Twenty Years on: Myoclonus-Dystonia and ε-Sarcoglycan — Neurodevelopment, Channel, and Signaling Dysfunction

Elisa Menozzi, MD,1,2 Bettina Balint, MD,2,3 Anna Latorre, MD,2,4 Enza Maria Valente, MD, PhD,5,6 John C. Rothwell, PhD,2 and Kailash P. Bhatia, MD, FRCP2*

1 Department of Biomedical, Metabolic and Neural Sciences, University-Hospital of Modena and Reggio Emilia, Modena, Italy
2 Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK
3 Department of Neurology, University Hospital Heidelberg, Heidelberg, Germany
4 Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy
5 Department of Molecular Medicine, University of Pavia, Pavia, Italy
6 Neurogenetics Unit, IRCCS Santa Lucia Foundation, Rome, Italy

ABSTRACT: Myoclonus-dystonia is a clinical syndrome characterized by a typical childhood onset of myoclonic jerks and dystonia involving the neck, trunk, and upper limbs. Psychiatric symptomatology, namely, alcohol dependence and phobic and obsessive-compulsive disorder, is also part of the clinical picture. Zonisamide has demonstrated effectiveness at reducing both myoclonus and dystonia, and deep brain stimulation seems to be an effective and long-lasting therapeutic option for medication-refractory cases. In a subset of patients, myoclonus-dystonia is associated with pathogenic variants in the epsilon-sarcoglycan gene, located on chromosome 7q21, and up to now, more than 100 different pathogenic variants of the epsilon-sarcoglycan gene have been described. In a few families with a clinical phenotype resembling myoclonus-dystonia associated with distinct clinical features, variants have been identified in genes involved in novel pathways such as calcium channel regulation and neurodevelopment. Because of phenotypic similarities with epsilon-sarcoglycan gene–related myoclonus-dystonia, these conditions can be collectively classified as “myoclonus-dystonia syndromes.” In the present article, we present myoclonus-dystonia caused by epsilon-sarcoglycan gene mutations, with a focus on genetics and underlying disease mechanisms. Second, we review those conditions falling within the spectrum of myoclonus-dystonia syndromes, highlighting their genetic background and involved pathways. Finally, we critically discuss the normal and pathological function of the epsilon-sarcoglycan gene and its product, suggesting a role in the stabilization of the dopaminergic membrane via regulation of calcium homeostasis and in the neurodevelopmental process involving the cerebello-thalamo-pallido-cortical network. © 2019 International Parkinson and Movement Disorder Society

Key Words: epsilon-sarcoglycan; genetics; myoclonus-dystonia; pathophysiology

In 1983 the first description of a clinical syndrome characterized by myoclonus as the most prominent sign and dystonia was provided, subsequently identified as “inherited myoclonus-dystonia.”1-3 Myoclonus-dystonia is a rare condition, with an estimated prevalence of about 2 per 1,000,000 in Europe.4 Usually presenting in early childhood and following a benign course, it was described to follow an autosomal-dominant pattern with variable penetrance and expression.2 Twenty years ago, the first locus for myoclonus-dystonia was mapped to chromosomal region 7q21-q31.5-8 Two years later, heterozygous pathogenic variants in the epsilon-sarcoglycan (SGCE) gene were reported to be causative for myoclonus-dystonia,9 implicating a member of the sarcoglycan family generally associated with muscular dystrophies was involved in the pathogenesis of a central nervous system (CNS) disorder.9 From then, mutational screenings for SGCE in cohorts of patients presenting with myoclonus-dystonia have revealed
that SGCE is the main causative gene for this syndrome.\textsuperscript{10,11} As a consequence, the designation DYT-SGCE (OMIM 604149) now replaces the classic locus symbol DYT11.\textsuperscript{12,13}

Over the years, patients presenting with a combination of features typical of SGCE-related-myoclonus-dystonia and additional distinct aspects have been reported to carry pathogenic or likely pathogenic variants in genes involved in neurodevelopment, channel, and signaling pathways. As these genetic conditions share a number of clinical features with SGCE-related-myoclonus-dystonia, they can collectively be included in the phenotypic spectrum of myoclonus-dystonia syndromes.

The aim of the present article is to provide an overview of the clinical syndrome of myoclonus-dystonia because of SGCE mutations, hereafter referred to as SGCE-myoclonus-dystonia (SGCE-MD), discussing the clinical and electrophysiological features and the current therapeutic options, and highlighting the genetic background and underlying disease mechanisms. We then describe the conditions within the spectrum of myoclonus-dystonia syndromes, focusing on their genetic basis and involved pathways. Finally, as identifying different genetic causes associated with similar phenotypes may provide new clues to pathophysiology,\textsuperscript{14} we discuss and compare the pathophysiological mechanisms of SGCE-MD in light of the pathways unraveled by genetic determinants of myoclonus-dystonia syndromes.

