REVIEW

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

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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

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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

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that *SGCE* is the main causative gene for this syndrome.[10,11] As a consequence, the designation DYT-*SGCE* (OMIM 604149) now replaces the classic locus symbol DYT11.[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,[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

Clinical Spectrum: Motor and Neuropsychiatric Features

SGCE-MD usually manifests in childhood, with a mean age of onset of 6 years,[15] and earlier onset is associated with female sex.[16] Although rare, very early onset (before 1 year)[17-20] and onset in early adulthood (21 to 41 years)[18,21-24] or after 40 years[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.[27,28] Less frequently, other body parts, such as the face,[7,29-31] larynx,[30-33] and lower limbs,[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.[15,20,31] It is important to note that a subset of patients can present with postural tremor of the upper limbs,[39,40] which is often clinically indistinguishable from high-frequency myoclonic jerks.[41]

Dystonia is associated with myoclonus in more than half of patients, usually as torticollis or writing difficulty.[28] However, dystonia can involve other body parts such as the cranial region,[17] larynx,[31,36,42,43] and often lower limbs,[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.[35,36] Although isolated writer's cramp presenting as the first manifestation of *SGCE*-MD in early adulthood has been reported,[36] a screening of 43 patients with simple or complex writer's cramp failed to identify any association with *SGCE* mutations.[49] Other studies also failed to identify *SGCE* mutations in patients with different subtypes of focal, segmental, or generalized dystonia[50,51]; hence, except for pediatric writer's cramp,[52] *SGCE* mutation analysis is not recommended in sporadic isolated dystonia in the absence of myoclonic jerks, or additional nonmotor features (see below).[51]

Amelioration of motor signs with alcohol is a classic feature of *SGCE*-MD,[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.[55] The disease course of *SGCE*-MD is generally benign, with variable progression.[20,56] Spontaneous remission has been found at a rate of 5% of patients for myoclonus and in 22% for dystonia, especially during childhood and adolescence,[31] but also in early adulthood.[57] Therefore, this variability should be taken into account when invasive therapeutic options are considered.[31]

Psychiatric symptomatology is part of the clinical spectrum of *SGCE*-MD.[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.[64] Among them, specific phobias and social phobia were the most common diagnoses, followed by alcohol dependence and obsessive-compulsive disorder.[64] Anxiety and depression have also been frequently reported.[62,63,65] As few studies failed to detect any psychiatric symptoms assessing patients by clinical scales rather than comprehensive diagnostic interviews,[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.[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,[59,64] and others did not report any difference between *SGCE* carriers and noncarriers.[66]

Positive and Negative Predictors for *SGCE*-MD

Although *SGCE* is the main causative gene for myoclonus-dystonia,[11] *SGCE* mutations have been found in a variable proportion from 21% to 80% of patients displaying this phenotype,[10] probably because of the lack of standardized diagnostic criteria.[65] *SGCE*-negative patients can display a very similar phenotype[11] and many studies have tried to define clinical features predicting *SGCE* mutational status.[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 antagonist muscles or erratically in various segments of the body, either arrhythmicly or less frequently rhythmicly.[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 normal[80,81] 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 conditioning,[84] and the reduced levels of saccadic adaptation,[85] as tested by the saccadic adaptation task,[86-88] suggest cerebellar dysfunction. In a [^{18}F]-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 myoclonus[89]; 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 dystonia[91] 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

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

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

levetiracetam,[20,93] valproate,[20,32,46,93,98,101] gabapentin,[46] pimozide,[32] trihexiphenidyl,[26,57] and botulinum toxin injections[26,32,102] have also been tried with variable results. Anecdotally, dopaminergic drugs, either levodopa[33] or dopamine-blocking agents like tetrabenazine,[103] have been reported to improve motor signs in patients with *SGCE* deletions. Few clinical trials have been conducted, namely, an open-label trial of sodium oxybate, which demonstrated improvement in myoclonus with satisfactory tolerance,[104] and a randomized, controlled, double-blind crossover trial of zonisamide, which revealed improvement in both myoclonus and dystonia with good tolerance.[105]

DBS has been reported to be effective in several medical-refractory cases,[39,92,93,106-118] but no controlled trials have been conducted so far. The preferred reported targets were the GPi, the VIM, or a combination of them, both good at improving myoclonus, with the GPi better than the VIM at improving dystonia.[119] Mean amelioration of 72.6% in myoclonus scores in all patients and of 52.6% in dystonia scores in approximately 88% of patients has been reported.[120] Only a few studies have quantified motor improvement after DBS by neurophysiological measurement.[92,113] Regarding stimulation programming, variable parameters have been used, most frequently pulse width of 60 microseconds and frequency of 130 Hz.[106,109] Satisfying response to high pulse width (180–210 microseconds) and lower frequency (60 Hz) has also been reported.[93,121] No deterioration of psychiatric symptoms has been found,[93,112] except for a small group of patients who underwent GPi DBS.[109] Hence, DBS seems to be a relatively safe and long-lasting treatment[112,117] that should be offered to patients refractory to medical treatment.[106,112]

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.[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.[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.[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,[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."[153] Sgce-KO mice also exhibited abnormal nuclear envelopes in the striatal medium spiny neurons[154] and reduced pre- and postsynaptic striatal dopamine D2 receptor (D2R) levels,[155] supporting a possible role of ε-sarcoglycan in stabilizing the membrane of dopaminergic neurons.[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.[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.[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),[145] which together with the α- and β-dystroglycans and the cytoplasmic subcomplex of dystrophin, dystrobrevins, and the syntrophin protein family,[158] composes the dystrophin-associated glycoprotein complex (DGC),[145] whose function is to protect muscle from mechanical damage and maintain physiological calcium homeostasis (Fig. 1A).[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.[160] Thus, the SGC members are functional only when they exist as a tetramer,[161] and based on this hypothesis, mutations in genes encoding for one of the SGC members lead

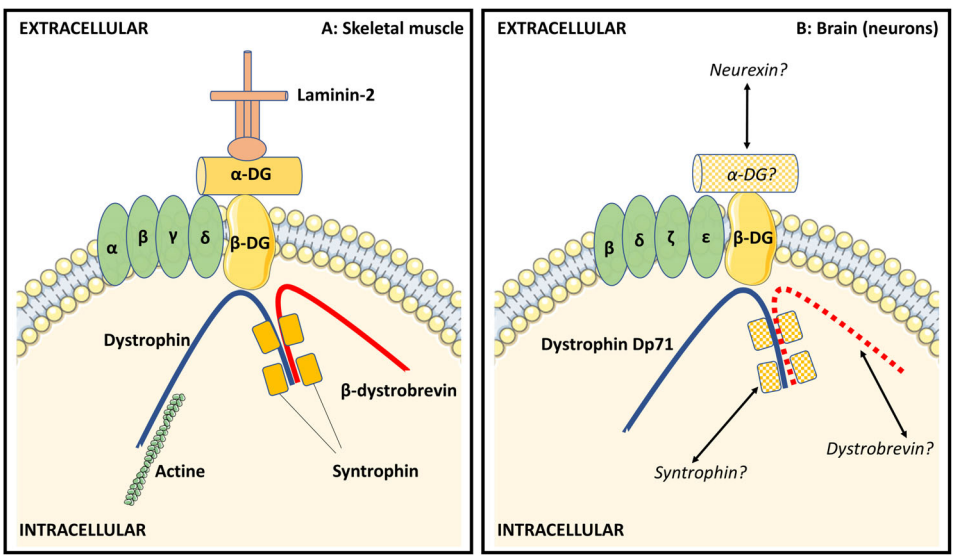

FIG. 1. Models depicting DGC in skeletal muscles and prototypical DGC-like complex in brian. Legend – This figure shows the structural similarities between DGC in skeletal muscles and brain. (**A**) Skeletal muscles: the SGC, composed by the tetramer αβγδ, reinforces the bolt composed by dystrophin, ß-DG, and α-DG. These components connect actin filaments in the subsarcolemmal cytoskeletal network and lamininin the basal lamina. (**B**) Brain: ε-sarcoglycan, other members of the sarcoglycan proteins family (βδζ) 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).[162]

