuals with DYT1 or other forms of primary dystonia, it was called myoclonic dystonia syndrome.

Prevalence

Little is known about the prevalence of M-D; however, the disease has been described in families of many nationalities including European, Turkish, Brazilian, and Canadian.

Differential Diagnosis

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

GeneReviews GeneReviews GeneReviews GeneReviews

Familial conditions with DYT1, including Wilson disease, spinocerebellar ataxia type 3 (SCA3), and secondary forms of dystonia, can generally be differentiated from M-D based on laboratory tests and neuroimaging studies (including MRI) (for a review of various genetic and secondary forms of dystonia, see the GeneReview Dystonia Overview and de Carvalho Aguiar & Ozelius 2002).

An individual with dopa-responsive dystonia had myoclonus dystonia [Leuzzi et al 2002].

Most other conditions in which myoclonus is a prominent feature are characterized by a variety of neurologic signs and symptoms generally not associated with a diagnosis of M-D. Genetically defined conditions with myoclonus as a major component include the following:

- Progressive myoclonus epilepsy, also known as Baltic myoclonus (EPM1), caused by mutations in the cystatin B gene *(CSTB)* [Pennacchio et al 1996]
- Myoclonus epilepsy of the Lafora type, associated with mutations in the *EPM2A* gene [Minassian et al 1998, Ganesh et al 2002]
- Myoclonus epilepsy associated with ragged-red fibers (abbreviated as MERRF), caused by mutations in mitochondrial genes
- Dentatorubral-pallidoluysian atrophy (DRPLA) [Naito & Oyanagi 1982]

Management

Treatment of Manifestations

Although the symptoms of M-D usually resolve with ingestion of alcohol, the risk of long-term addiction to alcohol renders it an unacceptable treatment option.

Medications may improve either the myoclonus or the dystonia or both:

- Benzodiazepines, particularly clonazepam, improve mostly myoclonus and tremor [Kurlan et al 1988, Kyllerman et al 1990, Bressman & Greene 1990, Nygaard et al 1999, Goetz & Horn 2001].
- Anti-epileptic drugs (AEDs), typically valproate but also topiramate, may improve myoclonus [Bressman & Greene 1990, Nygaard et al 1999].
- Anticholinergic medication may improve dystonia [Bressman & Greene 1990, Goetz & Horn 2001] and botulinum toxin injection may be especially helpful for cervical dystonia [Bressman & Greene 2000, Goetz & Horn 2001, Beradelli & Curra 2002].
- Improvement with L-5-hydroxytryptophan [Scheidtmann et al 2000] and with L-dopa [Leuzii et al 2002] has been reported.

Surgery. Stereotactic thalamotomy can improve myoclonus, but has caused dysarthria in one individual and mild hemiparesis in another [Gasser et al 1996]. In two others, myoclonus improved, but without significant gain in function [Suchowersky et al 2000].

Deep brain stimulation. Deep brain stimulation of the medial globus pallidus improved both myoclonus and dystonia at an eight-week follow-up [Liu et al 2002]. In an individual with medically intractable and progressing inherited M-D, neurostimulation of the ventral intermediate thalamic nucleus was safe and effective [Trottenberg et al 2001]. Deep brain stimulation in the internal segment of the globus pallidus (GPi) improved myoclonus and dystonia in two individuals [Cif et al 2004, Magarinos-Ascone et al 2005], one of whom had a confirmed *SGCE* mutation [Cif et al 2004].

GeneReviews GeneReviews GeneReviews GeneReviews

Prevention of Secondary Complications

As self-treatment with alcohol is common, proper treatment and counseling regarding alcohol abuse may decrease alcohol-related toxicities.

Therapies Under Investigation

Initial promising results with gamma-hydroxy-butyric acid [Priori et al 2000] and with its cousin sodium oxybate [Frucht et al 2005] have been reported, but potential for abuse exists for both of these drugs.

Search ClinicalTrials.gov 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, 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

Myoclonus-dystonia is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with M-D have an affected parent.
- Because M-D shows reduced penetrance, the parent of an affected individual may have the disease-causing allele without showing clinical signs. The mechanism of reduced penetrance is related to maternal imprinting and therefore based on the parental origin of the mutation.
  - Greater than 95% of individuals who inherit the disease-causing allele from their mothers do not have clinical signs; however, approximately 5% of individuals who inherit the disease-causing allele from their mothers have M-D.
  - The majority of individuals who inherit the disease-causing allele from their fathers have clinical symptoms. In two cases the probands appeared to represent simplex cases, but after the mutation was identified, the father was found to have the mutation [Muller et al 2002, Hedrich et al 2004, Kock et al 2004].
- A proband with M-D may have the disorder as the result of a *de novo* gene mutation [Hedrich et al 2004]; the proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include obtaining a detailed medical and family history, examination by a neurologist specializing in movement disorders, and molecular genetic testing if the family-specific *SGCE* mutation has been identified.