**SGCE-MD: A Clinical Overview**

**Motor and Neuropsychiatric Features**

SGCE-MD usually manifests in childhood, with a mean age of onset of 6 years,\textsuperscript{15} and earlier onset is associated with female sex.\textsuperscript{16} Although rare, very early onset (before 1 year)\textsuperscript{17-20} and onset in early adulthood (21 to 41 years)\textsuperscript{18,21-24} or after 40 years\textsuperscript{25,26} have also been reported. The predominant motor sign in SGCE-MD is myoclonus, presenting with very brief, “lightning-like” or “tic-tac” jerks, typically involving the upper part of the body (neck, trunk, limb), more in the proximal than distal muscles.\textsuperscript{7,29-31} Less frequently, other body parts, such as the face,\textsuperscript{7,29-31} larynx,\textsuperscript{30-33} and lower limbs,\textsuperscript{16,20,22,23,31,34-38} can be affected. The myoclonic jerks may be present at rest but are typically aggravated or elicited by action, posture, and psychological stress.\textsuperscript{15,20,31} It is important to note that a subset of patients can present with postural tremor of the upper limbs,\textsuperscript{39,40} which is often clinically indistinguishable from high-frequency myoclonic jerks.\textsuperscript{41}

Dystonia is associated with myoclonus in more than half of patients, usually as torticollis or writing difficulty.\textsuperscript{28} However, dystonia can involve other body parts such as the cranial region,\textsuperscript{17} larynx,\textsuperscript{31,36,42,43} and often lower limbs,\textsuperscript{17,21,23,32,33,35,39,40,44-48} the latter being predominantly in pediatric cases, in whom it may be the sole presenting feature.\textsuperscript{35,36} Although isolated writer’s cramp presenting as the first manifestation of SGCE-MD in early adulthood has been reported,\textsuperscript{36} a screening of 43 patients with simple or complex writer’s cramp failed to identify any association with SGCE mutations.\textsuperscript{49} Other studies also failed to identify SGCE mutations in patients with different subtypes of focal, segmental, or generalized dystonia\textsuperscript{50,51}; hence, except for pediatric writer’s cramp,\textsuperscript{52} SGCE mutation analysis is not recommended in sporadic isolated dystonia in the absence of myoclonic jerks, or additional nonmotor features (see below).\textsuperscript{51}

Amelioration of motor signs with alcohol is a classic feature of SGCE-MD,\textsuperscript{53,54} likely because of the GABAergic deficit caused by Purkinje cell dysfunction secondary to SGCE mutations (see below), which alcohol might improve by increasing GABAergic transmission.\textsuperscript{55} The disease course of SGCE-MD is generally benign, with variable progression.\textsuperscript{50,56} Spontaneous remission has been found at a rate of 5% of patients for myoclonus and in 22% for dystonia, especially during childhood and adolescence,\textsuperscript{31} but also in early adulthood.\textsuperscript{57} Therefore, this variability should be taken into account when invasive therapeutic options are considered.\textsuperscript{31}

Psychiatric symptomatology is part of the clinical spectrum of SGCE-MD.\textsuperscript{54,58-63} A recent multicenter study investigated psychiatric symptomatology in a large cohort of SGCE-MD patients, showing that 65% of manifesting carriers had at least 1 psychiatric diagnosis, one and a half times more than population estimates.\textsuperscript{64} Among them, specific phobias and social phobia were the most common diagnoses, followed by alcohol dependence and obsessive-compulsive disorder.\textsuperscript{64} Anxiety and depression have also been frequently reported.\textsuperscript{62,63,65} As few studies failed to detect any psychiatric symptoms assessing patients by clinical scales rather than comprehensive diagnostic interviews,\textsuperscript{58,62} we would discourage the use of these tools in the clinical practice. Whether psychiatric symptomatology represents the expression of a pleiotropic function of the SGCE gene in the CNS or is secondary to motor signs is still debated.\textsuperscript{59,60,64} Some studies have shown an excess of psychiatric symptoms in manifesting SGCE carriers versus asymptomatic subjects, including nonmanifesting carriers and normal controls,\textsuperscript{59,64} and others did not report any difference between SGCE carriers and noncarriers.\textsuperscript{66}

**Positive and Negative Predictors for SGCE-MD**

Although SGCE is the main causative gene for myoclonus-dystonia,\textsuperscript{11} SGCE mutations have been found in a variable proportion from 21% to 80% of patients displaying this phenotype,\textsuperscript{10} probably because of the lack of standardized diagnostic criteria.\textsuperscript{65} SGCE-negative patients can display a very similar phenotype\textsuperscript{11} and many studies have tried to define clinical features predicting SGCE mutational status.\textsuperscript{10,17,67} The main clinical features predicting...
the presence of pathogenic variants in the SGCE gene, thus supporting a diagnosis of SGCE-MD, and conversely the atypical signs suggesting a negative carrier status, are listed in Table 1. Overall, the weighted sum of age at onset and presence of psychiatric symptoms in patients presenting with a typical motor phenotype, seems to better discriminate mutation carriers from noncarriers.65

