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SGCE Myoclonus-Dystonia

Synonyms: Dystonia 11 (DYT11), DYT-SGCE

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Summary

Clinical characteristics

SGCE myoclonus-dystonia (*SGCE*-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 *SGCE*-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. Non-motor features may include alcohol abuse, obsessive-compulsive disorder (OCD), and anxiety disorders. Symptom onset is usually in the first decade of life and almost always by age 20 years, but ranges from age six months to 80 years. Most affected adults report a dramatic reduction in myoclonus in response to alcohol ingestion. *SGCE*-M-D is compatible with an active life of normal span.

Diagnosis/testing

The diagnosis of *SGCE*-M-D is established in a proband with characteristic clinical features by identification of a heterozygous pathogenic variant in *SGCE*.

Management

Treatment of manifestations: Class 1 evidence supports the improvement of myoclonus and dystonia with zonisamide. Benzodiazepines (particularly clonazepam) and anti-seizure drugs used to treat myoclonus (especially valproate and levitiracetam) also improve myoclonus in individuals with myoclonus-dystonia. The response to other anti-seizure drugs (e.g., topiramate) is more variable. Anticholinergic medication may improve dystonia. Botulinum toxin injection may be especially helpful for cervical dystonia. Improvement with L-5-hydroxytryptophan, L-dopa, and the salt of sodium oxybate has been reported. Deep brain stimulation has improved both myoclonus and dystonia, with most targeting the globus pallidus interna (GPi); however, success with ventral intermediate nucleus of the thalamus (VIM) target has also been reported.

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Other: Symptoms of *SGCE*-M-D often improve short term with ingestion of alcohol, but the risk of addiction recommends against its long-term use.

Genetic counseling

SGCE-M-D is inherited in an autosomal dominant manner with penetrance determined by the parental origin of the altered *SGCE* allele: an *SGCE* pathogenic variant on the paternally derived (expressed) *SGCE* allele generally results in disease; a pathogenic variant on the maternally derived (silenced) *SGCE* allele typically does not result in disease. Most individuals with *SGCE*-M-D inherited the disorder from a heterozygous parent who may or may not have clinical signs of M-D (as phenotypic expression in the parent would depend on the sex of the transmitting grandparent). Each child of an individual with *SGCE*-M-D has a 50% chance of inheriting the pathogenic variant. Almost all children who inherit an *SGCE* pathogenic variant from their father develop symptoms, whereas only ~5% of children who inherit an *SGCE* pathogenic variant from their mother develop symptoms. Once the *SGCE* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic diagnosis are possible.

Diagnosis

Suggestive Findings

SGCE myoclonus-dystonia (*SGCE*-M-D) **should be suspected** in individuals with myoclonus alone or with dystonia that begins in the first or second decade of life. It less frequently presents with isolated dystonia. Recently suggested criteria for the diagnosis of M-D require four major criteria and no exclusionary criteria OR three major criteria, two minor criteria, and no exclusionary criteria [Roze et al 2018].

Major criteria

- Myoclonus isolated or predominating over dystonia
- Prominence of the motor manifestations in the upper body
- Absence of truncal dystonia
- Positive family history
- Onset before age 18 years

Minor criteria

- Obsessive-compulsive disorder, anxiety-related disorder, or alcohol dependence
- Spontaneous remission of limb dystonia during childhood or adolescence
- Alcohol responsiveness

Exclusionary criteria

- Other neurologic manifestation in addition to myoclonus and/or dystonia (except seizures, which may be present in some individuals with *SGCE*-M-D)
- Abnormal brain MRI examination
- Neurophysiologic findings that do not support the diagnosis (defined as muscle contractions shorter than 300 ms that can occur in body parts not affected by dystonia)

Establishing the Diagnosis

The diagnosis of *SGCE*-M-D **is established** in a proband with myoclonus and/or dystonia by identification of a heterozygous pathogenic variant in *SGCE* on molecular genetic testing (see Table 1).

