Marked phenotypic variability in two siblings affected by congenital myasthenic syndrome caused by mutations in *MUSK*

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Congenital myasthenic syndromes (CMS) are rare genetic diseases of the neuromuscular junction¹ with 18 causative genes identified to date. Among many patients investigated worldwide, *MUSK* mutations were identified in only 9 patients.²⁻⁵ Here, we describe clinical, neurophysiological, muscle MRI and molecular features of two Italian siblings who carry compound heterozygous mutations in *MUSK* one of which is novel.

Case reports

The first sibling is a 27-year-old female. At birth, she had laryngeal stridor and respiratory failure requiring mechanical ventilation and tube feeding in the first month of life. She had recurring respiratory failure at age 3 months and frequent pulmonary infections during infancy. Her subsequent clinical course was characterized by bilateral fluctuating eyelid ptosis, ophthalmoparesis, mild dysphagia, mild exertional dyspnoea, severe upper and lower limb weakness, and limited ambulation. Menstrual periods and fever worsened her bulbar symptoms and fatigability. At age 8 years, a right deltoid muscle biopsy done elsewhere showed type I fiber predominance and muscle fiber atrophy. At age 13, a biopsy of left biceps brachii was interpreted as normal. At age 18, 3-Hz repetitive stimulation of the axillary nerve elicited a 37% decrement and needle EMG revealed a myopathic pattern in several muscles. Antibodies to MuSK and AChR were absent. She was treated with 240 mg/day pyridostigmine but this soon had to be discontinued due to rapidly worsening symptoms and severe side effects. At age 26, she was readmitted with waddling gait, bilateral eyelid ptosis, oculoparesis on lateral and vertical gaze, double vision on extreme lateral gaze, mild tongue weakness and atrophy, mild nasal speech, severe orbicularis oculi and oris weakness, severe proximal and neck flexors muscle weakness (MRC 2-3/5) and mild foot dorsal flexion muscle weakness (MRC 4/5). She also had mild leg muscle atrophy but no scoliosis or contractures. Treatment with 40 mg/day of 3,4-diaminopyridine only improved the fatigable leg weakness and was discontinued. Muscle MRI performed at the age 27 was normal.

The second sibling is a 29-year-old man. He had bilateral fluctuating eyelid ptosis since birth and later developed mild fatigable leg weakness on running that did not limit his daily

activities. Examination age 28 demonstrated only mild tongue weakness and atrophy, mild bilateral eyelid ptosis, limitation of lateral and vertical ductions without diplopia, and mild facial and proximal leg muscle weakness. Three-Hz repetitive stimulation of the accessory nerve elicited a 20% decremental response. The needle EMG examination showed mild myopathic changes. He has never taken pyridostigmine.

A search for mutations in *RAPSN* and *DOK7* in the brother gave negative results. Direct sequencing all *MUSK* exons and their flanking intronic regions in both siblings revealed a previously identified c.2368G>A (p.Val790Met) mutation in exon 15, reported by Chevessier et al.,² and a novel c.467delA (p.Lys156Argfsstop20) mutation in exon 4, resulting in frame-shift and premature termination of translation. The parents are not consanguineous and each carries one of the 2 mutations.

Discussion

Few patients with MuSK-CMS have been reported so far. Table 1 shows clinical and molecular features of these patients and of the patients described in this report. According to other studies, eyelid ptosis and respiratory problems at birth or early life are common feature of MuSK-CMS.^{2–5} Oculoparesis was present in all patients.^{2–5} Hence, early ocular and respiratory problems in a CMS patients can point to *MUSK* as one of the likely CMS genes. Pyridostigmine therapy is ineffective or only slightly beneficial^{2–5} and worsened the symptoms in the sister we report here. Pyridostigmine in relatively high doses is also poorly tolerated in patients MuSK-antibody-positive myasthenia gravis.⁶

Interestingly, most identified mutations in *MUSK* are missense and positioned in exons 14–15,^{2–5} but one was located exon 8,³ and one in exon 3² is frameshifting. In our kinship, the sister is much more severely affected than the brother. To our knowledge, marked intrafamily phenotypic heterogeneity has not been noted in MuSK-CMS patients to date.

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Table 1

Clinical and molecular features in *MUSK*-CMS patients reported in literature

Pt	Ethnic origin	Onset	Ptosis/oculoparesis	Facial/Bulbar weakness	Proximal/axial weakness	Fatigability on walking	Respiratory problems	RNS	PD response	Mutations	Exon
1/F	French	Neonatal	+/+	-/+	+/+	+	+	+	-	C.220insC (codon 92) and c.2368G>A (p. V790M)	3, 15
2/M*	French	Neonatal	na/na	na/+	na/na	na	+	na	na	C.220insC (codon 92) and c.2368G>A (p. V790M)	3, 15
3/M	Sudanese	< 3 years	+/+	+/-	+/+	+	+	na	+	Homozygous c.1031C>G (p.P344R)	8
4/M	Sudanese	< 3 years	+/+	+/-	+/-	+	-	na	+	Homozygous c.1031C>G (p.P344R)	8
5/M	Sudanese	< 3 years	+/+	+/-	+/-	+	-	na	+	Homozygous c.1031C>G (p.P344R)	8
6/F	Sudanese	< 3 years	+/+	+/+	-/-	+	-	na	+	Homozygous c.1031C>G (p.P344R)	8
7/F	Sudanese	< 3 years	+/+	+/-	+/-	+	-	na	+	Homozygous c.1031C>G (p.P344R)	8
8/F	US	Birth	+/+	+/+	+/+	na	+	+	-	M605I and A727V	14, 15
9/M*	Iranian	Birth	+/+	-/-	+/+	+	+	-	-	Homozygous c.2503A>G (p. Met835Val)	15
10/F	Italian	Birth	+/+	+/+	+/+	-	+	+	-(W)	c.467delA (p.Lys156Argfsstop20) + c.2368G>A (p.Val790Met)	4, 15
11/M	Italian	Birth	+/+	+/+	+/-	-	-	+	nt	c.467delA (p.Lys156Argfsstop20) + c.2368G>A (p.Val790Met)	4, 15

RNS: repetitive nerve stimulation; PD : pyridostigmine; M: male; F: female; AV: assisted ventilation; na : not available; W: worsening; nt: not taken.

* Patients 2 and 9 died at the age of 18 months and 19 years respectively. No other patient died during follow-up period.

Patients 1–2 have been reported by Chevassier et al., 2004, patients 3–7 by Mihaylova et al., 2009, patient 8 by Maselli et al., 2010, patient 9 by Ben Ammar et al., 2013. Patient 10–11 are described in this paper.