So far, in many of the SGCE-negative carriers the causative genes remain undetermined.11 A locus has been mapped to chromosomal region 18p11 (OMIM 607488; DYT15) in a large Canadian family with myoclonus-dystonia,68 but the underlying causative gene has not yet been identified.69

**Neurophysiological Features**

The main question that several electrophysiological studies have tried to address is what is the generator of myoclonus in SGCE-MD. Results have shown both short and long duration of electromyographic (EMG) bursts, with a mean duration of 95 milliseconds (range, 25 to 256 milliseconds), occurring synchronously in antagonistic muscles or erratically in various segments of the body, either arrhythmically or less frequently rhythmically.31 No C-reflex, no electroencephalographic (EEG) activity at jerk-locked back-averaging, and normal somatosensory-evoked potentials were found.1,31,70 Negative myoclonus was recorded just in a few patients.31 Thus, although definite criteria for the classification of myoclonus are still lacking, the absence of primary and secondary neurophysiological features consistent with cortical myoclonus in SGCE-MD supports a subcortical origin.71 Further hints of the presumed subcortical source of myoclonus are provided by EEG-EMG coherence frequency analysis.72 In fact, in SGCE-MD there is little evidence for any coherence between cortical and muscular activity,73 in contrast with the clear coherence seen over a range of frequencies in cortical myoclonus.74-78

Cortical function has been explored in SGCE-MD by using noninvasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS).79 Motor cortical excitability measured by the active motor threshold was found normal when using single-pulse TMS,80 higher,81 or higher when using biphasic but not monophasic TMS pulses.82 Intracortical inhibition of the motor cortex, which is mediated by GABAa interneurons and is commonly reduced in dystonia,79,83 was found either normal80,81 or subtly reduced.70 Overall, even though the enhanced excitability to TMS was suggested to reflect a mild abnormality of axon membranes,81,82 there is no strong evidence for abnormalities of cortical function in SGCE-MD.

Having established that the source of myoclonus is not cortical, the next question is from which subcortical region it originates. Unfortunately, neurophysiological studies have not answered this question yet, and the mechanisms underlying myoclonus are not fully understood. The evidence to date seems to suggest that the cerebellum is involved in myoclonus. In fact, the abnormal response to cerebellar conditioning,55,82 as tested by eyeblink classical conditioning84 and the reduced levels of saccadic adaptation,85 as tested by the saccadic adaptation task,86-88 suggest cerebellar dysfunction. In a [18F]-fluorodeoxyglucose positron emission tomography (PET) study a metabolic increase in the parasagittal cerebellum was found in SGCE-MD patients, similar to posthypoxic myoclonus, but not in nonmanifesting carriers, suggesting a direct link between cerebellum and myoclonus89; however, it is worth remembering that PET data are a measurement of static, and not dynamic, connectivity.90 Few studies have reported that lesions in the ventral intermediate nucleus of the thalamus (VIM) were associated with myoclonus and dystonia91 and that deep brain stimulation (DBS) targeting the VIM was effective in reducing myoclonus in SGCE-MD.92 Overall, these data on VIM suggest that this structure can be involved in myoclonus, too,93 but this does not necessarily mean that the VIM is the generator of myoclonus. In addition, although myoclonus is not classically reported in association with basal ganglia dysfunction in both clinical and experimental studies,94,95 myoclonus severity has been associated with a higher-frequency bursting pattern in the neurons of the internal globus pallidus (GPi) of SGCE-MD patients, thus suggesting that pallidal activity somehow correlates with myoclonic activity.96 Moreover, that GPi DBS can reduce myoclonus again confirms pallidal involvement,96 even though this does not represent proof of myoclonus generation. Finally, there is evidence of increased brain stem excitability investigated by the blink reflex recovery cycle test in SGCE-MD patients,70 similar to what has been described in patients with isolated dystonia.97

**TABLE 1.** Clinical features predicting SGCE mutational status (carrier versus noncarrier) in patients with myoclonus-dystonia

<table>
<thead>
<tr>
<th>Positive predictors</th>
<th>Negative predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonus as prominent motor sign</td>
<td>Truncal dystonia</td>
</tr>
<tr>
<td>associated or not with dystonia</td>
<td>Coexistence of action myoclonus and dystonia in the same body region</td>
</tr>
<tr>
<td>Predominant upper body involvement</td>
<td></td>
</tr>
<tr>
<td>Onset in the first 2 decades, especially in the first one</td>
<td></td>
</tr>
<tr>
<td>Positive family history</td>
<td></td>
</tr>
<tr>
<td>Psychiatric comorbidities (phobia, OCD, alcohol dependence)</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

Oral medications such as benzodiazepines that reduce neuronal excitability via GABAergic mechanisms have been reported to show mild or no improvement in SGCE-MD.20,29,46,93,98-100 Other therapies such as
SGCE-MD: Genetics and Pathophysiology