Note: (1) *SGCE* is maternally imprinted and, therefore, expressed only from the paternal allele. While rare cases of maternal inheritance have been reported (see Penetrance and Molecular Genetics), affected individuals typically have a pathogenic variant on the paternal allele. (2) A small number of individuals have been identified with either microdeletions of *SGCE* or maternal uniparental disomy resulting in methylation of both *SGCE* alleles (see Genetically Related Disorders).

Molecular genetic testing approaches can include **single-gene testing** and a **multigene panel**. However, for this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1):

- **Single-gene testing.** Sequence analysis of *SGCE* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications. Single-gene testing is most appropriate in individuals from families with a previously identified *SGCE* pathogenic variant.
- **A dystonia multigene panel** that includes *SGCE* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Table 1. Molecular Genetic Testing Used in *SGCE* Myoclonus-Dystonia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SGCE	Sequence analysis [3]	~75% [4]
	Gene-targeted deletion/duplication analysis [5]	~25% [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. Tezenas du Montcel et al [2006], Raymond et al [2008], Roze et al [2008]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. DeBerardinis et al [2003], Asmus et al [2005], Asmus et al [2007], Han et al [2007], Grünewald et al [2008], Ritz et al [2009], Peall et al [2014]

Clinical Characteristics

Clinical Description

SGCE myoclonus-dystonia (*SGCE*-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). Onset is most often in the first decade of life or in adolescence.

While most affected adults report a dramatic response of myoclonus to ingestion of alcohol [Quinn 1996], the alleviation of findings following alcohol ingestion varies within and between families. Alcohol dependence may be a comorbidity in those who do respond.

The myoclonic jerks typical of *SGCE*-M-D are brief, lightning-like movements most often affecting the neck, trunk, and upper limbs, with legs less prominently affected. In children, leg and trunk myoclonus may in rare cases lead to falls [Luciano et al 2009]. Myoclonus is usually the presenting manifestation of *SGCE*-M-D.

Approximately half of affected individuals (54%) have focal or segmental dystonia that manifests as cervical dystonia and/or writer's cramp [Asmus et al 2002, Klein et al 2002]. In contrast to primary torsion dystonia [Bressman et al 2000], dystonia in the lower limbs is rare, although it has been reported in individuals with infantile onset [Kyllerman et al 1990]. In addition, the dystonia does not tend to worsen or generalize in the course of the disease. Infrequently, dystonia is the only disease 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 [Kyllerman et al 1990], sudden noise [Asmus et al 2001, Trottenberg et al 2001], caffeine [Nygaard et al 1999], and tactile stimuli [Nygaard et al 1999].

Tremor (postural or other) may be a feature in a subset of individuals [Vidailhet et al 2001].

Psychiatric comorbidities have been reported. One systematic analysis of 307 participants with pathogenic variants in *SGCE* and M-D found that 65% had one or more psychiatric diagnoses, the most common of which were specific (33%) and social phobias (31%), followed by alcohol dependence (24%) and obsessive-compulsive disorder (OCD) (21%) [Peall et al 2015]. A further comparison of symptomatic and asymptomatic individuals with an *SGCE* pathogenic variant reported in this study found that OCD and social phobia were ten and 12 times more likely, respectively, in symptomatic individuals. It is unclear if psychiatric features seen in people with *SGCE*-M-D are a result of the *SGCE* pathogenic variant or a consequence of living with the disease. One argument against a purely reactive explanation, however, is that OCD is generally not considered a reactive condition.

Other neurologic signs and symptoms including dementia and ataxia are rare in *SGCE*-M-D [Gasser 1998]. Seizures are also rare, but have been reported in at least three families and are no longer considered exclusionary for diagnosis. However, the significance of this finding remains unclear [Foncke et al 2003, O'Riordan et al 2004, Haugarvoll et al 2014].

SGCE-M-D is compatible with an active life of normal span [Nygaard et al 1999].

Although spontaneous remission of *SGCE*-M-D has been reported [Roze et al 2008], *SGCE*-M-D may also be gradually progressive [Trottenberg et al 2001], leading to considerable functional disability and sometimes to early retirement [Hjermind et al 2003, Maréchal et al 2003].