Sibs of a proband

GeneReviews GeneReviews GeneReviews GeneReviews

- The risk to the sib of a proband depends on the genetic status of the parents.
- If a parent of the proband is affected, the risk to the sibs of inheriting the disease-causing allele is 50%.
- Expression of the mutation is influenced by the sex of the parent transmitting the disease-causing allele (imprinting).
  - If the M-D disease-causing allele is inherited from the father, most often the offspring is symptomatic.
  - If the M-D disease-causing allele is inherited from the mother, most often it is not expressed and the child remains symptom-free. Currently, about 5% of individuals who inherit the mutation from their mothers 'reverse' the imprint, resulting in a clinical phenotype. This phenotype may be milder than the phenotype in individuals who inherit the mutation from their fathers.
- Because of variable expressivity, sibs may be more or less severely affected, with different symptoms from the proband.
- If a disease-causing mutation cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband

- Each child of an individual with M-D has a 50% chance of inheriting the mutation.
- Almost all children who inherit the mutation from their fathers develop symptoms.
- Few than 5% of children who inherit the mutation from their mothers develop symptoms.
- Symptomatic offspring of a proband may be more or less severely affected than the proband.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected or to have a disease-causing allele, his or her family members are at risk.

Related Genetic Counseling Issues

Although most individuals diagnosed with M-D have inherited the disease-causing allele from a parent, the family history may appear to be negative either because of the effects of imprinting or because of failure to recognize the disorder in family members. Since it is possible for affected family members to self-medicate with alcohol, a family history of alcoholism may be indicative of additional affected relatives.

Non-medical considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has a disease-causing mutation or clinical evidence of the disorder, 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.

Testing of at-risk asymptomatic family members. Testing of at-risk asymptomatic family members for myoclonus-dystonia is available using the same techniques described in Molecular Genetic Testing. This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. However, adults are unlikely

GeneReviews GeneReviews GeneReviews GeneReviews

to become symptomatic, particularly when inheriting the gene through a mother. When testing at-risk individuals for myoclonus-dystonia, an affected family member should be tested first to confirm that the disorder in the family is actually myoclonus-dystonia caused by a mutation in the *SGCE* gene.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

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 of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal testing for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

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) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. 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 Myoclonus-Dystonia

Gene Symbol	Chromosomal Locus	Protein Name
SGCE	7q21	Epsilon-sarcoglycan

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 Myoclonus-Dystonia

159900	MYOCLONIC DYSTONIA
604149	SARCOGLYCAN, EPSILON; SGCE

Table C. Genomic Databases for Myoclonus-Dystonia

Gene Symbol	Entrez Gene	HGMD
SGCE	8910 (MIM No. 604149)	SGCE

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

Normal allelic variants: The normal *SGCE* gene comprises 12 exons with exon 10 being differentially spliced and absent from most transcripts [McNally et al 1998]. Other alternative

GeneReviews GeneReviews GeneReviews GeneReviews

splice variants in mouse brain that effect the C-terminal end of the encoded protein have been identified [Nishiyama et al 2004, Yokoi et al 2005].

Pathologic allelic variants: All types of mutations have been reported in *SGCE* including nonsense, missense, deletions, and insertions leading to frame shifts and splicing errors [Zimprich et al 2001, Asmus et al 2002, Doheny et al 2002, Klein et al 2002, Muller et al 2002, DeBerardinis et al 2003, Foncke et al 2003, Han et al 2003, Hjermind et al 2003, Marechal et al 2003, Hedrich et al 2004, Kock et al 2004, Schule et al 2004, Valente et al 2005]. Exonic deletions in SGCE may also cause M-D [Asmus et al 2005].

See Table 2 for a summary of all mutations known to date. Most of the mutations described to date have been localized to exons 3-7 and 9, implicating this region of the gene as important for function. Four nonsense mutations, R97X, W100X, R102X (all in exon 3), and R372X (in exon 9) as well as two small deletions (in exons 4 and 7) have been found in more than one proband and appear to be recurrent mutations. (For more information, see Genomic Databases table above.)

Normal gene product: The *SGCE* gene encodes epsilon-sarcoglycan. *SGCE* is a member of a gene family that also includes alpha, beta, gamma, delta, and zeta sarcoglycans. Recessive mutations in these other sarcoglycan family members result in various types of limb-girdle muscular dystrophies (see Hack et al 2000 for review). In muscles, these genes encode transmembrane components of the dystrophin-glycoprotein complex, which links the cytoskeleton to the extracellular matrix. However, *SGCE* is widely expressed in many tissues of the body [Ettinger et al 1997, McNally et al 1998] including various regions of the brain [Zimprich et al 2001, Xiao & LeDoux 2003, Nishiyama et al 2004, Chan et al 2005] both during development and adulthood. The function of epsilon-sarcoglycan in the brain is presently unknown.