The existence of DGC-like complexes in the brain has been demonstrated by immunochemical approaches.[159,163] Furthermore, a prototypical DGC-like complex has been recently purified from brain tissue by immunoaffinity chromatography and mass spectrometry[164]: 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.[165] In hypothetical models, additional components such as the dystrobrevins, syntrophins, α-dystroglycan, and the synaptic adhesion molecule neurexin, might be part of the DGC-like complex in neurons (Fig. 1B).[159] Thus, *SGCE*-MD could be the expression of DGC dysfunction in brain,[164] 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 βγ) in brain,[164] contrary to skeletal muscles,[166] 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.[154] 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 *NKX2-1* 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 (DYT/PARK-*GCH1*, DYT5a; OMIM 128230), the commonest cause of autosomal-dominant dopa-responsive dystonia,[167] have been reported with early onset of myoclonic jerks and dystonia responsive to levodopa.[168] Mutations in the tyrosine hydroxylase gene, a rare cause of autosomal-recessive dopa-responsive dystonia (DYT/PARK-*TH*, DYT5b; OMIM 191290),[169] have also been related to an unusual phenotype of early onset of hypotonia, followed by the development of severe myoclonus and dystonia.[170] 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[168,170-176] 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 craniocervical and speech involvement.[177] 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.[178] In the normal adult brain, *KCDT17* expression is highest in the putamen, where it is probably involved in the regulation of dopaminergic transmission.[177] 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.[177]

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.[179,180] Because the clinical presentation pointed to a possible

TABLE 2. List of the most relevant genetic conditions mimicking *SGCE*-MD

Gene	Gene product	Inheritance	AAO	Myoclonus	Dystonia	Alcohol response	Psychiatric features	Disease course	Clinical clues	Reference
GNAL	Guanine nucleotide-binding protein G(olf), subunit alpha	AD	Fourth decade	ULs	Neck >> oro-mandibular, larynx	No	No	Slightly progressive	Larynx involvement, tremor (head, ULs)	170
ANO3	Anoctamin 3	AD	Childhood	Neck, ULs	Oro-mandibular, BPS, larynx	No	No	Slowly progressive	Tremor (head, ULs >> voice)	175
TUBB2B	Tubulin beta-2B chain	De novo	Adolescence (earlier motor delay symptoms)	Neck, trunk, ULs	Neck	NA	No	Slowly progressive	Motor developmental delay, cognitive impairment, epilepsy	174
PRKCG (SCA14)	Protein kinase C gamma type	AD	Early childhood / adolescence	Neck, ULs, LLs	Neck, trunk	NA	Yes	Progressive	Trunk tremor, gait ataxia	173
TTPA	Alpha-tocopherol transfer protein	AR	Early childhood	Neck	Neck, trunk	NA	NA	Progressive	Absent LLs reflexes, ataxia, vibratory and proprioceptive sensory loss	172
NKX2-1	Thyroid transcription factor-1	AD	Childhood	ULs, LLs, Neck	No	Not frequent	Not described	Stationary or slightly progressive	Choreoathetosis, thyroid dysfunction, recurrent pulmonary infections	129
ADCY5	Adenyl cyclase 5	AD	Infancy to childhood	Face, trunk, ULs	Generalized	NA	Not specific	Progressive	Axial hypotonia, delayed milestones, dysarthria, eye movement abnormalities, nocturnal dyskinesia exacerbations	176
GCH1	GTP cyclohydrolase I	AD	Childhood	ULs, then spreading to LLs, face, trunk	Neck, ULs	NA	NA	Slightly progressive	Parkinsonism, levodopa responsiveness	168
TH	Tyrosine hydroxylase	AR	6 months	ULs, LLs, neck, trunk. Clinical features: stimulus sensitive, increased with posture, action. Electrophysiological features: supportive of subcortical origin.	Cranial, ULs, then generalized	NA	NA	Progressive	Hypotonia at onset, delayed milestones, levodopa responsiveness	170

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.[180] 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[181]; therefore, the pathogenic role of this variant is questionable. The *CACNA1B* gene encodes for the main pore-forming alpha-1 subunit of a presynaptic neuronal voltage-gated calcium channel complex, $Ca_v2.2$, which underlies N-type current in neurons.[182] Preferentially located at nerve terminals, the N-type channel plays a critical role in controlling transmitter release,[183] like dopamine in particular in the neostriatum.[184] The 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 $Ca_v2.2$.[180] This increased calcium influx is likely to affect synaptic activity and release of neurotransmitters.[185]

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.[186] Reelin is a critical extracellular matrix glycoprotein, encoded by the *RELN* gene on chromosome 7q22.1.[187,188] 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,[189,190] 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,[191] and reelin-deficient mice show largely inverted cortical layers and cerebellar hypoplasia.[187,191] 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,[192] suggesting a different role of reelin in the adult brain like modulation of synaptic function.[191,193]