Multiple studies support a different disease mechanism for *SGCE*-M-D than for isolated dystonia. Currently, the leading hypotheses suggest dysfunction of the cerebello-thalamo-cortical or striato-pallido-thalmo-cortical pathways [Popa et al 2014, Roze et al 2015].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Reduced penetrance on maternal transmission of the disease allele has been observed, suggesting that maternal genomic imprinting of *SGCE* suppresses expression of the maternally inherited *SGCE* allele [Zimprich et al 2001].

- Consistent with this hypothesis, two studies demonstrated both paternal transmission of an *SGCE* pathogenic variant in affected individuals and DNA methylation differences consistent with maternal imprinting [Müller et al 2002, Grabowski et al 2003].
- Because about 5% of affected individuals inherit the *SGCE* pathogenic variant from their mothers [Zimprich et al 2001, Grabowski et al 2003], the apparent suppression of the M-D phenotype on maternal transmission of the *SGCE* allele is incomplete. In these instances, the phenotype may be milder. The reasons for loss of the maternal imprint are unknown.

Nomenclature

"Myoclonus-dystonia" is the term used for individuals with an *SGCE*-like phenotype [Roze et al 2018]. It is distinguished from "myoclonic dystonia," a condition having a primarily dystonic phenotype with longer duration jerks co-occurring in the dystonic body regions. Additional terms used in the past for *SGCE*-M-D include "inherited myoclonus-dystonia syndrome," "alcohol-responsive myoclonic dystonia," and "hereditary essential myoclonus" [Quinn et al 1988, Quinn 1996, Lang 1997].

Prevalence

Little is known about the prevalence of *SGCE*-M-D. The disease has been described in families of many nationalities including mixed European, German, Irish, Turkish, Brazilian, and Canadian.

Genetically Related (Allelic) Disorders

No other phenotype is known to be associated with intragenic pathogenic variants in *SGCE*.

Microdeletion 7q21. At least 15 individuals with 7q21 microdeletions have been reported; most have typical symptoms of *SGCE*-M-D with a variety of additional features including short stature, facial dysmorphism, intrauterine growth deficiency, microcephaly, cognitive impairment, language delay, psychosis, joint laxity, and bone fractures [Carecchio et al 2013, Peall et al 2014]. Sibs in one family were found to have M-D and cognitive impairment; the father and three of his sibs had adult-onset psychosis with no movement disorder [Dale et al 2011].

One additional individual with M-D, language delay, dysmorphic features, and a seemingly balanced *de novo* reciprocal translocation was subsequently found to have microdeletions of 7q21 and 9q23 [Bonnet et al 2008].

Maternal uniparental disomy (mUPD) of chromosome 7 has also been observed in three persons with M-D and Silver-Russell syndrome (SRS) where M-D is presumably due to methylation of both *SGCE* alleles [Guettard et al 2008, Stark et al 2010, Sheridan et al 2013].

Differential Diagnosis

Myoclonic dystonia 26 (OMIM 616398), associated with heterozygous pathogenic variants in *KCTD17*, is closest in phenotype to *SGCE* myoclonus-dystonia (*SGCE*-M-D). For further information about myoclonic dystonia 26 and other disorders to consider in the differential diagnosis of *SGCE*-M-D, see Table 2.

Table 2. Other Genes of Interest in the Differential Diagnosis of *SGCE* Myoclonus-Dystonia