Abnormal gene product: It is speculated that because *SGCE* is maternally imprinted and the vast majority of affected individuals inherit their disease gene from their fathers, the disease is caused by loss of function of this protein. However, as many as 10% of affected individuals inherit their mutated allele from their mothers and presumably also express the wild-type allele from their fathers. Therefore, the mechanism of disease is not entirely clear.

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.

Dystonia Medical Research Foundation
One East Wacker Drive, Suite 2430
Chicago, Illinois 60601-1905
Phone: 312-755-0198; 800-361-8061 (in Canada)
Fax: 312-803-0138
Email: dystonia@dystonia-foundation.org
www.dystonia-foundation.org

The Dystonia Society
46/47 Britton Street
London EC1M 5UJ
Phone: (+44) 20 7490 5671

Fax: (+44) 20 7490 5672
Email: info@dystonia.org.uk
www.dystonia.org.uk

National Institute of Neurological Disorders and Stroke
Dystonias Information Page

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York, NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org
www.wemove.org

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

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Asmus F, Salih F, Hjermind LE, Ostergaard K, Munz M, Kuhn AA, Dupont E, Kupsch A, Gasser T. Myoclonus-dystonia due to genomic deletions in the epsilon-sarcoglycan gene. Ann Neurol. 2005;58:792–7. [PubMed: 16240355]

Asmus F, Zimprich A, Naumann M, Berg D, Bertram M, Ceballos-Baumann A, Pruszak-Seel R, Kabus C, Dichgans M, Fuchs S, Muller-Myhsok B, Gasser T. Inherited Myoclonus-dystonia syndrome: narrowing the 7q21-q31 locus in German families. Ann Neurol. 2001;49:121–4. [PubMed: 11198282]

Asmus F, Zimprich A, Tezenas Du Montcel S, Kabus C, Deuschl G, Kupsch A, Ziemann U, Castro M, Kuhn AA, Strom TM, Vidailhet M, Bhatia KP, Durr A, Wood NW, Brice A, Gasser T. Myoclonus-dystonia syndrome: epsilon-sarcoglycan mutations and phenotype. Ann Neurol. 2002;52:489–92. [PubMed: 12325078]

Beradelli A, Curra A. Pathophysiology and treatment of cranial dystonia. Mov Disord. 2002;17:70–74. [PubMed: 11836760]

Borges V, Ferraz HB, de Andrade LA. Alcohol-sensitive hereditary essential myoclonus with dystonia: a study of 6 Brazilian patients. Neurol Sci. 2000;21:373–7. [PubMed: 11441575]

Bressman SB, Greene PE. Treatment of hyperkinetic movement disorders. Neurol Clin. 1990;8:51–75. [PubMed: 2181268]

Bressman SB, Greene PE. Dystonia. Curr Treat Options Neurol. 2000;2:275–285. [PubMed: 11096754]

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: 10802779]

Chan P, Gonzalez-Maeso J, Ruf F, Bishop DF, Hof PR, Sealfon SC. Epsilon-sarcoglycan immunoreactivity and mRNA expression in mouse brain. J Comp Neurol. 2005;482:50–73. [PubMed: 15612018]

Cif L, Valente EM, Hemm S, Coubes C, Vayssiere N, Serrat S, Di Giorgio A, Coubes P. Deep brain stimulation in myoclonus-dystonia syndrome. Mov Disord. 2004;19:724–7. [PubMed: 15197720]

de Carvalho Aguiar PM, Ozelius LJ. Classification and genetics of dystonia. Lancet Neurol. 2002;1:316–25. [PubMed: 12849429]

GeneReviews GeneReviews GeneReviews GeneReviews

GeneReviews GeneReviews GeneReviews GeneReviews

DeBerardinis RJ, Conforto D, Russell K, Kaplan J, Kollros PR, Zackai EH, Emanuel BS. Myoclonus in a patient with a deletion of the epsilon-sarcoglycan locus on chromosome 7q21. Am J Med Genet. 2003;121A:31–6. [PubMed: 12900898]

Doheny DO, Brin MF, Morrison CE, Smith CJ, Walker RH, Abbasi S, Muller B, Garrels J, Liu L, De Carvalho Aguiar P, Schilling K, Kramer P, De Leon D, Raymond D, Saunders-Pullman R, Klein C, Bressman SB, Schmand B, Tijssen MA, Ozelius LJ, Silverman JM. Phenotypic features of myoclonus-dystonia in three kindreds. Neurology. 2002;59:1187–96. [PubMed: 12391346]