The SGCE Gene (DYT-SGCE, DYT11)

In SGCE-MD, SGCE mutations are inherited in an autosomal-dominant pattern with reduced penetrance of maternally transmitted mutations.40 This is because of maternal imprinting of the SGCE gene,122 resulting in selective methylation of the maternal allele and consequent expression of the paternal allele only.123 Thus, although most patients carrying SGCE mutations have a positive family history, a genetic screening is also recommended in the presence of a sporadic presentation of myoclonus-dystonia.124 Until now, more than 100 different pathogenic variants in the SGCE gene have been described, including nonsense mutations, missense mutations,125 small insertions/deletions,23 and whole-exon deletions, often resulting in the introduction of premature termination codons.39 Gene dosage analyses such as multiple ligation-dependent probe amplification have therefore become part of the SGCE testing strategy.65 Patients with large genomic deletions usually exhibit a complex phenotype resulting from the concurrent deletion of neighboring genes (“contiguous gene syndrome”).65 For instance, deletion of COL1A2 can cause variable collagen abnormalities such as blue sclerae, hypodontia, recurrent subluxations, ligamentous laxity, and short stature, whereas KRIT1 haploinsufficiency has been related to the presence of cavernous cerebral malformations type I.126 An updated list of known pathogenic variants of the SGCE gene is summarized in Supplementary Table 1 (missense, nonsense, and splice-site pathogenic variants)127-130 and Supplementary Table 2 (deletions, insertions, and complex rearrangements).127,131-138

Curiously, in Silver-Russel syndrome (SRS, OMIM 180860), a growth disorder caused by maternal uniparental disomy of chromosome 7 (mUPD7) in 5%-10% of cases,139,140 children do not express the SGCE gene; nevertheless, only a few cases have been described with myoclonic and dystonic features.141-144 Affected children show intrauterine growth restriction and postnatal growth retardation with proportionate short stature, relative macrocephaly, triangular facial appearance, fifth finger clinodactyly, body asymmetry, and feeding difficulties.139,140 Testing for mUPD7 should therefore be considered in any patient with myoclonus, dystonia, and such additional features, and the recognition of hyperkinetic movement disorders should be mandatory in patients with SRS to address the specific multidisciplinary management (endocrinologists for monitoring of growth and consideration of growth hormone treatment, dieticians for advice regarding food intake, and orthopedists for limb asymmetry surgery).140,141

The Epsilon-Sarcoglycan Protein

The SGCE gene has 12 exons, whose product consists of 3 isoforms, encoding 437-, 451-, and 462-amino acid-long fragments depending on alternative splicing.15 SGCE encodes a single-pass transmembrane protein named epsilon-sarcoglycan. The sarcoglycans are a family of transmembrane glycoproteins with 6 different isoforms (α-, β-, γ-, δ-, ε-, and ζ-sarcoglycan). Epsilon-sarcoglycan is highly homologous to α-sarcoglycan: they both have a cadherin-like domain and calcium-binding pockets, which are present close to a signal sequence.145 In contrast to α-sarcoglycan, ε-sarcoglycan is widely expressed in multiple human tissues, either muscular or nonmuscular such as brain and lung,146 of both embryos and adults, suggesting an important role for embryonic development and integrity of nonmuscular tissues.147 Then, although ε-sarcoglycan mRNA expression dramatically declines during development in rats’ striated muscle, it is preserved in neurons, with high levels in the cerebellum.148 In mice, ε-sarcoglycan mRNA transcripts are highly expressed in neurons of the substantia nigra, ventral tegmental area, dorsal raphe nucleus, locus coeruleus, cerebellar Purkinje cells, and olfactory bulb mitral cell layer,149 and because of the
alternative splicing, 2 major SGCE isoforms can be found.\textsuperscript{150} The form including exon 8 is broadly expressed in various tissues, whereas the transcript including exon 11b is exclusively expressed in brain; these 2 isoforms are respectively enriched in postsynaptic and presynaptic membrane fractions, suggesting different roles in the synaptic function of the CNS.\textsuperscript{150} In human brain, up to 23 alternatively spliced exons have been detected, although only 4 of them (exons 1c, 2, 8, and 11b) at frequencies above 1%, and among them exon 11b has shown a high brain-specific expression pattern, especially in the cerebellum (namely, in the Purkinje cells and neurons of the dentate nucleus), making it the major brain-specific isoform.\textsuperscript{151}