Gene(s)	DiffDx Disorder	MOI	Key Clinical Features of DiffDx Disorder	
			Overlapping w/*SGCE*-M-D	Distinguishing from *SGCE*-M-D
ADCY5	*ADCY5*-related dyskinesia	AD	• Possible cause of isolated M-D [1] • Often childhood onset [2]	Typically assoc w/addl features (e.g., chorea, early motor delay, alternating hemiplegia of childhood)
ATM	Variant ataxia-telangiectasia [3]	AR	Dystonia only or dystonia w/ myoclonus may be present.	• Observed in Mennonite families of Russian origin • High cancer frequency & adverse responses to chemotherapeutic agents assoc w/a common *ATM* haplotype & homozygosity for c.6200C>A
ATN1	DRPLA	AD	Myoclonus, epilepsy	In children: • Ataxia • Progressive intellectual deterioration In adults: • Ataxia • Choreoathetosis • Dementia or character changes
ATP7B	Wilson disease	AR	Dystonia	• Biochemical findings: ↓ serum copper & ceruloplasmin concentrations; ↑ urinary copper excretion • Kayser-Fleischer corneal ring
ATXN3	Spinocerebellar ataxia type 3	AD	Dystonia in 1 person	Cerebellar ataxia, pyramidal signs, pontocerebellar atrophy
CSTB	Unverricht-Lundborg disease	AR	Myoclonus, seizures	• Ataxia, incoordination, intentional tremor, & dysarthria • Emotional lability, depression, & mild ↓ in intellectual performance over time
EPM2A *NHLRC1*	Progressive myoclonus epilepsy, Lafora type	AR	Myoclonus, seizures	• ↑ frequency & intractability of seizures • Cognitive decline apparent at or soon after onset of seizures • Dysarthria & ataxia appear early; spasticity appears late.
GCH1	GTP cyclohydrolase 1-deficient dopa-responsive dystonia	AD	M-D in 1 person [4]	• Dramatic & sustained response to levodopa • Typically presents w/gait disturbance, later development of parkinsonism, & diurnal fluctuation of symptoms

Table 2. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Key Clinical Features of DiffDx Disorder	
			Overlapping w/*SGCE*-M-D	Distinguishing from *SGCE*-M-D
GNB1	*GNB1* encephalopathy	AD	M-D in 1 person w/comorbid OCD & mild DD, [5] neurodevelopmental delay, & other features incl dystonia in 46 others [6]	1 person w/M-D: • Mild ID • Limited upgaze, hypotonia, & OCD In others w/dystonia: • Notable DD & growth delay, seizures, hypotonia, abnormal MRI • Other symptoms may incl genitourinary & gastrointestinal abnormality, vision, hearing, cardiac, & hematologic abnormalities.
KCTD17	Myoclonic dystonia 26 (OMIM 616398)	AD	Early-onset myoclonic jerks; development of dystonia later in life (in 4 persons)	Early motor delay, severe lingual dystonia, & mild cognitive delay in 2 families w/splice variants [7]
mtDNA	MERRF	Mat	Myoclonus; seizures	Ataxia & ragged red fibers on muscle biopsy
NKX2-1 [8]	Benign hereditary chorea (OMIM 118700)	AD	Myoclonus	Does not demonstrate aggravation of jerks w/ complex motor tasks (in contrast to action-induced myoclonus of M-D).
PRKCG	Spinocerebellar ataxia type 14	AD	M-D in 1 person [9]	Slowly progressive cerebellar ataxia, dysarthria, & nystagmus
RELN	*RELN* myoclonus-dystonia [7]	AD	• Seemingly typical adult-onset M-D reported in 3 families & 2 simplex cases • Alcohol responsiveness & psychiatric comorbidities (5 persons) [10]	• Mean onset: age 22 yrs • Latest onset: age 53 yrs
TOR1A	DYT1 early-onset isolated dystonia	AD	Unusual presentation of alcohol-responsive M-D in 1 person [11]	Cervical dystonia is uncommon in DYT1 dystonia.
TTPA	Ataxia with vitamin E deficiency	AR	Dystonia	• 1st symptoms incl progressive ataxia, clumsiness of hands, loss of proprioception, & areflexia. • Cerebellar atrophy

Table 2. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Key Clinical Features of DiffDx Disorder	
			Overlapping w/*SGCE*-M-D	Distinguishing from *SGCE*-M-D
TUBB2B	*TUBB2B* tubulinopathy (mild form) [12] (See Tubulinopathies Overview.)	AD	M-D in 1 person	• Mild cognitive impairment & skeletal anomalies • Asymmetric pachygyria & dysmorphic basal ganglia on neuroimaging [12]