Ettinger AJ, Feng G, Sanes JR. Epsilon-sarcoglycan, a broadly expressed homologue of the gene mutated in limb-girdle muscular dystrophy 2D. J Biol Chem. 1997;272:32534–8. [PubMed: 9405466]

Fahn S, Sjaastad O. Hereditary essential myoclonus in a large Norwegian family. Mov Disord. 1991;6:237–47. [PubMed: 1922129]

Foncke EM, Klein C, Koelman JH, Kramer PL, Schilling K, Muller B, Garrels J, de Carvalho Aguiar P, Liu L, de Froe A, Speelman JD, Ozelius LJ, Tijssen MA. Hereditary myoclonus-dystonia associated with epilepsy. Neurology. 2003;60:1988–90. [PubMed: 12821748]

Frucht SJ, Bordelon Y, Houghton WH. Marked amelioration of alcohol-responsive posthypoxic myoclonus by gamma-hydroxybutyric acid (Xyrem). Mov Disord. 2005;20:745–51. [PubMed: 15751049]

Ganesh S, Delgado-Escueta AV, Suzuki T, Francheschetti S, Riggio C, Avanzini G, Rabinowicz A, Bohlega S, Bailey J, Alonso ME, Rasmussen A, Thomson AE, Ochoa A, Prado AJ, Medina MT, Yamakawa K. Genotype-phenotype correlations for EPM2A mutations in Lafora's progressive myoclonus epilepsy: exon 1 mutations associate with an early-onset cognitive deficit subphenotype. Hum Mol Genet. 2002;11:1263–71. [PubMed: 12019207]

Gasser T. Inherited myoclonus-dystonia syndrome. Adv Neurol. 1998;78:325–34. [PubMed: 9750929]

Gasser T, Bereznai B, Muller B, Pruszak-Seel R, Damrich R, Deuschl G, Oertel WH. Linkage studies in alcohol-responsive myoclonic dystonia. Mov Disord. 1996;11:363–70. [PubMed: 8813214]

Goetz CG, Horn SS. Treatment of tremor and dystonia. Neurol Clin. 2001;19:129–44. [PubMed: 11471761]

Grabowski M, Zimprich A, Lorenz-Depiereux B, Kalscheuer V, Asmus F, Gasser T, Meitinger T, Strom TM. The epsilon-sarcoglycan gene (SGCE), mutated in myoclonus-dystonia syndrome, is maternally imprinted. Eur J Hum Genet. 2003;11:138–44. [PubMed: 12634861]

Grimes DA, Han F, Lang AE, St George-Hyssop P, Racacho L, Bulman DE. A novel locus for inherited myoclonus-dystonia on 18p11. Neurology. 2002;59:1183–6. [PubMed: 12391345]

Grundmann K, Laubis-Herrmann U, Dressler D, Vollmer-Haase J, Bauer P, Stuhrmann M, Schulte T, Schols L, Topka H, Riess O. Lack of mutations in the epsilon-sarcoglycan gene in patients with different subtypes of primary dystonias. Mov Disord. 2004;19:1294–7. [PubMed: 15390016]

Hack AA, Groh ME, McNally EM. Sarcoglycans in muscular dystrophy. Microsc Res Tech. 2000;48:167–80. [PubMed: 10679964]

Han F, Lang AE, Racacho L, Bulman DE, Grimes DA. Mutations in the epsilon-sarcoglycan gene found to be uncommon in seven myoclonus-dystonia families. Neurology. 2003;61:244–6. [PubMed: 12874409]

Hedrich K, Meyer EM, Schule B, Kock N, de Carvalho Aguiar P, Wiegers K, Koelman JH, Garrels J, Durr R, Liu L, Schwinger E, Ozelius LJ, Landwehrmeyer B, Stoessl AJ, Tijssen MA, Klein C. Myoclonus-dystonia: detection of novel, recurrent, and de novo SGCE mutations. Neurology. 2004;62:1229–31. [PubMed: 15079037]

Hjermind LE, Werdelin LM, Eiberg H, Krag-Olsen B, Dupont E, Sorensen SA. A novel mutation in the epsilon-sarcoglycan gene causing myoclonus-dystonia syndrome. Neurology. 2003;60:1536–9. [PubMed: 12743249]

Klein C. Myoclonus and myoclonus-dystonias. In: Pulst S (ed) Genetics of Movement Disorders. Academic Press, San Diego, pp 449-69. 2002

Klein C, Brin MF, Kramer P, Sena-Esteves M, de Leon D, Doheny D, Bressman S, Fahn S, Breakefield XO, Ozelius LJ. Association of a missense change in the D2 dopamine receptor with myoclonus dystonia. Proc Natl Acad Sci U S A. 1999;96:5173–6. [PubMed: 10220438]

