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ORIGINAL ARTICLE

SIGMAR1 gene mutation causing Distal Hereditary Motor Neuropathy in a Portuguese family

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***SIGMAR1* gene encodes a non-opioid endoplasmic reticulum (ER) protein which is involved in a large diversity of cell functions and is expressed ubiquitously in both central and peripheral nervous systems. Alterations of its normal function may contribute to two different phenotypes: juvenile amyotrophic lateral sclerosis (ALS 16) and distal hereditary motor neuropathies (dHMN). We present the case of a female patient, of 37-years-old, with distal muscle weakness and atrophy beginning in childhood and slowly progressive in the first two decades of life. Neurological examination revealed a symmetrical severe muscle wasting and weakness in distal lower and upper limbs, with claw hands, footdrop with equinovarus deformity and hammer toes, generalized areflexia and normal sensory examination. The electrodiagnostic study revealed a pure chronic motor peripheral nerve involvement without signs of demyelination. The molecular study found the deletion c.561_576del on exon 4 and a deletion of all exon 4, in the *SIGMAR1* gene.**

Key words: *SIGMAR1* gene, motor neuron disease, distal hereditary motor neuropathy

Introduction

The Distal Hereditary Motor Neuropathies (dHMN) comprise a heterogeneous group of diseases that share the common feature of a length-dependent predominantly motor neuropathy (1). To date 19 causative genes and four loci have been identified with autosomal dominant, recessive and X-linked patterns of inheritance (2). Despite advances in the identification of novel gene mutations, 80% of patients with dHMN have a mutation in an as-yet undiscovered gene (3).

The sigma-1 receptor (s1R) encoded by the *SIGMAR1* gene, is a non-opioid endoplasmic reticulum (ER) protein, with a molecular mass of 24 kDa, which is involved in a large diversity of cell functions and is expressed ubiquitously in both central and peripheral nervous systems (4, 5). It is enriched in motor neurons of the brainstem and spinal cord and plays a role in wide variety of cellular functions being critical for neuronal survival and maintenance (6). Protein abnormal function has been implicated in several diseases such as Alzheimer's disease, schizophrenia, stroke, cognition and depression (5). More recently it has been associated with two different phenotypes of motor neuron disease: juvenile amyotrophic lateral sclerosis (ALS 16) (7) and distal hereditary motor neuropathy (dHMN) (2).

We present the clinical, neurophysiologic and molecular findings of a Portuguese patient with dHMN caused by a heterozygous compound mutation in the *SIGMAR1* gene.

Case report

The patient is a 37-year-old woman, the second offspring of a non-consanguineous couple. The patient's delivery was normal and she presented normal motor and intellectual development in the first years of life. She attended school successfully until the age of 15. There was no history of neuromuscular diseases in the family.

At the age of 4 it was noticed a different way of walk-

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ing, clumsier with increasing falls. By the same time, she developed progressive distal muscle wasting and weakness of the lower limbs, more evident on the right foot. Her medical records from the pediatric orthopedic appointments reported feet orthopedic corrective surgeries performed at 8 and 10 years of age.

At the age of 16, the muscle weakness had progressed to involve the distal parts of upper limbs, with significant difficulty with fine hand movements. Since the end of the second decade, her neurological condition became stable.

At the age of 37, she presented symmetrically severe muscle wasting and weakness in distal lower and upper limbs, bilateral footdrop with equinovarus deformity and claw hands (Fig. 1). Walking was impossible on tiptoes and heels. There was no evidence of fasciculation or upper motor neuron signs, nor signs of bulbar involvement. Muscle stretch reflexes were abolished throughout. Sensory examination was normal.

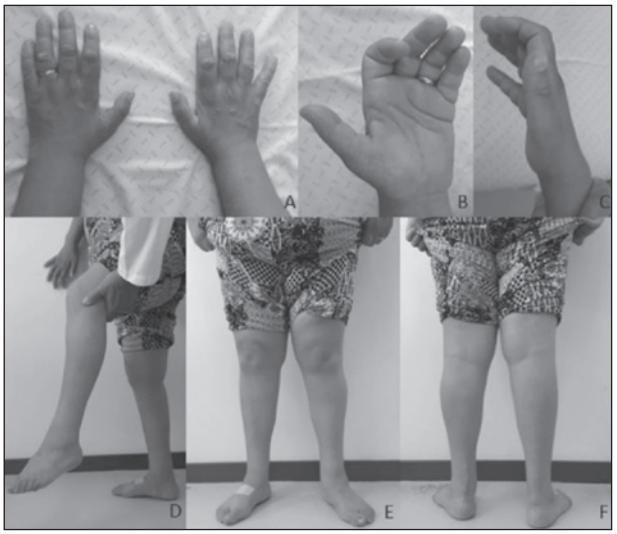

Figure 1. Claw hands with atrophy of the intrinsic hand muscles (**A**, **B**, **C**); Circumferential atrophy of distal legs with footdrop (**D**, **E**, **F**).