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnoisis; ID = intellectual disability; Mat = maternal inheritance; M-D = myoclonus-dystonia; MOI = mode of inheritance; OCD = obsessive-compulsive disorder

1. Douglas et al [2017]
2. Chen et al [2015]
3. Saunders-Pullman et al [2012], Levy & Lang [2018]
4. Leuzzi et al [2002]
5. Jones et al [2019]
6. Petrovski et al [2016], Steinrücke et al [2016], Lohmann et al [2017], Hemati et al [2018]
7. Mencacci et al [2015], Graziola et al [2019], Marcé-Grau et al [2019]
8. Because of the association of hypothyroidism with pathogenic variants in *NKX2-1*, thyroid hormone screening should be considered in affected individuals. See OMIM 118700, 610978, 600635.
9. Foncke et al [2010]
10. Groen et al [2015]
11. A male with alcohol-responsive M-D who had the typical three-base pair deletion in *TOR1A* and no pathogenic variant in *SGCE* was reported [Tezenas du Montcel et al 2006]. His mother was Ashkenazi Jewish and had only writer's cramp.
12. Geiger et al [2017]

Myoclonic dystonia 15 (OMIM 607488). A clinically similar M-D phenotype in a large Canadian family without an identifiable *SGCE* pathogenic variant showed significant evidence for linkage to markers on chromosome 18p (locus DYT15) [Grimes et al 2002, Han et al 2007]. The M-D phenotype of two other families may also be linked to this chromosome region [Schüle et al 2004]. The overall contribution of this locus to M-D cannot be determined until the gene is identified.

For a review of various genetic and secondary forms of dystonia, see Hereditary Dystonia Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *SGCE* myoclonus-dystonia (*SGCE*-M-D) the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Clinical examination to evaluate the location, severity, and progression of dystonia and the severity and progression of myoclonus. This is best done by a neurologic specialist in movement disorders.
- Consultation with a clinical geneticist and/or genetic counselor.

Treatment of Manifestations

Medications may improve myoclonus and/or dystonia:

- While multiple anti-seizure medications have been reported in case series or individual reports, zonisamide is the first to demonstrate class I evidence of improvement of both myoclonus and dystonia in a double-blind study [Hainque et al 2016].

Valproate and levetiracetam may also be used. Topiramate and carbamazepine have been reported to improve myoclonus [Nygaard et al 1999, Sanjari Moghaddam et al 2018].

- Benzodiazepines, particularly clonazepam, improve mostly myoclonus and tremor [Goetz & Horn 2001].
- Anticholinergic medication may improve dystonia [Goetz & Horn 2001] and botulinum toxin injection may be especially helpful for cervical dystonia [Berardelli & Curra 2002].
- Improvement of dystonia with L-5-hydroxytryptophan has been reported [Scheidtmann et al 2000].
- Improvement with both L-dopa [Luciano et al 2009] and the dopamine-depleting medication tetrabenazine has been reported [Luciano et al 2014].
- One individual with *SGCE*-M-D who represented a simplex case (i.e., a single occurrence of M-D in the family) showed a robust response to zolpidem [Park et al 2009].
- Gamma-hydroxybutyrate [Priori et al 2000] and sodium oxybate may improve myoclonus [Frucht et al 2005].

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

Deep brain stimulation (DBS). Studies of globus pallidus interna (Gpi) and/or ventral intermediate nucleus of the thalamus (VIM) DBS in individuals with M-D determined that both were effective long-term treatments, although GPi is now the more frequently chosen target. Marked improvement in both myoclonus and dystonia as well as good quality of life and social adjustment were seen in a cohort of nine individuals with *SGCE*-M-D who had GPi DBS for at least five years [Kosutzka et al 2019]. In individuals with a predominant myoclonus phenotype undergoing VIM DBS (3 individuals with *SGCE* M-D; 2 individuals without an *SGCE* pathogenic variant), sustained improvement of both myoclonus and dystonia was found over 50 months [Zhang et al 2019].