Klein C, Gurvich N, Sena-Esteves M, Bressman S, Brin MF, Ebersole BJ, Fink S, Forsgren L, Friedman J, Grimes D, Holmgren G, Kyllerman M, Lang AE, de Leon D, Leung J, Prioleau C, Raymond D,

GeneReviews GeneReviews GeneReviews GeneReviews

Sanner G, Saunders-Pullman R, Vieregge P, Wahlstrom J, Breakefield XO, Kramer PL, Ozelius LJ, Sealfon SC. Evaluation of the role of the D2 dopamine receptor in myoclonus dystonia. Ann Neurol. 2000;47:369–73. [PubMed: 10716258]

Klein C, Liu L, Doheny D, Kock N, Muller B, de Carvalho Aguiar P, Leung J, de Leon D, Bressman SB, Silverman J, Smith C, Danisi F, Morrison C, Walker RH, Velickovic M, Schwinger E, Kramer PL, Breakefield XO, Brin MF, Ozelius LJ. Epsilon-sarcoglycan mutations found in combination with other dystonia gene mutations. Ann Neurol. 2002;52:675–9. [PubMed: 12402271]

Klein C, Schilling K, Saunders-Pullman RJ, Garrels J, Breakefield XO, Brin MF, deLeon D, Doheny D, Fahn S, Fink JS, Forsgren L, Friedman J, Frucht S, Harris J, Holmgren G, Kis B, Kurlan R, Kyllerman M, Lang AE, Leung J, Raymond D, Robishaw JD, Sanner G, Schwinger E, Tabamo RE, Tagliati M. A major locus for myoclonus-dystonia maps to chromosome 7q in eight families. Am J Hum Genet. 2000;67:1314–9. [PubMed: 11022010]

Kock N, Kasten M, Schule B, Hedrich K, Wiegers K, Kabakci K, Hagenah J, Pramstaller PP, Nitschke MF, Munchau A, Sperner J, Klein C. Clinical and genetic features of myoclonus-dystonia in 3 cases: a video presentation. Mov Disord. 2004;19:231–4. [PubMed: 14978685]

Korten JJ, Notermans SL, Frenken CW, Gabreels FJ, Joosten EM. Familial essential myoclonus. Brain. 1974;97:131–8. [PubMed: 4434166]

Kurlan R, Behr J, Medved L, Shoulson I. Myoclonus and dystonia: a family study. Adv Neurol. 1988;50:385–9. [PubMed: 3400497]

Kyllerman M, Forsgren L, Sanner G, Holmgren G, Wahlstrom J, Drugge U. Alcohol-responsive myoclonic dystonia in a large family: dominant inheritance and phenotypic variation. Mov Disord. 1990;5:270–9. [PubMed: 2259350]

Lang AE. Essential myoclonus and myoclonic dystonia. Mov Disord. 1997;12:127. [PubMed: 8990070]

Leung JC, Klein C, Friedman J, Vieregge P, Jacobs H, Doheny D, Kamm C, DeLeon D, Pramstaller PP, Penney JB, Eisengart M, Jankovic J, Gasser T, Bressman SB, Corey DP, Kramer P, Brin MF, Ozelius LJ, Breakefield XO. Novel mutation in the TOR1A (DYT1) gene in atypical early onset dystonia and polymorphisms in dystonia and early onset parkinsonism. Neurogenetics. 2001;3:133–43. [PubMed: 11523564]

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

Liu X, Griffin IC, Parkin SG, Miall RC, Rowe JG, Gregory RP, Scott RB, Aziz TZ, Stein JF. Involvement of the medial pallidum in focal myoclonic dystonia: a clinical and neurophysiological case study. Mov Disord. 2002;17:346–53. [PubMed: 11921122]

Mahloudji M, Pikielny RT. Hereditary essential myoclonus. Brain. 1967;90:669–74. [PubMed: 6058147]

Magarinos-Ascone CM, Regidor I, Martinez-Castrillo JC, Gomez-Galan M, Figueiras-Mendez R. Pallidal stimulation relieves myoclonus-dystonia syndrome. J Neurol Neurosurg Psychiatry. 2005;76:989–91. [PubMed: 15965208]

Marechal L, Raux G, Dumanchin C, Lefebvre G, Deslandre E, Girard C, Campion D, Parain D, Frebourg T, Hannequin D. Severe myoclonus-dystonia syndrome associated with a novel epsilon-sarcoglycan gene truncating mutation. Am J Med Genet. 2003;119B:114–7. [PubMed: 12707948]

McNally EM, Ly CT, Kunkel LM. Human epsilon-sarcoglycan is highly related to alpha-sarcoglycan (adhalin), the limb girdle muscular dystrophy 2D gene. FEBS Lett. 1998;422:27–32. [PubMed: 9475163]