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

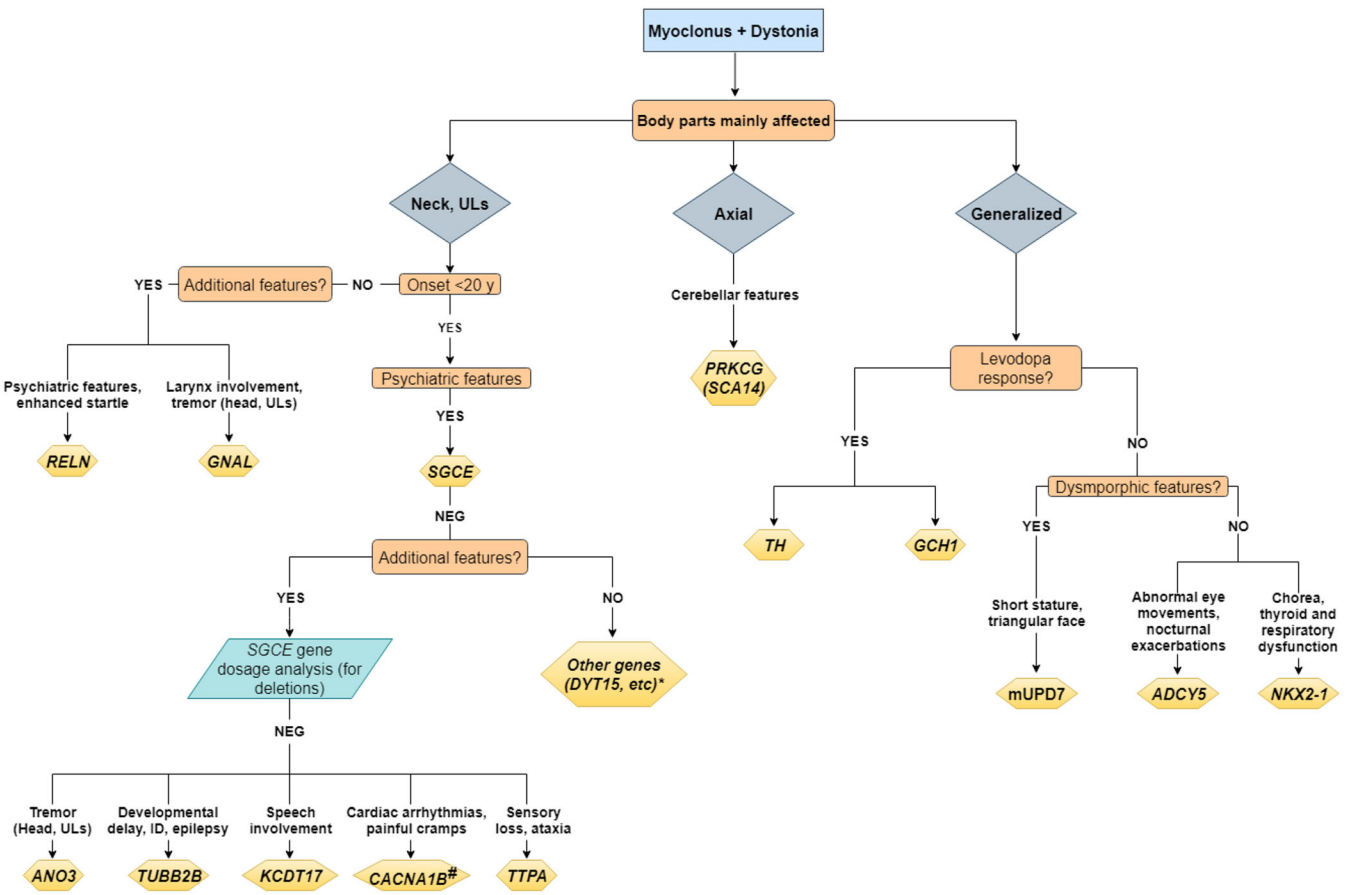

FIG. 2. A clinical-approached algorithm to differentiate the clinical spectrum of myoclonus-dystonia. Legend – In the era of genetic panels, addressing the genetic testing to a single gene has become less essential, and gene panels or WES are recommended if applicable. However, the explosive growth in 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 tot his locus (WES is recommended). [Color figure can be viewed at wileyonlinelibrary.com]

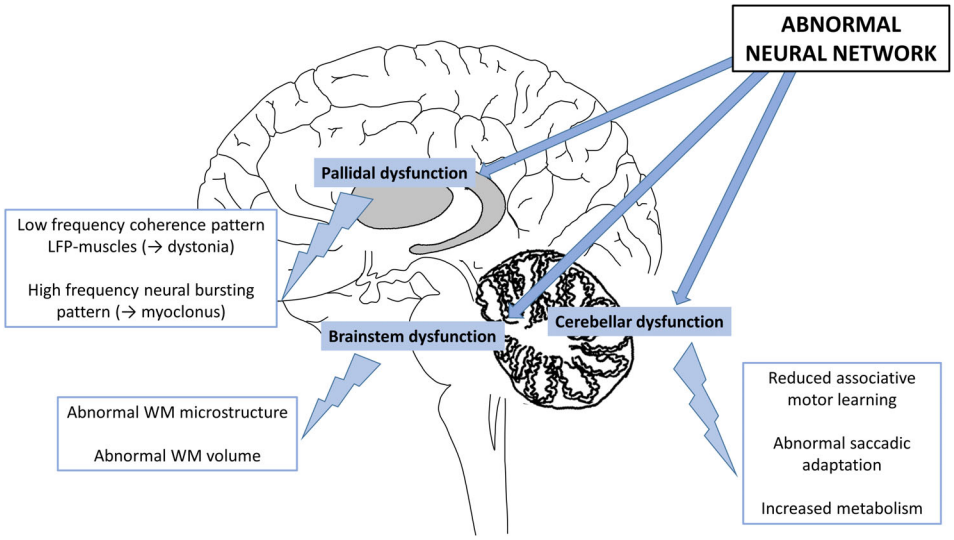

FIG. 3. The abnormal neural network in SGCE-MD. Legend – This figure summarizes the amount of evidence supporting the presence of an abnormal neural network involving different and interconnected brain regions in SGCE-MD. Overall, functional imaging and neurophysiological studies, together with the good 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]

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).

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,[122] whose product is highly expressed in embryonic tissues.[147] Imprinted genes are vulnerable loci, widely and highly expressed during prenatal stages when they are involved in multiple developmental and growth processes[194] and whose mutations lead to severe development defects.[195] 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.[196] 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,[55,73,82,85,89,96,110,197-199] 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,[164] 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.[200] As ε-sarcoglycan copurifies with dystrophin in brain,[164] 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,[201,202] and increased striatal dopamine level and reduced D2R expression have been found in *SGCE*-MD animal models[153,155] and in a group of *SGCE* carriers, mostly affected.[203] 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.