Stereotactic thalamotomy can improve myoclonus, but 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].

Prevention of Secondary Complications

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

Surveillance

Table 3. Recommended Surveillance for Individuals with Myoclonus-Dystonia

System/Concern	Evaluation	Frequency
Neurologic	Neurologic exam to assess burden of myoclonus & dystonia & review therapy & side effects	Annually
Psychiatric	Eval for psychiatric features	Annually

Agents/Circumstances to Avoid

Use of alcohol to ameliorate symptoms should be avoided due to the risk of alcohol dependence.

Evaluation of Relatives at Risk

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

Pregnancy Management

There is concern about teratogenicity with certain anti-seizure medications that are sometimes used in the treatment of myoclonus-dystonia. These should be avoided in women considering pregnancy or who are known to be pregnant. Discussion of the risks and benefits of using a given anti-seizure drug during pregnancy should ideally take place prior to conception. Women with M-D should be counseled about abstaining from alcohol during pregnancy, particularly during the first trimester, as alcohol negatively affects fetal development.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

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

Genetic Counseling

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

Mode of Inheritance

SGCE myoclonus-dystonia (*SGCE*-M-D) is inherited in an autosomal dominant manner with penetrance determined by the parental origin of the altered *SGCE* allele. An *SGCE* pathogenic variant on the paternally derived (expressed) *SGCE* allele generally results in disease; a pathogenic variant on the maternally derived (silenced) *SGCE* allele typically does not result in disease.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *SGCE*-M-D inherited a pathogenic variant from a heterozygous parent who may or may not have clinical signs of M-D. Because *SGCE*-M-D shows reduced penetrance, the parent of an affected individual may have the pathogenic allele without showing clinical signs [Müller et al 2002, Hedrich et al 2004, Kock et al 2004, Gerrits et al 2009]. The mechanism of reduced penetrance is related to maternal imprinting and, therefore, based on the parental origin of the pathogenic variant. In general, maternally derived alleles are silenced and paternally derived *SGCE* alleles are expressed.
- A proband with M-D may have the disorder as the result of a *de novo SGCE* pathogenic variant [Hedrich et al 2004, Asmus et al 2007, Borges et al 2007]; to date only three *de novo* cases have been reported.
- Molecular genetic testing is recommended for the parents of a proband who appears to represent a simplex case (i.e., a single occurrence in a family). Since the *SGCE* variant was likely inherited from the father, it may be appropriate to evaluate the father first.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- Although most individuals diagnosed with M-D inherited the pathogenic allele from a parent, the family history may appear to be negative because of either the effects of imprinting or 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. Therefore, an apparently

negative family history cannot be confirmed unless appropriate molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs 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 pathogenic allele is 50%. Expression of the pathogenic *SGCE* allele is influenced by the sex of the parent transmitting the allele (imprinting).
  - If the *SGCE* pathogenic variant is inherited from the father, it is typically expressed and most often the offspring is symptomatic.
  - If the *SGCE* pathogenic variant is inherited from the mother, most often it is not expressed and the child remains symptom-free. However, about 5% of individuals who inherit the pathogenic variant from their mother do develop symptoms, indicating that the apparent suppression of the phenotype by maternal inheritance of a pathogenic *SGCE* allele is incomplete and loss of the maternal imprint occurs at a low frequency. Symptoms in individuals who have a maternally derived *SGCE* pathogenic variant may be milder than in those who inherit the pathogenic variant from their fathers.
- Because of intrafamilial clinical variability, symptomatic sibs may be more or less severely affected than the proband and have different M-D-related findings.
- If the proband has a known *SGCE* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the risk to sibs of inheriting a pathogenic variant is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SGCE* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for *SGCE*-M-D because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *SGCE*-M-D has a 50% chance of inheriting the pathogenic variant.