Minassian BA, Lee JR, Herbrick JA, Huizenga J, Soder S, Mungall AJ, Dunham I, Gardner R, Fong CY, Carpenter S, Jardim L, Satishchandra P, Andermann E, Snead OC III, Lopes-Cendes I, Tsui LC, Delgado-Escueta AV, Rouleau GA, Scherer SW. Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. Nat Genet. 1998;20:171–4. [PubMed: 9771710]

Muller B, Hedrich K, Kock N, Dragasevic N, Svetel M, Garrels J, Landt O, Nitschke M, Pramstaller PP, Reik W, Schwinger E, Sperner J, Ozelius L, Kostic V, Klein C. Evidence that paternal expression of

GeneReviews GeneReviews GeneReviews GeneReviews

the epsilon-sarcoglycan gene accounts for reduced penetrance in myoclonus-dystonia. Am J Hum Genet. 2002;71:1303–11. [PubMed: 12444570]

Naito H, Oyanagi S. Familial myoclonus epilepsy and choreoathetosis: hereditary dentatorubral-pallidoluysian atrophy. Neurology. 1982;32:798–807. [PubMed: 6808417]

Nishiyama A, Endo T, Takeda S, Imamura M. Identification and characterization of epsilon-sarcoglycans in the central nervous system. Brain Res Mol Brain Res. 2004;125:1–12. [PubMed: 15193417]

Nygaard TG, Raymond D, Chen C, Nishino I, Greene PE, Jennings D, Heiman GA, Klein C, Saunders-Pullman RJ, Kramer P, Ozelius LJ, Bressman SB. Localization of a gene for myoclonus-dystonia to chromosome 7q21-q31. Ann Neurol. 1999;46:794–8. [PubMed: 10554001]

O'Riordan S, Ozelius LJ, de Carvalho Aguiar P, Hutchinson M, King M, Lynch T. Inherited myoclonus-dystonia and epilepsy: further evidence of an association? Mov Disord Jun 16 [Epub ahead of print]. 2004 [PubMed: 15389977]

Pennacchio LA, Lehesjoki AE, Stone NE, Willour VL, Virtaneva K, Miao J, D'Amato E, Ramirez L, Faham M, Koskiniemi M, Warrington JA, Norio R, de la Chapelle A, Cox DR, Myers RM. Mutations in the gene encoding cystatin B in progressive myoclonus epilepsy (EPM1) Science. 1996;271:1731–4. [PubMed: 8596935]

Priori A, Bertolasi L, Pesenti A, Cappellari A, Barbieri S. Gamma-hydroxybutyric acid for alcohol-sensitive myoclonus with dystonia. Neurology. 2000;54:1706. [PubMed: 10762526]

Quinn NP. Essential myoclonus and myoclonic dystonia. Mov Disord. 1996;11:119–24. [PubMed: 8684380]

Quinn NP, Rothwell JC, Thompson PD, Marsden CD. Hereditary myoclonic dystonia, hereditary torsion dystonia and hereditary essential myoclonus: an area of confusion. Adv Neurol. 1988;50:391–401. [PubMed: 3400498]

Saunders-Pullman R, Ozelius L, Bressman SB. Inherited myoclonus-dystonia. Adv Neurol. 2002;89:185–91. [PubMed: 11968443]

Saunders-Pullman R, Shriberg J, Heiman G, Raymond D, Wendt K, Kramer P, Schilling K, Kurlan R, Klein C, Ozelius LJ, Risch NJ, Bressman SB. Myoclonus dystonia: possible association with obsessive-compulsive disorder and alcohol dependence. Neurology. 2002;58:242–5. [PubMed: 11805251]

Scheidtmann K, Muller F, Hartmann E, Koenig E. Familial myoclonus-dystonia syndrome associated with panic attacks. Nervenarzt. 2000;71:839–42. [PubMed: 11082816]

Schule B, Kock N, Svetel M, Dragasevic N, Hedrich K, De Carvalho Aguiar P, Liu L, Kabakci K, Garrels J, Meyer EM, Berisavac I, Schwinger E, Kramer PL, Ozelius LJ, Klein C, Kostic V. Genetic heterogeneity in ten families with myoclonus-dystonia. J Neurol Neurosurg Psychiatry. 2004;75:1181–5. [PubMed: 15258227]

Suchowersky O, Davis JL, et al. Thalamic surgery for essential myoclonus results in clinical but not functional improvement. Mov Disord. 2000;15(S3):P332.