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References

1. Obeso JA, Rothwell JC, Lang AE, Marsden CD. Myoclonic dystonia. Neurology 1983;33(7):825–830.
2. Gasser T. Inherited myoclonus-dystonia syndrome. Adv Neurol 1998;78:325–334.
3. Quinn NP. Essential myoclonus and myoclonic dystonia. Mov Disord 1996;11(2):119–124.
4. Asmus F, Gasser T. Dystonia-plus syndromes. Eur J Neurol 2010; 17(Suppl 1):37–45.
5. Asmus F, Zimprich A, Naumann M, et al. Inherited Myoclonus-dystonia syndrome: narrowing the 7q21-q31 locus in German families. Ann Neurol 2001;49(1):121–124.
6. Klein C, Schilling K, Saunders-Pullman RJ, et al. A major locus for myoclonus-dystonia maps to chromosome 7q in eight families. Am J Hum Genet 2000;67(5):1314–1319.
7. Nygaard TG, Raymond D, Chen C, et al. Localization of a gene for myoclonus-dystonia to chromosome 7q21-q31. Ann Neurol 1999;46(5):794–798.
8. Vidailhet M, Tassin J, Durif F, et al. A major locus for several phenotypes of myoclonus--dystonia on chromosome 7q. Neurology 2001;56(9):1213–1216.
9. Zimprich A, Grabowski M, Asmus F, et al. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. Nat Genet 2001;29(1):66–69.
10. Peall KJ, Kurian MA, Wardle M, et al. SGCE and myoclonus dystonia: motor characteristics, diagnostic criteria and clinical predictors of genotype. J Neurol 2014;261(12):2296–2304.
11. Roze E, Lang AE, Vidailhet M. Myoclonus-dystonia: classification, phenomenology, pathogenesis, and treatment. Curr Opin Neurol 2018;31(4):484–490.
12. Charlesworth G, Bhatia KP, Wood NW. The genetics of dystonia: new twists in an old tale. Brain 2013;136(Pt 7):2017–2037.
13. Marras C, Lang A, van de Warrenburg BP, et al. Nomenclature of genetic movement disorders: Recommendations of the international Parkinson and movement disorder society task force. Mov Disord 2016;31(4):436–457.
14. Domingo A, Erro R, Lohmann K. Novel Dystonia Genes: Clues on Disease Mechanisms and the Complexities of High-Throughput Sequencing. Mov Disord 2016;31(4):471–477.
15. Kinugawa K, Vidailhet M, Clot F, Apartis E, Grabli D, Roze E. Myoclonus-dystonia: an update. Mov Disord 2009;24(4):479–489.
16. Raymond D, Saunders-Pullman R, de Carvalho Aguiar P, et al. Phenotypic spectrum and sex effects in eleven myoclonus-dystonia families with epsilon-sarcoglycan mutations. Mov Disord 2008;23 (4):588–592.
17. Gerrits MC, Foncke EM, de Haan R, et al. Phenotype-genotype correlation in Dutch patients with myoclonus-dystonia. Neurology 2006;66(5):759–761.
18. Grunewald A, Djarmati A, Lohmann-Hedrich K, et al. Myoclonus-dystonia: significance of large SGCE deletions. Hum Mutat 2008; 29(2):331–332.
19. Koide N, Dateki S, Watanabe K, Moriuchi H. Novel SGCE mutation (p.Glu65*) in a Japanese family with myoclonus-dystonia. Pediatr Int 2017;59(9):1018–1020.
20. Nardocci N, Zorzi G, Barzaghi C, et al. Myoclonus-dystonia syndrome: clinical presentation, disease course, and genetic features in 11 families. Mov Disord 2008;23(1):28–34.
21. Marechal L, Raux G, Dumanchin C, et al. Severe myoclonus-dystonia syndrome associated with a novel epsilon-sarcoglycan gene truncating mutation. Am J Med Genet B Neuropsychiatr Genet 2003;119B(1):114–117.
22. Szubiga M, Rudzinska M, Bik-Multanowski M, Pietrzyk JJ, Szczudlik A. A novel conserved mutation in SGCE gene in 3 unrelated patients with classical phenotype myoclonus-dystonia syndrome. Neurol Res 2013;35(6):659–662.
23. Tezenas du Montcel S, Clot F, Vidailhet M, et al. Epsilon sarcoglycan mutations and phenotype in French patients with myoclonic syndromes. J Med Genet 2006;43(5):394–400.
24. Valente EM, Edwards MJ, Mir P, et al. The epsilon-sarcoglycan gene in myoclonic syndromes. Neurology 2005;64(4):737–739.
25. Foncke EM, Gerrits MC, van Ruissen F, et al. Distal myoclonus and late onset in a large Dutch family with myoclonus-dystonia. Neurology 2006;67(9):1677–1680.
26. Wong SH, Steiger MJ, Larner AJ, Fletcher NA. Hereditary myoclonus dystonia (DYT11): a novel SGCE gene mutation with intrafamilial phenotypic heterogeneity. Mov Disord 2010;25(7): 956–957.
27. Edwards MJ, Stamelou M, Quinn N, Bhatia KP. Parkinson's Disease and Other Movement Disorders. 2nd ed. Oxford, UK: Oxford University Press; 2016.
28. Nardocci N. Myoclonus-dystonia syndrome. Handb Clin Neurol 2011;100:563–575.
29. Bonello M, Larner AJ, Alusi SH. Myoclonus-dystonia (DYT11) with novel SGCE mutation misdiagnosed as a primary psychiatric disorder. J Neurol Sci 2014;346(1-2):356–357.
30. Isaacs DA, Hedera P. Speech-activated Myoclonus Mimicking Stuttering in a Patient with Myoclonus-Dystonia Syndrome. Tremor Other Hyperkinet Mov (N Y) 2016;6:405.
31. Roze E, Apartis E, Clot F, et al. Myoclonus-dystonia: clinical and electrophysiologic pattern related to SGCE mutations. Neurology 2008;70(13):1010–1016.
32. 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(9): 1536–1539.
33. Luciano MS, Ozelius L, Sims K, Raymond D, Liu L, Saunders-Pullman R. Responsiveness to levodopa in epsilon-sarcoglycan deletions. Mov Disord 2009;24(3):425–428.
34. Drivenes B, Born AP, Ek J, Dunoe M, Uldall PV. A child with myoclonus-dystonia (DYT11) misdiagnosed as atypical opsoclonus myoclonus syndrome. Eur J Paediatr Neurol 2015;19(6):719–721.
35. Hartmann CJ, Leube B, Wojtecki L, et al. A novel mutation of the SGCE-gene in a German family with myoclonus-dystonia syndrome. J Neurol 2011;258(6):1186–1188.

