



# Myoclonus-dystonia (DYT11, DYT-SGCE) — a channelopathy?

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## ABSTRACT

**Introduction.** Kaczyńska et al. reported a family with myoclonus-dystonia (M-D) caused by a truncating *SGCE* mutation, in which two members had epilepsy. Further, patients had mild psychiatric and developmental deficits.

**Clinical reflections.** Characteristic motor features of M-D include myoclonus, dystonia and tremor. A wide range of additional disease manifestations are known. A few patients with M-D have seizures.

**Clinical implications.** Altered neuronal excitability has been found in the pathogenesis of M-D. This may explain the partial effectiveness of antiepileptics and a lower seizure threshold, and could encourage trials of other membrane stabilisers. Careful clinical observations of seemingly well-known diseases remain important.

**Key words:** myoclonus-dystonia, DYT11, *SGCE*, phenotype

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In this edition of the Polish Journal of Neurology and Neurosurgery, Dr. Kaczyńska et al. report the case of a Polish family with myoclonus-dystonia (M-D) and a novel truncating mutation in the gene for epsilon-sarcoglycan (*SGCE*) [1]. Six members of the family were affected by upper-body-predominant myoclonic jerks, dystonia, and/or tremor, such as classically characterise this disorder [2, 3]. Age at onset was between 18 months and 35 years. Genetic analyses showed a deletion of four bases in exon 7 of the *SGCE* gene that is predicted to cause a premature stop codon. This variant has never been reported previously from M-D patients, and is not included in the gnomAD database.

The authors' careful clinical assessment of the patients highlights the fact that non-motor symptoms can be prominent in M-D: two siblings with symptom onset at 1.5 and 2.5 years showed obsessive-compulsive behaviours, dyslexia and dysgraphia, as well as generalised epilepsy with absence seizures. One patient underwent a psychological assessment as a teenager because of difficulties at school. Although overall intellectual abilities were within the normal range, arithmetic reasoning, direct auditory memory and long-term memory were decreased. The sibling had below average intellectual

abilities on psychological assessment. Additional work-up included a slight reduction of metabolism in medial temporal lobes on FDG-PET.

Variants in *SGCE* were reported as being the cause of M-D in 2001. This enabled the delineation of this syndrome, the establishment of diagnostic criteria, and research into its underlying pathomechanisms [2–5]. Studies on larger numbers of patients have identified obsessive compulsive disorder and social and specific phobias to be recurrent psychiatric features [6, 7], and psychosis may occur [4].

Interestingly, Kaczyńska et al. also report generalised epilepsy with absence seizures in two siblings. Although the great majority of M-D patients do not have epilepsy, there have been previous reports on seizures in M-D patients (Tab. 1), and a causal association has been discussed [8–12]. This is supported by the findings of altered membrane excitability in M-D patients in neurophysiological studies [13, 14].

Furthermore, Kaczyńska et al. found mild clinical signs of atrophy of head and neck muscles, and frequent choking, in one of the patients. Mutations in the other sarcoglycans can cause limb girdle muscular dystrophies. However, a previous study of six unrelated M-D patients showed no structural

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**Table 1.** Reports in the literature on epileptic seizures in M-D. Additionally, seizures during alcohol withdrawal have been described [12]

Publication (First author, year, reference)	Number of patients with M-D and epilepsy in family*	Description of seizures	SGCE variant as reported
Foncke 2003 [9]	Three of four affected mutation carriers*	Absence and partial complex seizures with or without secondary generalisation, in one patient preceded by strange feeling in stomach	c.885Tins, truncating at amino acid position 297
O’Riordan 2004 [11]	Two of three affected mutation carriers*	Complex partial seizures with or without secondary generalisation, preceded by experience of a pungent smell. Lip smacking	c.289C>T, p.(Arg97Ter)
Haugarvoll 2014 [10]	Four of six affected mutation carriers*	Febrile, absence and generalised tonic-clonic seizures	c.372delG, p.(Lys125SerfsTer7)
Kaczyńska 2020 [1]	Two of three affected mutation carriers*	Generalised epilepsy with absence seizures	c.806-809delACTG, truncating

\*Figures include only individuals examined clinically and genetically in the study

changes in biopsies from proximal lower or upper skeletal muscles, or cardiac muscle [15]. This is in line with the normal creatine kinase and histopathological muscle examination (albeit for practical reasons taken from the clinically unaffected vastus medialis) in the patient from the Polish family. Although molecular characterisation of sarcoglycan complexes from skeletal muscle have revealed important differences to those found in the brain [16], it cannot be excluded that some M-D patients may have atrophy in specific musculature in the head and neck that is not easily accessible for biopsy. Or it may be that disturbances of membrane excitability also may affect muscle function in this disorder [13].

We compared Dr. Kaczyńska et al.’s findings with those of our patients with M-D. In one family with M-D and a previously reported [17] heterozygous missense variant SGCE c.812G>A p.(Cys271Tyr) in exon 6, the index patient had involuntary jerky head and arm movements from the age of five, and developed cervical dystonia. Neuropsychological evaluation revealed pronounced fatigability, reduced working memory, difficulty in concentrating, increased sensibility to stress, marked anxiety, and depressive symptoms. When tested at age 36, the patient made mistakes in alphabetical ordering, which might indicate similar learning deficits as in the Polish family [1]. A sibling had myoclonus since the age of six, cervical and arm/hand dystonia, and developed anxiety and depression. The myoclonic jerks were triggered by sudden unexpected sounds startling the patient, who had consequently adapted strategies to avoid situations where sudden noises can occur, trying to stay in control of their surroundings. This had led to a degree of social isolation, and might be interpreted as obsessive behaviour observed in M-D. There were no cognitive deficits in test batteries. The patient experienced difficulties in initiating swallowing, but no choking as in the Polish patient, and a mild stutter. Evaluation by an otolaryngologist and speech therapist, including a fibre-endoscopic laryngeal examination, showed oral motor difficulties and late initiation of swallowing, but a normal pharyngeal reflex. Palate and tongue root were normal shape. A DBS-operation (bilaterally in GPi) improved

motor symptoms in both siblings, and the male patient has become less socially isolated [18, 19].

In a second family, a patient had hand tremor, writer’s cramp, and pronounced psychiatric disorder with schizoaffective symptomatology. This patient’s sibling reportedly had mild intellectual disability, tremor in limbs, and myoclonic jerks in the neck. Both siblings and their asymptomatic father carried a different SGCE mutation, a heterozygous 14kb microdeletion encompassing the entire exon 6 (NM\_001099401,uc003unm.2). Their father’s mother reportedly had neurological symptoms, compatible with the known maternal imprinting mechanism in M-D. No patient in either of these two families reported seizures or displayed any obvious amyotrophy.

The molecular pathogenesis of the wide spectrum of neurological and psychiatric manifestations of M-D remains incompletely understood. Epsilon-sarcoglycan is found in membranes of neurons and muscle cells [20] and it has previously been suggested that the mechanism behind M-D may more closely resemble that of a disturbance in an ion channel than that of other forms of dystonia [14]. Careful clinical observations, like the study by Kaczyńska et al., can stimulate research into the underlying cellular and subcellular mechanisms, with the aim of improving clinicians’ ability to treat the various manifestations of this disorder.

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