Tezenas du Montcel S, Clot F, Vidailhet M, Roze E, Damier P, Jedynak CP, Camuzat A, Lagueny A, Vercueil L, Doummar D, Guyant-Marechal L, Houeto JL, Ponsot G, Thobois S, Cournelle MA, Durr A, Durif F, Echenne B, Hannequin D, Tranchant C, Brice A. Epsilon sarcoglycan mutations and phenotype in French patients with myoclonic syndromes. J Med Genet [Epub ahead of print]. 2005 [PubMed: 16227522]

Trottenberg T, Meissner W, Kabus C, Arnold G, Funk T, Einhaupl KM, Kupsch A. Neurostimulation of the ventral intermediate thalamic nucleus in inherited myoclonus-dystonia syndrome. Mov Disord. 2001;16:769–71. [PubMed: 11481711]

Valente EM, Edwards MJ, Mir P, DiGiorgio A, Salvi S, Davis M, Russo N, Bozi M, Kim HT, Pennisi G, Quinn N, Dallapiccola B, Bhatia KP. The epsilon-sarcoglycan gene in myoclonic syndromes. Neurology. 2005;64:737–9. [PubMed: 15728306]

Valente EM, Misbahuddin A, Brancati F, Placzek MR, Garavaglia B, Salvi S, Nemeth A, Shaw-Smith C, Nardocci N, Bentivoglio AR, Berardelli A, Eleopra R, Dallapiccola B, Warner TT. Analysis of the epsilon-sarcoglycan gene in familial and sporadic myoclonus-dystonia: evidence for genetic heterogeneity. Mov Disord. 2003;18:1047–51. [PubMed: 14502674]

Vidailhet M, Tassin J, Durif F, Nivelon-Chevallier A, Agid Y, Brice A, Durr A. A major locus for several phenotypes of myoclonus—dystonia on chromosome 7q. Neurology. 2001;56:1213–6. [PubMed: 11342690]

Xiao J, LeDoux MS. Cloning, developmental regulation and neural localization of rat epsilon-sarcoglycan. Brain Res Mol Brain Res. 2003;119:132–43. [PubMed: 14625080]

Yokoi F, Dang MT, Mitsui S, Li Y. Exclusive paternal expression and novel alternatively spliced variants of epsilon-sarcoglycan mRNA in mouse brain. FEBS Lett. 2005;579:4822–8. [PubMed: 16099459]

Zimprich A, Grabowski M, Asmus F, Naumann M, Berg D, Bertram M, Scheidtmann K, Kern P, Winkelmann J, Muller-Myhsok B, Riedel L, Bauer M, Muller T, Castro M, Meitinger T, Strom TM, Gasser T. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. Nat Genet. 2001;29:66–9. [PubMed: 11528394]

Suggested Readings

Tycko B, Morison IM. Physiological functions of imprinted genes. J Cell Physiol. 2002;192:245–58. [PubMed: 12124770]

Weinstein LS. The role of tissue-specific imprinting as a source of phenotypic heterogeneity in human disease. Biol Psychiatry. 2001;50:927–31. [PubMed: 11750888]

Chapter Notes

Revision History

- 19 December 2005 (me) Comprehensive update posted to live Web site
- 11 June 2004 (ljo/cd) Revision: testing
- 21 May 2003 (me) Review posted to live Web site
- 5 May 2003 (ljo) Original submission

Table 2. Published Mutations in the *SGCE* Gene in Individuals with Myoclonus-Dystonia

Exon	Mutation	Family History	Reference
2	164delG	Yes	*Hedrich et al 2004*
2	H60P	No	*Hedrich et al 2004*
3	276delG	No	*Asmus et al 2002*
3	R97X	Yes	*Zimprich et al 2001*
3	R102X [1]	Yes [2]	*Zimprich et al 2001*, *Asmus et al 2002*, *Han et al 2003*, *Hedrich et al 2004*
3	233-1G↓A	Yes	*Asmus et al 2002*
4	484delAATT	Yes	*Marechal et al 2003*
4	463+6T↓C	No	*Asmus et al 2002*
4	488-97del	Yes	*Zimprich et al 2001*
5	565delA	Yes	*Zimprich et al 2001*
5	625insG	Yes [2]	*Muller et al 2002*, *Kock et al 2004*
5	L196R	Yes	*Klein et al 2002*
6	R237X	Yes	*Doheny et al 2002*
6	733delAATT	Yes	*Asmus et al 2002*
6	907+1G↓A	Yes	*Zimprich et al 2001*
7	832delAAAAC	Yes	*Han et al 2003*
7	835delACAAA	Yes	*Klein et al 2002*
7	855insT	Yes	*Foncke et al 2003*
7	966delT	Yes	*Muller et al 2002*
7	974delC	Yes	*Hjermind et al 2003*
7	Q286X	Yes	*Asmus et al 2002*
7	1037+5G↓A	Yes	*Asmus et al 2002*
All	Interstitial del 7q21	No	*DeBerardinis et al 2003*

1. This mutation has been reported in nine unrelated families.

2. The proband appeared to be a simplex case, but the mutation was found in their unaffected father due to reduced penetrance (only one of the R102X cases appeared simplex [*Hedrich et al 2004*]).