36. Koukouni V, Valente EM, Cordivari C, Bhatia KP, Quinn NP. Unusual familial presentation of epsilon-sarcoglycan gene mutation with falls and writer's cramp. Mov Disord 2008;23(13): 1913–1915.
37. Ritz K, Gerrits MC, Foncke EM, et al. Myoclonus-dystonia: clinical and genetic evaluation of a large cohort. J Neurol Neurosurg Psychiatry 2009;80(6):653–658.
38. Saugier-Veber P, Doummar D, Barthez MA, et al. Myoclonus dystonia plus syndrome due to a novel 7q21 microdeletion. Am J Med Genet A 2010;152A(5):1244–1249.
39. Asmus F, Salih F, Hjermind LE, et al. Myoclonus-dystonia due to genomic deletions in the epsilon-sarcoglycan gene. Ann Neurol 2005;58(5):792–797.
40. Asmus F, Zimprich A, Tezenas Du Montcel S, et al. Myoclonus-dystonia syndrome: epsilon-sarcoglycan mutations and phenotype. Ann Neurol 2002;52(4):489–492.
41. Asmus F, Langseth A, Doherty E, et al. "Jerky" dystonia in children: spectrum of phenotypes and genetic testing. Mov Disord 2009;24(5):702–709.
42. Blackburn JS, Cirillo ML. Clinical reasoning: A 13-year-old boy presenting with dystonia, myoclonus, and anxiety. Neurology 2012;78(11):e72–e76.
43. Doheny DO, Brin MF, Morrison CE, et al. Phenotypic features of myoclonus-dystonia in three kindreds. Neurology 2002;59(8): 1187–1196.
44. Han F, Racacho L, Yang H, et al. Large deletions account for an increasing number of mutations in SGCE. Mov Disord 2008;23(3): 456–460.
45. Klein C, Liu L, Doheny D, et al. Epsilon-sarcoglycan mutations found in combination with other dystonia gene mutations. Ann Neurol 2002;52(5):675–679.
46. Schule B, Kock N, Svetel M, et al. Genetic heterogeneity in ten families with myoclonus-dystonia. J Neurol Neurosurg Psychiatry 2004;75(8):1181–1185.
47. Tedroff K, Rolfs A, Norling A. A novel SGCE gene mutation causing myoclonus dystonia in a family with an unusual phenotype. Acta Paediatr 2012;101(2):e90–e92.
48. Wada T, Takano K, Tsurusaki Y, et al. Japanese familial case of myoclonus-dystonia syndrome with a splicing mutation in SGCE. Pediatr Int 2015;57(2):324-326.
49. Ritz K, Groen JL, Kruisdijk JJ, Baas F, Koelman JH, Tijssen MA. Screening for dystonia genes DYT1, 11 and 16 in patients with writer's cramp. Mov Disord 2009;24(9):1390–1392.
50. Contarino MF, Berger-Plantinga E, Foncke EM, et al. Clinical and genetic characterization of a large Dutch family with primary focal dystonia. Mov Disord 2008;23(14):1998–2003.
51. Grundmann K, Laubis-Herrmann U, Dressler D, et al. Lack of mutations in the epsilon-sarcoglycan gene in patients with different subtypes of primary dystonias. Mov Disord 2004;19(11):1294–1297.
52. Gerrits MC, Foncke EM, Koelman JH, Tijssen MA. Pediatric writer's cramp in myoclonus-dystonia: maternal imprinting hides positive family history. Eur J Paediatr Neurol 2009;13(2):178–180.
53. Hess CW, Saunders-Pullman R. Movement disorders and alcohol misuse. Addict Biol 2006;11(2):117–125.
54. Saunders-Pullman R, Shriberg J, Heiman G, et al. Myoclonus dystonia: possible association with obsessive-compulsive disorder and alcohol dependence. Neurology 2002;58(2):242–245.
55. Weissbach A, Werner E, Bally JF, et al. Alcohol improves cerebellar learning deficit in myoclonus-dystonia: A clinical and electrophysiological investigation. Ann Neurol 2017;82(4):543–553.
56. Thobois S, Gervais-Bernard H, Xie-Brustolin J, Zyss J, Ostrowsky K, Broussolle E. Evidence for progressive changes in clinical presentation of myoclonus-dystonia. Mov Disord 2007;22 (10):1516–1517.
57. Lee JH, Lyoo CH, Lee MS. A patient with genetically confirmed myoclonus-dystonia responded to anticholinergic treatment and improved spontaneously. J Clin Neurol 2011;7(4):231–232.
58. Foncke EM, Cath D, Zwinderman K, Smit J, Schmand B, Tijssen M. Is psychopathology part of the phenotypic spectrum of myoclonus-dystonia?: a study of a large Dutch M-D family. Cogn Behav Neurol 2009;22(2):127–133.
59. Hess CW, Raymond D, Aguiar Pde C, et al. Myoclonus-dystonia, obsessive-compulsive disorder, and alcohol dependence in SGCE mutation carriers. Neurology 2007;68(7):522–524.
60. Peall KJ, Smith DJ, Kurian MA, et al. SGCE mutations cause psychiatric disorders: clinical and genetic characterization. Brain 2013; 136(Pt 1):294–303.
61. Peall KJ, Waite AJ, Blake DJ, Owen MJ, Morris HR. Psychiatric disorders, myoclonus dystonia, and the epsilon-sarcoglycan gene: a systematic review. Mov Disord 2011;26(10):1939–1942.
62. van Tricht MJ, Dreissen YE, Cath D, et al. Cognition and psychopathology in myoclonus-dystonia. J Neurol Neurosurg Psychiatry 2012;83(8):814–820.
63. Weissbach A, Kasten M, Grunewald A, et al. Prominent psychiatric comorbidity in the dominantly inherited movement disorder myoclonus-dystonia. Parkinsonism Relat Disord 2013;19(4):422–425.
64. Peall KJ, Dijk JM, Saunders-Pullman R, et al. Psychiatric disorders, myoclonus dystonia and SGCE: an international study. Ann Clin Transl Neurol 2016;3(1):4–11.
65. Carecchio M, Magliozzi M, Copetti M, et al. Defining the epsilon-sarcoglycan (SGCE) gene phenotypic signature in myoclonus-dystonia: a reappraisal of genetic testing criteria. Mov Disord 2013;28(6):787–794.
66. Kim JY, Lee WW, Shin CW, et al. Psychiatric symptoms in myoclonus-dystonia syndrome are just concomitant features regardless of the SGCE gene mutation. Parkinsonism Relat Disord 2017;42:73–77.
67. Zutt R, Dijk JM, Peall KJ, et al. Distribution and Coexistence of Myoclonus and Dystonia as Clinical Predictors of SGCE Mutation Status: A Pilot Study. Front Neurol 2016;7:72.
68. 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(8):1183–1186.
69. Han F, Racacho L, Lang AE, Bulman DE, Grimes DA. Refinement of the DYT15 locus in myoclonus dystonia. Mov Disord 2007;22 (6):888–892.
70. Marelli C, Canafoglia L, Zibordi F, et al. A neurophysiological study of myoclonus in patients with DYT11 myoclonus-dystonia syndrome. Mov Disord 2008;23(14):2041–2048.
71. Latorre A, Rocchi L, Berardelli A, Rothwell JC, Bhatia KP, Cordivari C. Reappraisal of cortical myoclonus: A retrospective study of clinical neurophysiology. Mov Disord 2018;33(2):339–341.
72. Grosse P, Cassidy MJ, Brown P. EEG-EMG, MEG-EMG and EMG-EMG frequency analysis: physiological principles and clinical applications. Clin Neurophysiol 2002;113(10):1523–1531.
73. Foncke EM, Bour LJ, van der Meer JN, Koelman JH, Tijssen MA. Abnormal low frequency drive in myoclonus-dystonia patients correlates with presence of dystonia. Mov Disord 2007;22(9): 1299–1307.
74. Brown P, Farmer SF, Halliday DM, Marsden J, Rosenberg JR. Coherent cortical and muscle discharge in cortical myoclonus. Brain 1999;122 (Pt 3):461–472.
75. Grosse P, Kuhn A, Cordivari C, Brown P. Coherence analysis in the myoclonus of corticobasal degeneration. Mov Disord 2003;18 (11):1345–1350.
76. Kristeva R, Popa T, Chakarov V, Hummel S. Cortico-muscular coupling in a patient with postural myoclonus. Neurosci Lett 2004; 366(3):259–263.
77. Marsden JF, Ashby P, Rothwell JC, Brown P. Phase relationships between cortical and muscle oscillations in cortical myoclonus: electrocorticographic assessment in a single case. Clin Neurophysiol 2000;111(12):2170–2174.
78. van Rootselaar AF, Maurits NM, Koelman JH, et al. Coherence analysis differentiates between cortical myoclonic tremor and essential tremor. Mov Disord 2006;21(2):215–222.
79. Chen R, Cros D, Curra A, et al. The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 2008;119(3):504–532.

80. van der Salm SM, van Rootselaar AF, Foncke EM, et al. Normal cortical excitability in Myoclonus-Dystonia--a TMS study. Exp Neurol 2009;216(2):300–305.

81. Roze E, Apartis E, Trocello JM. Cortical excitability in DYT-11 positive myoclonus dystonia. Mov Disord 2008;23(5):761–764.

82. Popa T, Milani P, Richard A, et al. The neurophysiological features of myoclonus-dystonia and differentiation from other dystonias. JAMA Neurol 2014;71(5):612–619.

83. Edwards MJ, Huang YZ, Wood NW, Rothwell JC, Bhatia KP. Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the DYT1 gene mutation. Brain 2003; 126(Pt 9):2074-2080.

84. Gerwig M, Kolb FP, Timmann D. The involvement of the human cerebellum in eyeblink conditioning. Cerebellum 2007;6(1):38–57.

85. Hubsch C, Vidailhet M, Rivaud-Pechoux S, et al. Impaired saccadic adaptation in DYT11 dystonia. J Neurol Neurosurg Psychiatry 2011;82(10):1103–1106.

86. Gaymard B, Rivaud-Pechoux S, Yelnik J, Pidoux B, Ploner CJ. Involvement of the cerebellar thalamus in human saccade adaptation. Eur J Neurosci 2001;14(3):554–560.

87. McLaughlin S. Parametric adjustment in saccadic eye movements. Perception & Psychophysics 1967;2(8):359–362.

88. Straube A, Deubel H, Ditterich J, Eggert T. Cerebellar lesions impair rapid saccade amplitude adaptation. Neurology 2001;57 (11):2105–2108.

89. Carbon M, Raymond D, Ozelius L, et al. Metabolic changes in DYT11 myoclonus-dystonia. Neurology 2013;80(4):385–391.

90. Aiello M, Cavaliere C, Salvatore M. Hybrid PET/MR Imaging and Brain Connectivity. Frontiers in neuroscience 2016;10:64.

91. Lehericy S, Grand S, Pollak P, et al. Clinical characteristics and topography of lesions in movement disorders due to thalamic lesions. Neurology 2001;57(6):1055–1066.

92. Kuncel AM, Turner DA, Ozelius LJ, Greene PE, Grill WM, Stacy MA. Myoclonus and tremor response to thalamic deep brain stimulation parameters in a patient with inherited myoclonus-dystonia syndrome. Clin Neurol Neurosurg 2009;111(3):303–306.