SGCE-MD Animal Models

Little is known about the role of ε-sarcoglycan in the brain. To tackle the issue, several animal models of SGCE-MD have been developed. Paternally inherited SGCE heterozygous knockout (Sgce-KO) mice, which do not express maternally inherited wild-type SGCE in the brain,\textsuperscript{152} showed myoclonus, psychiatric alterations, and positive correlation between compulsive-checking behaviors and striatal dopaminergic levels, suggesting that the loss of ε-sarcoglycan could cause “hyperdopaminergic striatum.”\textsuperscript{153} Sgce-KO mice also exhibited abnormal nuclear envelopes in the striatal medium spiny neurons\textsuperscript{154} and reduced pre- and postsynaptic striatal dopamine D2 receptor (D2R) levels,\textsuperscript{155} supporting a possible role of ε-sarcoglycan in stabilizing the membrane of dopaminergic neurons.\textsuperscript{153,155} To better clarify the role of ε-sarcoglycan in different brain structures, paternally inherited striatum- and cerebellum-specific SGCE-conditional knockout mice were raised, neither of them exhibiting myoclonus or abnormal nuclear envelopes.\textsuperscript{154,156} Taken together, these findings suggest that in SGCE-MD animal models, the loss of ε-sarcoglycan function in the striatum and the cerebellar Purkinje cells per se does not contribute either to myoclonus or to nuclear envelope abnormalities.\textsuperscript{157}

The Dystrophin-Associated Glycoprotein Complex in Muscle and Brain: Different or Same Role?

In striated muscles the 4 sarcoglycan proteins, α, β, γ, and δ, form the heterotetrameric subcomplex called the sarcoglycan complex (SGC),\textsuperscript{145} which together with the α- and β-dystroglycans and the cytoplasmic subcomplex of dystrophin, dystrobrevins, and the syntrophin protein family,\textsuperscript{158} composes the dystrophin-associated glycoprotein complex (DGC),\textsuperscript{145} whose function is to protect muscle from mechanical damage and maintain physiological calcium homeostasis (Fig. 1A).\textsuperscript{159} The sarcoglycanopathy hypothesis in striated muscles is that the loss of a member of the SGC should reduce the amount of the other members and affect the stability of the whole complex.\textsuperscript{160} Thus, the SGC members are functional only when they exist as a tetramer,\textsuperscript{161} and based on this hypothesis, mutations in genes encoding for one of the SGC members lead

![FIG. 1. Models depicting DGC in skeletal muscles and prototypical DGC-like complex in brain. Legend – This figure shows the structural similarities between DGC in skeletal muscles and brain. (A) Skeletal muscle: the SGC, composed by the tetramer αβγδ, reinforces the bolt composed by dystrophin, β-DG, and α-DG. These components connect actin filaments in the subsarcolemmal cytoskeletal network and laminin in the basal lamina. (B) Brain: ε-sarcoglycan, other members of the sarcoglycan proteins family (ζΔ) and dystrophin Dp71, copurify in the brain, where they may compose a specific neuronal DGC-like complex. Hypothetical additional components of the neuronal DGC-like complex, such as dystrobrevins, syntrophins and the α-dystroglycan-neurexin complex, are represented with dashed lines or chequered fills. Despite the structural similarities, the DGC complexes in skeletal muscles and brain seem to function in a different way, and SGCE-MD represents an interesting disease model to gain further insight about normal and pathological function of DGC in brain. DG: dystroglycan; DGC: dystrophin-associated glycoprotein complex. [Color figure can be viewed at wileyonlinelibrary.com]]
to different forms of recessively inherited limb-girdle muscular dystrophies (LGMDs). The existence of DGC-like complexes in the brain has been demonstrated by immunohistochemical approaches. Furthermore, a prototypical DGC-like complex has been recently purified from brain tissue by immunofluorescence chromatography and mass spectrometry: ubiquitous and brain-specific exon 11b ε-sarcoglycan isoforms seem to form a canonical DGC-associated sarcoglycan complex in brain because they copurify with other components of DGC, such as β-, δ-, and ζ-sarcoglycan, β-dystroglycan, and dystrophin Dp71, which is the most abundant product of the Duchenne muscular dystrophy (DMD) gene expressed in brain, found in both neurons and glia. In hypothetical models, additional components such as the dystrobrevins, syntrophins, α-dystroglycan, and the synaptic adhesion molecule neurexin, might be part of the dystroglycan complex in neurons (Fig. 1B). Thus, SGCE-MD could be the expression of DGC dysfunction in brain, the same as LGMDs are the result of DGC dysfunction in skeletal muscle. However, the role of ε-sarcoglycan protein is crucially different in the brain and in peripheral tissues, as (1) ε-sarcoglycan seems to traffic and function independently of the core sarcoglycan complex (the βγδζ) in brain, contrary to skeletal muscles, and (2) the loss of ε-sarcoglycan did not affect other sarcoglycans’ levels in the striatum of Sgce-KO mice, suggesting that the classic sarcoglycanopathy hypothesis is not valid for DGC in brain. Therefore, the current evidence seems to suggest that whatever structure exists in the brain is fundamentally different from that seen in muscular tissues, and further significant work is required to fully elucidate the structure of DGC in the brain.