Asmus F, Zimprich A, Tezenas Du Montcel S, Kabus C, Deuschl G, Kupsch A, Ziemann U, Castro M, Kuhn AA, Strom TM, Vidailhet M, Bhatia KP, Durr A, Wood NW, Brice A, Gasser T (2002) Myoclonus-dystonia syndrome: epsilon-sarcoglycan mutations and phenotype. *Ann Neurol* 52:489-92 [Medline]

DeBerardinis RJ, Conforto D, Russell K, Kaplan J, Kollros PR, Zackai EH, Emanuel BS (2003) Myoclonus in a patient with a deletion of the epsilon-sarcoglycan locus on chromosome 7q21. *Am J Med Genet* 121A:31-6 [Medline]

Doheny DO, Brin MF, Morrison CE, Smith CJ, Walker RH, Abbasi S, Muller B, Garrels J, Liu L, De Carvalho Aguiar P, Schilling K, Kramer P, De Leon D, Raymond D, Saunders-Pullman R, Klein C, Bressman SB, Schmand B, Tijssen MA, Ozelius LJ, Silverman JM (2002) Phenotypic features of myoclonus-dystonia in three kindreds. *Neurology* 59:1187-96 [Medline]

Foncke EM, Klein C, Koelman JH, Kramer PL, Schilling K, Muller B, Garrels J, de Carvalho Aguiar P, Liu L, de Froe A, Speelman JD, Ozelius LJ, Tijssen MA (2003) Hereditary myoclonus-dystonia associated with epilepsy. *Neurology* 60:1988-90 [Medline]

Han F, Lang AE, Racacho L, Bulman DE, Grimes DA (2003) Mutations in the epsilon-sarcoglycan gene found to be uncommon in seven myoclonus-dystonia families. *Neurology* 61:244-6 [Medline]

Hedrich K, Meyer EM, Schule B, Kock N, de Carvalho Aguiar P, Wiegers K, Koelman JH, Garrels J, Durr R, Liu L, Schwinger E, Ozelius LJ, Landwehrmeyer B, Stoessl AJ, Tijssen MA, Klein C (2004) Myoclonus-dystonia: detection of novel, recurrent, and de novo SGCE mutations. *Neurology* 62:1229-31 [Medline]

GeneReviews GeneReviews GeneReviews GeneReviews

GeneReviews GeneReviews GeneReviews GeneReviews

Hjermind LE, Werdelin LM, Eiberg H, Krag-Olsen B, Dupont E, Sorensen SA (2003) A novel mutation in the epsilon-sarcoglycan gene causing myoclonus-dystonia syndrome. *Neurology* 60:1536-9 [Medline]

Klein C, Liu L, Doheny D, Kock N, Muller B, de Carvalho Aguiar P, Leung J, de Leon D, Bressman SB, Silverman J, Smith C, Danisi F, Morrison C, Walker RH, Velickovic M, Schwinger E, Kramer PL, Breakefield XO, Brin MF, Ozelius LJ (2002) Epsilon-sarcoglycan mutations found in combination with other dystonia gene mutations. *Ann Neurol* 52:675-9 [Medline]

Kock N, Kasten M, Schule B, Hedrich K, Wiegers K, Kabakci K, Hagenah J, Pramstaller PP, Nitschke MF, Munchau A, Sperner J, Klein C (2004) Clinical and genetic features of myoclonus-dystonia in 3 cases: a video presentation. *Mov Disord* 19:231-4 [Medline]

Marechal L, Raux G, Dumanchin C, Lefebvre G, Deslandre E, Girard C, Campion D, Parain D, Frebourg T, Hannequin D (2003) Severe myoclonus-dystonia syndrome associated with a novel epsilon-sarcoglycan gene truncating mutation. *Am J Med Genet* 119B:114-7 [Medline]

Muller B, Hedrich K, Kock N, Dragasevic N, Svetel M, Garrels J, Landt O, Nitschke M, Pramstaller PP, Reik W, Schwinger E, Sperner J, Ozelius L, Kostic V, Klein C (2002) Evidence that paternal expression of the epsilon-sarcoglycan gene accounts for reduced penetrance in myoclonus-dystonia. *Am J Hum Genet* 71:1303-11 [Medline]

Zimprich A, Grabowski M, Asmus F, Naumann M, Berg D, Bertram M, Scheidtmann K, Kern P, Winkelmann J, Muller-Myhsok B, Riedel L, Bauer M, Muller T, Castro M, Meitinger T, Strom TM, Gasser T (2001) Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. *Nat Genet* 29:66-9 [Medline]