93. Fernandez-Pajarin G, Sesar A, Relova JL, et al. Bilateral pallidal deep brain stimulation in myoclonus-dystonia: our experience in three cases and their follow-up. Acta Neurochir (Wien) 2016;158 (10):2023–2028.

94. Bejot Y, Giroud M, Moreau T, Benatru I. Clinical spectrum of movement disorders after stroke in childhood and adulthood. Eur Neurol 2012;68(1):59–64.

95. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13(7):281–285.

96. Welter ML, Grabli D, Karachi C, et al. Pallidal activity in myoclonus dystonia correlates with motor signs. Mov Disord 2015;30(7): 992–996.

97. Nakashima K, Rothwell JC, Thompson PD, et al. The blink reflex in patients with idiopathic torsion dystonia. Arch Neurol 1990;47 (4):413–416.

98. Borges V, Aguiar Pde C, Ferraz HB, Ozelius LJ. Novel and de novo mutations of the SGCE gene in Brazilian patients with myoclonus-dystonia. Mov Disord 2007;22(8):1208–1209.

99. DeBerardinis RJ, Conforto D, Russell K, et al. Myoclonus in a patient with a deletion of the epsilon-sarcoglycan locus on chromosome 7q21. Am J Med Genet A 2003;121A(1):31–36.

100. Misbahuddin A, Placzek M, Lennox G, Taanman JW, Warner TT. Myoclonus-dystonia syndrome with severe depression is caused by an exon-skipping mutation in the epsilon-sarcoglycan gene. Mov Disord 2007;22(8):1173–1175.

101. Thummler S, Giuliano F, Pincemaille O, Saugier-Veber P, Perelman S. Myoclonus in fraternal twin toddlers: a French family with a novel mutation in the SGCE gene. Eur J Paediatr Neurol 2009;13(6):559–561.

102. Huang CL, Lan MY, Chang YY, et al. Large SGCE deletion contributes to Taiwanese myoclonus-dystonia syndrome. Parkinsonism Relat Disord 2010;16(9):585–589.

103. Luciano AY, Jinnah HA, Pfeiffer RF, Truong DD, Nance MA, LeDoux MS. Treatment of myoclonus-dystonia syndrome with tetrabenazine. Parkinsonism Relat Disord 2014;20(12):1423–1426.

104. Frucht SJ, Bordelon Y, Houghton WH, Reardan D. A pilot tolerability and efficacy trial of sodium oxybate in ethanol-responsive movement disorders. Mov Disord 2005;20(10):1330–1337.

105. Hainque E, Vidailhet M, Cozic N, et al. A randomized, controlled, double-blind, crossover trial of zonisamide in myoclonus-dystonia. Neurology 2016;86(18):1729–1735.

106. Azoulay-Zyss J, Roze E, Welter ML, et al. Bilateral deep brain stimulation of the pallidum for myoclonus-dystonia due to epsilon-sarcoglycan mutations: a pilot study. Arch Neurol 2011;68(1):94–98.

107. Beukers RJ, Contarino MF, Speelman JD, Schuurman PR, Booij J, Tijssen MA. Deep Brain Stimulation of the Pallidum is Effective and Might Stabilize Striatal D(2) Receptor Binding in Myoclonus-Dystonia. Front Neurol 2012;3:22.

108. Cif L, Valente EM, Hemm S, et al. Deep brain stimulation in myoclonus-dystonia syndrome. Mov Disord 2004;19(6):724–727.

109. Contarino MF, Foncke EM, Cath DC, Schuurman PR, Speelman JD, Tijssen MA. Effect of pallidal deep brain stimulation on psychiatric symptoms in myoclonus-dystonia due to epsilon-sarcoglycan mutations. Arch Neurol 2011;68(8):1087–1088; author reply 1088–1089.

110. Foncke EM, Bour LJ, Speelman JD, Koelman JH, Tijssen MA. Local field potentials and oscillatory activity of the internal globus pallidus in myoclonus-dystonia. Mov Disord 2007;22(3):369–376.

111. Gruber D, Kuhn AA, Schoenecker T, et al. Pallidal and thalamic deep brain stimulation in myoclonus-dystonia. Mov Disord 2010; 25(11):1733–1743.

112. Kosutzka Z, Tisch S, Bonnet C, et al. Long-term GPi-DBS improves motor features in myoclonus-dystonia and enhances social adjustment. Mov Disord 2019;34(1):87–94.

113. Kurtis MM, San Luciano M, Yu Q, et al. Clinical and neurophysiological improvement of SGCE myoclonus-dystonia with GPi deep brain stimulation. Clin Neurol Neurosurg 2010;112(2):149–152.

114. Papuc E, Obszanska K, Rejdak K, Stelmasiak Z, Trojanowski T. Atypical symptomatology of myoclonus dystonia (DYT-11) with positive response to bilateral pallidal deep brain stimulation. Mov Disord 2014;29(7):E3.

115. Ramdhani RA, Frucht SJ, Behnegar A, Kopell BH. Improvement of Isolated Myoclonus Phenotype in Myoclonus Dystonia after Pallidal Deep Brain Stimulation. Tremor Other Hyperkinet Mov (N Y) 2016;6:369.

116. Rocha H, Linhares P, Chamadoira C, Rosas MJ, Vaz R. Early deep brain stimulation in patients with myoclonus-dystonia syndrome. J Clin Neurosci 2016;27:17–21.

117. Roze E, Vidailhet M, Hubsch C, Navarro S, Grabli D. Pallidal stimulation for myoclonus-dystonia: Ten years' outcome in two patients. Mov Disord 2015;30(6):871–872.

118. Uruha A, Kimura K, Okiyama R. An Asian Patient with Myoclonus-Dystonia (DYT11) Responsive to Deep Brain Stimulation of the Globus Pallidus Internus. Case Rep Neurol Med 2014; 2014:937095.

119. Vidailhet M, Jutras MF, Grabli D, Roze E. Deep brain stimulation for dystonia. J Neurol Neurosurg Psychiatry 2013;84(9):1029–1042.

120. Rughani AI, Lozano AM. Surgical treatment of myoclonus dystonia syndrome. Mov Disord 2013;28(3):282–287.

121. Sarva H, Miravite J, Swan MC, et al. A Case of Myoclonus-Dystonia Responding to Low-frequency Pallidal Stimulation. Tremor Other Hyperkinet Mov (N Y) 2017;7:460.

122. Grabowski M, Zimprich A, Lorenz-Depiereux B, et al. The epsilon-sarcoglycan gene (SGCE), mutated in myoclonus-dystonia syndrome, is maternally imprinted. Eur J Hum Genet 2003;11(2):138–144.

123. Muller B, Hedrich K, Kock N, et al. Evidence that paternal expression of the epsilon-sarcoglycan gene accounts for reduced penetrance in myoclonus-dystonia. Am J Hum Genet 2002;71(6):1303–1311.

124. Rachad L, El Kadmiri N, Slassi I, El Otmani H, Nadifi S. Genetic Aspects of Myoclonus-Dystonia Syndrome (MDS). Mol Neurobiol 2017;54(2):939–942.

125. Esapa CT, Waite A, Locke M, et al. SGCE missense mutations that cause myoclonus-dystonia syndrome impair epsilon-sarcoglycan trafficking to the plasma membrane: modulation by ubiquitination and torsinA. Hum Mol Genet 2007;16(3):327–342.

126. Asmus F, Hjermind LE, Dupont E, et al. Genomic deletion size at the epsilon-sarcoglycan locus determines the clinical phenotype. Brain 2007;130(Pt 10):2736–2745.