**Beyond SGCE-Myoclonus Dystonia**

**Distinct Movement Disorders Occasionally Mimicking Myoclonus-Dystonia**

Clinical features mimicking myoclonus-dystonia have been occasionally reported in genetic conditions that are usually characterized by different, well-defined clinical presentations. These include, for instance, some primary dystonia syndromes such as those associated with GNAL or ANO3 mutations or the pediatric hyperkinetic disorders caused by NKKX2-1 or ADCY5 mutations. Albeit rare, it is important to be aware of these potential phenotypic overlaps, as a genetic diagnosis may have relevant implications for counseling and treatment.

A similar situation may occur with dopa-responsive dystonia syndromes. Heterozygous mutations in the GTP cyclohydrolase I gene (DYTPARK-GCH1, DYT5a; OMIM 128230), the commonest cause of autosomal-dominant dopa-responsive dystonia, have been reported with early onset of myoclonic jerks and dystonia responsive to levodopa. Mutations in the tyrosine hydroxylase gene, a rare cause of autosomal-recessive dopa-responsive dystonia (DYT/PARK-TH, DYT5b; OMIM 191290), have also been related to an unusual phenotype of early onset of hypotonia, followed by the development of severe myoclonus and dystonia. Despite being rarely reported, we would recommend including dopamine synthesis pathway disorders in the differential diagnosis of early-onset myoclonus and dystonia, considering that these disorders are treatable.

A summary of distinct conditions occasionally mimicking SGCE-MD is reported in Table 2.

**Novel Genes Associated With Myoclonus-Dystonia Syndromes**

The quest for novel genes causative of myoclonus-dystonia phenotypes in SGCE-negative patients has been going on for a long time, yet only a few candidate genes have been reported to date, with confirmation in additional families often lacking. Here, we have reviewed the available evidence regarding clinical and genetic features of novel myoclonus-dystonia syndromes and discuss the underlying disease mechanisms and involved pathways. The main features of these conditions are summarised in Supplementary Table 3.

Mutations in the KCTD17 gene (potassium channel tetramerization domain-containing 17, OMIM 616386) have been detected in SGCE-negative myoclonus-dystonia patients, with predominant craniovascular and speech involvement. A dominantly inherited missense variant (c.434G>A, p.R145H) was identified in a British and then unrelated German family. Treatment with bilateral GPi DBS resulted in marked improvement in cervical dystonia and upper limb myoclonus in 1 patient. KCDT17 encodes for 1 of the 26 members of a family of highly conserved proteins with different functions such as transcriptional repression, cytoskeleton regulation, gating of ion channels, protein degradation via the ubiquitin-proteasome system, and regulation of G protein–coupled receptors. In the normal adult brain, KCDT17 expression is highest in the putamen, where it is probably involved in the regulation of dopaminergic transmission. Functional studies on fibroblasts bearing the p.R145H variant showed that KCDT17 might have a significant impact on intracellular endoplasmic reticulum (ER) calcium homeostasis, suggesting that defective ER calcium signaling might represent the pathogenic mechanism involved.