- If the proband is male, it is likely that all of his children who inherit the pathogenic variant will develop symptoms.
- If the proband is female, about 5% of her children who inherit the pathogenic variant will develop symptoms.
- Symptomatic offspring of a proband may be more or less severely affected than the proband.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or is known to have an *SGCE* pathogenic variant, 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 identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SGCE* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. The results of prenatal testing are not useful in predicting age of onset, severity, type of symptoms, or rate of progression of *SGCE*-M-D.

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

Resources

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

- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org
- **Dystonia Society**
  89 Albert Embankment
  3rd Floor
  London SE1 7TP
  United Kingdom
  Phone: 0845 458 6211; 0845 458 6322 (Helpline)
  Fax: 0845 458 6311
  Email: support@dystonia.org.uk
  www.dystonia.org.uk
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Dystonias Information Page
- **Global Dystonia Registry**
  www.globaldystoniaregistry.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. SGCE Myoclonus-Dystonia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

SGCE	7q21.3	Epsilon-sarcoglycan	SGCE homepage - Leiden Muscular Dystrophy pages	SGCE	SGCE

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 SGCE Myoclonus-Dystonia (View All in OMIM)

159900	DYSTONIA 11, MYOCLONIC; DYT11
604149	SARCOGLYCAN, EPSILON; SGCE

The sarcoglycan gene family includes alpha, beta, gamma, delta, epsilon, and zeta sarcoglycans. In muscles, these genes encode transmembrane components of the dystrophin-glycoprotein complex, which link the cytoskeleton to the extracellular matrix. *SGCE* encodes epsilon-sarcoglycan, which is widely expressed in many tissues of the body [Ettinger et al 1997, McNally et al 1998] including various regions of the brain both during development and adulthood [Ritz et al 2011, Xiao et al 2017]. The function of epsilon-sarcoglycan in the brain is unknown.

SGCE comprises 13 exons; exon 10 is differentially spliced and absent from most transcripts, exon 11b is brain specific, and exon 8 is rarely expressed in the brain. Other alternatively spliced exons have been noted but account for >1% of transcripts [Ritz et al 2011]. See Table A, **Gene** for a detailed summary of gene and protein information.

Mechanism of disease causation. It is speculated that because maternal imprinting transcriptionally silences *SGCE* and the vast majority of affected individuals inherit their disease allele from their fathers, the disease is caused by loss of function of this protein. However, about 5% of affected individuals inherit their abnormal allele from their mothers and presumably also express the wild type allele from their fathers. Therefore, the mechanism of disease pathogenesis is not entirely clear.

More than 100 pathogenic variants in *SGCE* have been reported in HGMD (see Table A, **Genes and Databases**). Reported pathogenic variants include nonsense and missense variants, deletions, and insertions leading to frame shifts and splicing errors as well as exon deletions [Zimprich et al 2001, Asmus et al 2002, Doheny et al 2002, Klein et al 2002, Müller et al 2002, DeBerardinis et al 2003, Foncke et al 2003, Han et al 2003, Hjermind et al 2003, Maréchal et al 2003, Hedrich et al 2004, Kock et al 2004, Schüle et al 2004, Asmus et al 2005, Valente et al 2005, Asmus et al 2007, Han et al 2007, Grünewald et al 2008, Ritz et al 2009].

Gene deletions in *SGCE* also cause M-D usually with other features (see 7q21 microdeletions) [Carecchio et al 2013, Peall et al 2014].

Of note, while only about 50% of individuals with clinical features of M-D are found to have a pathogenic variant in *SGCE*, the detection rate increases when paternal transmission is recognized [Ritz et al 2009].

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Chapter Notes

Revision History

- 4 June 2020 (cm) Revision: revised information on *GNB1*; link to *GNB1* Encephalopathy
- 8 August 2019 (sw) Comprehensive update posted live
- 26 January 2012 (me) Comprehensive update posted live
- 19 December 2005 (me) Comprehensive update posted live
- 11 June 2004 (ljo/cd) Revision: testing
- 21 May 2003 (me) Review posted live
- 5 May 2003 (ljo) Original submission

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