127. Hedrich K, Meyer EM, Schule B, et al. Myoclonus-dystonia: detection of novel, recurrent, and de novo SGCE mutations. Neurology 2004;62(7):1229–1231.

128. Johnston JJ, Lewis KL, Ng D, et al. Individualized iterative phenotyping for genome-wide analysis of loss-of-function mutations. Am J Hum Genet 2015;96(6):913–925.

129. Asmus F, Devlin A, Munz M, Zimprich A, Gasser T, Chinnery PF. Clinical differentiation of genetically proven benign hereditary chorea and myoclonus-dystonia. Mov Disord 2007;22(14):2104–2109.

130. Chung EJ, Lee WY, Kim JY, et al. Novel SGCE gene mutation in a Korean patient with myoclonus-dystonia with unique phenotype mimicking Moya-Moya disease. Mov Disord 2007;22(8):1206–1207.

131. Kubler D, Borngraber F, Lohmann K, Kuhn AA. Novel SGCE mutation in a patient with myoclonus-dystonia syndrome - Diagnostic delay of more than 40years. J Clin Neurosci 2018;50:131–132.

132. Cilia R, Reale C, Castagna A, et al. Novel DYT11 gene mutation in patients without dopaminergic deficit (SWEDD) screened for dystonia. Neurology 2014;83(13):1155–1162.

133. Haugarvoll K, Tzoulis C, Tran GT, et al. Myoclonus-dystonia and epilepsy in a family with a novel epsilon-sarcoglycan mutation. J Neurol 2014;261(2):358–362.

134. Dale RC, Nasti JJ, Peters GB. Familial 7q21.3 microdeletion involving epsilon-sarcoglycan causing myoclonus dystonia, cognitive impairment, and psychosis. Mov Disord 2011;26(9):1774–1775.

135. Xiao J, Nance MA, LeDoux MS. Incomplete nonsense-mediated decay facilitates detection of a multi-exonic deletion mutation in SGCE. Clin Genet 2013;84(3):276–280.

136. Akbari MT, Mirfakhraie R, Zare-Karizi S, Shahidi G. Myoclonus dystonia syndrome: a novel epsilon-sarcoglycan gene mutation with variable clinical symptoms. Gene 2014;548(2):306–307.

137. Chen XP, Zhang YW, Zhang SS, et al. A novel mutation of the epsilon-sarcoglycan gene in a Chinese family with myoclonus-dystonia syndrome. Mov Disord 2008;23(10):1472–1475.

138. Bonnet C, Gregoire MJ, Vibert M, Raffo E, Leheup B, Jonveaux P. Cryptic 7q21 and 9p23 deletions in a patient with apparently balanced de novo reciprocal translocation t(7;9)(q21;p23) associated with a dystonia-plus syndrome: paternal deletion of the epsilon-sarcoglycan (SGCE) gene. J Hum Genet 2008;53(10):876–885.

139. Kotzot D, Schmitt S, Bernasconi F, et al. Uniparental disomy 7 in Silver-Russell syndrome and primordial growth retardation. Hum Mol Genet 1995;4(4):583–587.

140. Wakeling EL. Silver-Russell syndrome. Arch Dis Child 2011;96 (12):1156–1161.

141. Augustine EF, Blackburn J, Pellegrino JE, Miller R, Mink JW. Myoclonus-dystonia syndrome associated with Russell Silver syndrome. Mov Disord 2013;28(6):841–842.

142. Guettard E, Portnoi MF, Lohmann-Hedrich K, et al. Myoclonus-dystonia due to maternal uniparental disomy. Arch Neurol 2008; 65(10):1380–1385.

143. Sheridan MB, Bytyci Telegrafi A, Stinnett V, et al. Myoclonus-dystonia and Silver-Russell syndrome resulting from maternal uniparental disomy of chromosome 7. Clin Genet 2013;84(4):368–372.

144. Stark Z, Ryan MM, Bruno DL, Burgess T, Savarirayan R. Atypical Silver-Russell phenotype resulting from maternal uniparental disomy of chromosome 7. Am J Med Genet A 2010;152A(9):2342–2345.

145. Ozawa E, Mizuno Y, Hagiwara Y, Sasaoka T, Yoshida M. Molecular and cell biology of the sarcoglycan complex. Muscle Nerve 2005;32(5):563–576.

146. 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(1):27–32.

147. 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(51):32534–32538.

148. Xiao J, LeDoux MS. Cloning, developmental regulation and neural localization of rat epsilon-sarcoglycan. Brain Res Mol Brain Res 2003;119(2):132–143.

149. 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(1):50–73.

150. 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(1-2):1–12.

151. Ritz K, van Schaik BD, Jakobs ME, et al. SGCE isoform characterization and expression in human brain: implications for myoclonus-dystonia pathogenesis? Eur J Hum Genet 2011;19(4):438–444.

152. 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(21):4822–4828.

153. Yokoi F, Dang MT, Li J, Li Y. Myoclonus, motor deficits, alterations in emotional responses and monoamine metabolism in epsilon-sarcoglycan deficient mice. J Biochem 2006;140(1):141–146.

154. Yokoi F, Dang MT, Zhou T, Li Y. Abnormal nuclear envelopes in the striatum and motor deficits in DYT11 myoclonus-dystonia mouse models. Hum Mol Genet 2012;21(4):916–925.

155. Zhang L, Yokoi F, Parsons DS, Standaert DG, Li Y. Alteration of striatal dopaminergic neurotransmission in a mouse model of DYT11 myoclonus–dystonia. PLoS One 2012;7(3):e33669.

156. Yokoi F, Dang MT, Yang G, et al. Abnormal nuclear envelope in the cerebellar Purkinje cells and impaired motor learning in DYT11 myoclonus-dystonia mouse models. Behav Brain Res 2012; 227(1):12–20.

157. Oleas J, Yokoi F, DeAndrade MP, Pisani A, Li Y. Engineering animal models of dystonia. Mov Disord 2013;28(7):990–1000.

158. Blake DJ, Weir A, Newey SE, Davies KE. Function and genetics of dystrophin and dystrophin-related proteins in muscle. Physiol Rev 2002;82(2):291–329.

159. Waite A, Brown SC, Blake DJ. The dystrophin-glycoprotein complex in brain development and disease. Trends Neurosci 2012;35 (8):487–496.

160. Ozawa E, Noguchi S, Mizuno Y, Hagiwara Y, Yoshida M. From dystrophinopathy to sarcoglycanopathy: evolution of a concept of muscular dystrophy. Muscle Nerve 1998;21(4):421–438.

161. Imamura M, Mochizuki Y, Engvall E, Takeda S. Epsilon-sarcoglycan compensates for lack of alpha-sarcoglycan in a mouse model of limb-girdle muscular dystrophy. Hum Mol Genet 2005; 14(6):775–783.

162. McNally EM, Pytel P. Muscle diseases: the muscular dystrophies. Annu Rev Pathol 2007;2:87–109.

163. Blake DJ, Hawkes R, Benson MA, Beesley PW. Different dystrophin-like complexes are expressed in neurons and glia. J Cell Biol 1999;147(3):645–658.

164. Waite AJ, Carlisle FA, Chan YM, Blake DJ. Myoclonus dystonia and muscular dystrophy: varepsilon-sarcoglycan is part of the dystrophin-associated protein complex in brain. Mov Disord 2016; 31(11):1694–1703.

165. Tadayoni R, Rendon A, Soria-Jasso LE, Cisneros B. Dystrophin Dp71: the smallest but multifunctional product of the Duchenne muscular dystrophy gene. Mol Neurobiol 2012;45(1):43–60.