A heterozygous missense variant (c.4166G>A; p.R1389H) in the CACNA1B gene (calcium channel, voltage-dependent, N-type, alpha-1B subunit, OMIM 601012), transmitted in an autosomal-dominant manner, has been reported in a Dutch pedigree presenting with myoclonus, dystonia and some atypical characteristics such as high-frequency orthostatic myoclonus, cardiac arrhythmias, and attacks of painful cramps in the 4 limbs. Because the clinical presentation pointed to a possible
**TABLE 2. List of the most relevant genetic conditions mimicking SGCE-MD**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene product</th>
<th>Inheritance</th>
<th>AAO</th>
<th>Myoclonus</th>
<th>Dystonia</th>
<th>Alcohol response</th>
<th>Psychiatric features</th>
<th>Disease course</th>
<th>Clinical clues</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNAL</td>
<td>Guanine nucleotide-binding protein G(olf), subunit alpha</td>
<td>AD</td>
<td>Fourth decade</td>
<td>ULs</td>
<td>Neck &gt;&gt; oro-mandibular, larynx</td>
<td>No</td>
<td>No</td>
<td>Slightly progressive</td>
<td>Larynx involvement, tremor (head, ULs)</td>
<td>170</td>
</tr>
<tr>
<td>ANO3</td>
<td>Anoctamin 3</td>
<td>AD</td>
<td>Childhood</td>
<td>Neck, ULs</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Slowly progressive</td>
<td>Tremor (head, ULs &gt;&gt; voice)</td>
<td>175</td>
</tr>
<tr>
<td>TUBB2B</td>
<td>Tubulin beta-2B chain</td>
<td>De novo</td>
<td>Adolescence</td>
<td>Neck, trunk, ULs</td>
<td>Neck</td>
<td>NA</td>
<td>No</td>
<td>Slowly progressive</td>
<td>Motor developmental delay, cognitive impairment, epilepsy</td>
<td>174</td>
</tr>
<tr>
<td>PRKCG</td>
<td>Protein kinase C gamma type</td>
<td>AD</td>
<td>Early childhood / adolescence</td>
<td>Neck, ULs, LLs</td>
<td>Neck, trunk</td>
<td>NA</td>
<td>Yes</td>
<td>Progressive</td>
<td>Trunk tremor, gait ataxia</td>
<td>173</td>
</tr>
<tr>
<td>TTPA</td>
<td>Alpha-bocopherol transfer protein</td>
<td>AR</td>
<td>Early childhood</td>
<td>Neck</td>
<td>Neck, trunk</td>
<td>NA</td>
<td>NA</td>
<td>Progressive</td>
<td>Absent LLs reflexes, ataxia, vibratory and proprioceptive sensory loss</td>
<td>172</td>
</tr>
<tr>
<td>NKX2-1</td>
<td>Thyroid transcription factor-1</td>
<td>AD</td>
<td>Childhood</td>
<td>ULs, LLs, Neck</td>
<td>No</td>
<td>Not frequent</td>
<td>Not described</td>
<td>Stationary or slightly progressive</td>
<td>Choreoathetosis, thyroid dysfunction, recurrent pulmonary infections</td>
<td>129</td>
</tr>
<tr>
<td>ADCY5</td>
<td>Adenyl cyclase 5</td>
<td>AD</td>
<td>Infancy to childhood</td>
<td>Face, trunk, ULs</td>
<td>Generalized</td>
<td>NA</td>
<td>Not specific</td>
<td>Progressive</td>
<td>Axial hypotonia, delayed milestones, dysarthria, eye movement abnormalities, nocturnal dyskinesia exacerbations</td>
<td>176</td>
</tr>
<tr>
<td>GCH1</td>
<td>GTP cyclohydrolase I</td>
<td>AD</td>
<td>Childhood</td>
<td>ULs, then spreading to LLs, face, trunk</td>
<td>Neck, ULs</td>
<td>NA</td>
<td>NA</td>
<td>Slightly progressive</td>
<td>Parkinsonism, levodopa responsiveness</td>
<td>168</td>
</tr>
<tr>
<td>TH</td>
<td>Tyrosine hydroxylase</td>
<td>AR</td>
<td>6 months</td>
<td>ULs, LLs, neck, trunk.</td>
<td>Cranial, ULs, then generalized</td>
<td>NA</td>
<td>NA</td>
<td>Progressive</td>
<td>Hypotonia at onset, delayed milestones, levodopa responsiveness</td>
<td>170</td>
</tr>
</tbody>
</table>

AAO, age at onset; AD, autosomal dominant; AR, autosomal recessive; BPS, blepharospasm; LLs, lower limbs; NA, Not Available; ULs, upper limbs.
channelopathy, the p.R1389H variant was initially considered as likely pathogenic. However, this variant was not identified in a large European multicenter cohort of SGCE-negative familial cases of myoclonus-dystonia, and its overall frequency was comparable between myoclonus-dystonia cases and controls; therefore, the pathogenic role of this variant is questionable. The CACNA1B gene encodes for the main pore-forming alpha-1 subunit of a pre-synaptic neuronal voltage-gated calcium channel complex, Ca2.2, which underlies N-type current in neurons. Preferentially located at nerve terminals, the N-type channel plays a critical role in controlling transmitter release, like dopamine in particular in the neostriatum. This missense variant found by Groen and colleagues is located in a region essential for calcium conductivity, and cells expressing the mutated channel showed increased calcium current through Ca2.2. This increased calcium influx is likely to affect synaptic activity and release of neurotransmitters.

Heterozygous missense variants in RELN (reelin, OMIM 600514) have been detected in 3 families with a autosomal-dominant pattern of inheritance and 2 sporadic patients, presenting with a phenotype very similar to SGCE-MD. Reelin is a critical extracellular matrix glycoprotein, encoded by the RELN gene on chromosome 7q22. In the prenatal period, reelin is mainly secreted by the Cajal-Retzius cells in the telencephalic marginal zone and granule cells of the external granular layer of the cerebellum, in which it plays a key regulator role in laminar formation, neuronal migration, cell aggregation (by controlling cell adhesion molecules such as N-cadherin), dendrite development, and synaptic plasticity, and reelin-deficient mice show largely inverted cortical layers and cerebellar hypoplasia. The distribution and expression of reelin dramatically change in the postnatal period, when the main source of reelin becomes a subpopulation of inhibitory GABAergic interneurons, suggesting a different role of reelin in the adult brain like modulation of synaptic function.

In summary, the adoption of techniques such as large next-generation sequencing-based genetic panels and whole-exome sequencing has widely expanded the list of genetic causes of myoclonus-dystonia syndromes beyond SGCE. Although the value of these new

---

**FIG. 2.** A clinical-approached algorithm to differentiate the clinical spectrum of myoclonus-dystonia. Legend – In the era of genetic panels, addressing the genetic testing to a single gene has become less essential, and gene panels or WES are recommended if applicable. However, the explosive growth in the number of WES studies has led to the discovery of thousands of genetic variants and verifying the consistency between a genetic variant and a specific phenotype is necessary. The proposed algorithm can be a guide to differentiate the clinical spectrum of myoclonus-dystonia and focus on the most relevant genes in case of identified variants in multiple genes, thus leading the clinicians in the correct interpretation of genetic results. ULs: upper limbs; ID: intellectual disability; #: uncertain pathogenicity; *: no specific test corresponding to this locus (WES is recommended). [Color figure can be viewed at wileyonlinelibrary.com]
techniques sometimes reduces the need to prioritize genetic testing, we believe that having a kind of prioritization in mind can be extremely useful to ease the interpretation of the many variants that often emerge from these studies. For this purpose, we propose a clinically oriented algorithm that may help clinicians to differentiate the wide clinical spectrum of myoclonus-dystonia and myoclonus-dystonia syndromes and to help the interpretation of genetic results (Fig. 2).

![Diagram of the abnormal neural network in SGCE-MD](image)

**FIG. 3.** The abnormal neural network in SGCE-MD. Legend – This figure summarizes the amount of evidence supporting the presence of an abnormal neural network involving different and interconnected brain regions in SGCE-MD. Overall, functional imaging and neurophysiological studies, together with the good response of motor signs (both myoclonus and dystonia) to DBS, suggest the presence of cerebellar, thalamic, and pallidal abnormalities. This multilevel dysfunction can support the view of SGCE-MD as a neurodevelopmental circuit disorder. LFP: local field potential; WM: white matter. [Color figure can be viewed at wileyonlinelibrary.com]

Novel Pathogenic Hypotheses in SGCE-MD

**SGCE-MD: a Neurodevelopment Disorder?**

The view of SGCE-MD as a neurodevelopment disorder is supported by the nature of the SGCE gene itself. In fact, SGCE is a maternally imprinted gene, whose product is highly expressed in embryonic tissues. Imprinted genes are vulnerable loci, widely and highly expressed during prenatal stages when they are involved in multiple developmental and growth processes and whose mutations lead to severe development defects. Thus, the hypothesis of imprinting defects of SGCE during neurodevelopment as a cause of SGCE-MD might be captivating. In addition, for some types of inherited dystonia, it has been proposed that abnormalities in resting brain function, pathway microstructure, sensorimotor network activity, and modulation of abnormal network activity by treatment such as DBS, overall create a paradigm for interpreting dystonia as a potential neurodevelopmental circuit disorder. In the past years, convincing evidence supporting an abnormal neural network mainly involving the cerebellum, brain stem, and basal ganglia has accumulated for SGCE-MD, thus suggesting that SGCE-MD might be considered a neurodevelopmental circuit disorder, too. The main results of the studies supporting this hypothesis are shown in Figure 3.

**SGCE-MD: Abnormal Signaling and Calcium Homeostasis Dysfunction?**

As the presence of a prototypical DGC has been demonstrated in the brain, it is plausible to assume that SGCE-MD may be related to DGC dysfunction. It is well known that in DMD the absence of dystrophin leads to increased activity of calcium channels in neurons. As ε-sarcoglycan copurifies with dystrophin in brain, we might speculate that the loss of ε-sarcoglycan could induce neuronal membrane damage via secondary dystrophin dysfunction, leading to calcium accumulation. This hypothesis is further supported by the evidence that calcium signaling is crucial in regulating D2R responses induced by high-dopaminergic states, and increased striatal dopamine level and reduced D2R expression have been found in SGCE-MD animal models and in a group of SGCE carriers, mostly affected. Hence, impaired dopaminergic metabolism because of abnormal calcium homeostasis might represent a possible pathogenic mechanism in SGCE-MD.

Conclusions and Outlook

In the present review, we have given a comprehensive update on SGCE-MD and then presented the range of genetic causes associated with myoclonus-dystonia...
syndromes; different mechanisms ranging from abnormality in calcium signaling, dopamine regulation, to neurodevelopment are involved in the pathophysiology of these syndromes. Despite these findings requiring further confirmation in additional families and some of the reported variants having a questionable pathogenic role, we think that they represent an interesting clue toward understanding SGCE pathophysiology. There is evidence that SGCE pathogenic variants might affect dopaminergic transmission because of defective calcium signaling and that SGCE may be crucial for neurodevelopment in different brain structures. However, key questions remain, such as: (1) what differentiates the functioning of ε-sarcoglycan in the CNS and other tissues; (2) if SGCE has a pleiotropic function in the CNS beyond the motor system and is therefore directly responsible for psychiatric symptomatology; and (3) if there is a CNS brain region that is primarily involved in the pathogenesis of SGCE-MD. Future studies may address these questions, thus identifying specific therapeutic targets and paving the way for better future therapies.

Acknowledgments: None.

References


180. Beuckmann CT, Sinton CM, Miyamoto N, Ino M, Yanagisawa M. N-type calcium channel alpha1B subunit (Cav.2.2) knock-out mice display hyperactivity and vigilance state differences. J Neurosci 2003;23(17):6799–6807.


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.