166. Holt KH, Campbell KP. Assembly of the sarcoglycan complex. Insights for muscular dystrophy. J Biol Chem 1998;273(52): 34667–34670.

167. Ichinose H, Ohye T, Takahashi E, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet 1994;8(3):236–242.

168. 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(8):1241–1243.

169. Ludecke B, Knappskog PM, Clayton PT, et al. Recessively inherited L-DOPA-responsive parkinsonism in infancy caused by a point mutation (L205P) in the tyrosine hydroxylase gene. Hum Mol Genet 1996;5(7):1023–1028.

170. Stamelou M, Mencacci NE, Cordivari C, et al. Myoclonus-dystonia syndrome due to tyrosine hydroxylase deficiency. Neurology 2012;79(5):435–441.

171. Carecchio M, Panteghini C, Reale C, et al. Novel GNAL mutation with intra-familial clinical heterogeneity: Expanding the phenotype. Parkinsonism Relat Disord 2016;23:66–71.

172. Stamelou M, Charlesworth G, Cordivari C, et al. The phenotypic spectrum of DYT24 due to ANO3 mutations. Mov Disord 2014; 29(7):928–934.

173. Geiger JT, Schindler AB, Blauwendraat C, Singer HS, Scholz SW. TUBB2B Mutation in an Adult Patient with Myoclonus-Dystonia. Case Rep Neurol 2017;9(2):216–221.

174. Foncke EM, Beukers RJ, Tijssen CC, Koelman JH, Tijssen MA. Myoclonus-dystonia and spinocerebellar ataxia type 14 presenting with similar phenotypes: trunk tremor, myoclonus, and dystonia. Parkinsonism Relat Disord 2010;16(4):288–289.

175. Angelini L, Erba A, Mariotti C, Gellera C, Ciano C, Nardocci N. Myoclonic dystonia as unique presentation of isolated vitamin E deficiency in a young patient. Mov Disord 2002;17(3):612–614.

176. Douglas AG, Andreoletti G, Talbot K, et al. ADCY5-related dyskinesia presenting as familial myoclonus-dystonia. Neurogenetics 2017;18(2):111–117.

177. Mencacci NE, Rubio-Agusti I, Zdebik A, et al. A missense mutation in KCTD17 causes autosomal dominant myoclonus-dystonia. Am J Hum Genet 2015;96(6):938–947.

178. Skoblov M, Marakhonov A, Marakasova E, et al. Protein partners of KCTD proteins provide insights about their functional roles in cell differentiation and vertebrate development. Bioessays 2013;35 (7):586–596.

179. Groen J, van Rootselaar AF, van der Salm SM, Bloem BR, Tijssen M. A new familial syndrome with dystonia and lower limb action myoclonus. Mov Disord 2011;26(5):896–900.

180. Groen JL, Andrade A, Ritz K, et al. CACNA1B mutation is linked to unique myoclonus-dystonia syndrome. Hum Mol Genet 2015; 24(4):987–993.

181. Mencacci NE, R'Bibo L, Bandres-Ciga S, et al. The CACNA1B R1389H variant is not associated with myoclonus-dystonia in a large European multicentric cohort. Hum Mol Genet 2015;24(18):5326–5329.

182. Beuckmann CT, Sinton CM, Miyamoto N, Ino M, Yanagisawa M. N-type calcium channel alpha1B subunit (Cav2.2) knock-out mice display hyperactivity and vigilance state differences. J Neurosci 2003;23(17):6793–6797.

183. Lipscombe D, Allen SE, Toro CP. Control of neuronal voltage-gated calcium ion channels from RNA to protein. Trends Neurosci 2013;36(10):598–609.

184. Phillips PE, Stamford JA. Differential recruitment of N-, P- and Q-type voltage-operated calcium channels in striatal dopamine release evoked by 'regular' and 'burst' firing. Brain Res 2000;884(1–2):139–146.

185. Weiss N. The first disease connection for Cav2.2 channels. Gen Physiol Biophys 2015;34(3):217–219.

186. Groen JL, Ritz K, Jalalzadeh H, et al. RELN rare variants in myoclonus-dystonia. Mov Disord 2015;30(3):415–419.

187. D'Arcangelo G, Miao GG, Chen SC, Soares HD, Morgan JI, Curran T. A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. Nature 1995;374(6524):719–723.

188. DeSilva U, D'Arcangelo G, Braden VV, et al. The human reelin gene: isolation, sequencing, and mapping on chromosome 7. Genome Res 1997;7(2):157–164.

189. Curran T, D'Arcangelo G. Role of reelin in the control of brain development. Brain Res Brain Res Rev 1998;26(2–3):285–294.

190. Meyer G, Goffinet AM. Prenatal development of reelin-immunoreactive neurons in the human neocortex. J Comp Neurol 1998;397(1):29–40.

191. Ishii K, Kubo KI, Nakajima K. Reelin and Neuropsychiatric Disorders. Front Cell Neurosci 2016;10:229.

192. Alcantara S, Ruiz M, D'Arcangelo G, et al. Regional and cellular patterns of reelin mRNA expression in the forebrain of the developing and adult mouse. J Neurosci 1998;18(19):7779–7799.

193. Herz J, Chen Y. Reelin, lipoprotein receptors and synaptic plasticity. Nat Rev Neurosci 2006;7(11):850–859.

194. Lozano-Urena A, Montalban-Loro R, Ferguson-Smith AC, Ferron SR. Genomic Imprinting and the Regulation of Postnatal Neurogenesis. Brain Plast 2017;3(1):89–98.

195. Cleaton MA, Edwards CA, Ferguson-Smith AC. Phenotypic outcomes of imprinted gene models in mice: elucidation of pre- and postnatal functions of imprinted genes. Annu Rev Genomics Hum Genet 2014;15:93–126.

196. Niethammer M, Carbon M, Argyelan M, Eidelberg D. Hereditary dystonia as a neurodevelopmental circuit disorder: Evidence from neuroimaging. Neurobiol Dis 2011;42(2):202–209.

197. Beukers RJ, Foncke EM, van der Meer JN, et al. Disorganized sensorimotor integration in mutation-positive myoclonus-dystonia: a functional magnetic resonance imaging study. Arch Neurol 2010; 67(4):469–474.

198. van der Meer JN, Beukers RJ, van der Salm SM, Caan MW, Tijssen MA, Nederveen AJ. White matter abnormalities in gene-positive myoclonus-dystonia. Mov Disord 2012;27(13): 1666–1672.

199. van der Salm SM, van der Meer JN, Nederveen AJ, Veltman DJ, van Rootselaar AF, Tijssen MA. Functional MRI study of response inhibition in myoclonus dystonia. Exp Neurol 2013; 247:623–629.

200. Haws CM, Lansman JB. Calcium-permeable ion channels in cerebellar neurons from mdx mice. Proc Biol Sci 1991;244(1311): 185–189.

201. Brini M, Cali T, Ottolini D, Carafoli E. Neuronal calcium signaling: function and dysfunction. Cell Mol Life Sci 2014;71(15): 2787–2814.

202. Dragicevic E, Poetschke C, Duda J, et al. Cav1.3 channels control D2-autoreceptor responses via NCS-1 in substantia nigra dopamine neurons. Brain 2014;137(Pt 8):2287–2302.

203. Beukers RJ, Booij J, Weisscher N, Zijlstra F, van Amelsvoort TA, Tijssen MA. Reduced striatal D2 receptor binding in myoclonus-dystonia. Eur J Nucl Med Mol Imaging 2009; 36(2):269–274.

Supporting Data

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