Neurophysiologic study showed normal sensory responses and unobtainable motor responses when recorded over the intrinsic muscles of the hands and feet. Muscle needle examination showed a few fibrillations potentials and positive sharp waves in the intrinsic muscles of the hands and feet and in the tibialis anterior bilaterally. These muscles were not voluntarily activated and motor unit potentials of increased duration and amplitude were recorded in the arm and forearm muscles and in the vastus medialis muscles, together with a significantly reduced muscle recruitment pattern. Ventilatory parameters were all normal, as well the cardiac evaluation. The parents had a normal clinical and neurophysiologic examination.

The molecular study (Fig. 2) included polymerase chain reaction and sequencing of the entire coding region, including the adjacent intronic regions, of the *SIGMAR1* gene (chromosome 9). Reference sequence: NM_005866.

It was found a frameshift/truncating hemizygous mutation, variant c.561_576del on exon 4 (p.Asp188Profs*69), and a macrodeletion encompassing all exon 4. These alterations were identified on father and mother, respectively. The c.561_576del on exon 4 (p.Asp188Profs*69) mutation is predicted to be pathogenic as it introduces a premature stop codon 69 aminoacids downstream, producing a truncated protein.

Discussion

The s1R plays an important role in cell maintenance and survival and its loss or malfunction causes

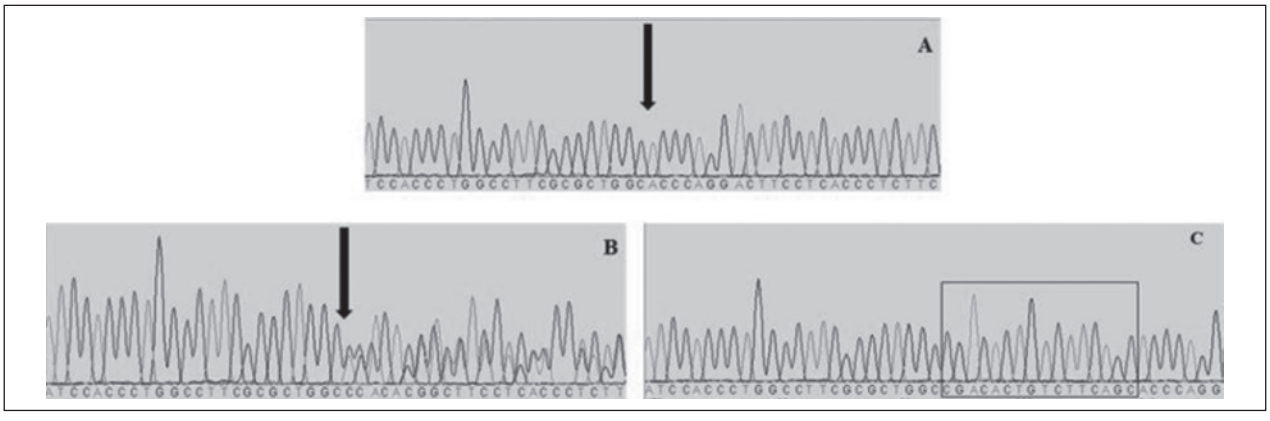

Figure 2. Sequencing electropherograms of proband (**A**) and both parents (**B**: father; **C**: mother). The deletion c.561_576del (arrow) is evident on both proband (**A**) and father (**B**). There is no evidence of the same deletion on mother's electropherogram (box) leading to the conclusion of a macrodeletion of all exon 4.

ER–mitochondria disconnection and ER stress activation and disrupts mitochondrial function and axonal transport, leading to axonal motor neuron degeneration with consequent cell death (8). This dying-back degeneration process would be consistent with the distal predominant pattern of motor involvement observed in patients with *SIGMAR1* gene mutations (9).

The clinical presentation of the first Portuguese patient with dHMN caused *SIGMAR1* gene mutations, has been previously reported (2). Similar to our patient, there was a clinical onset of a pure motor peripheral nerve involvement in the first decade of life, predominantly distal in lower limbs associated with feet deformities and subsequent progression to the upper limbs. There were no sensory symptoms or cognitive impairment, upper motor neuron signs or bulbar involvement. Our patient is still able to walk without support and she participated in the community activities.

However, recent reports suggest that *SIGMAR1* gene mutations should take part of the pool of genes that can cause overlapping motor neuron/nerve phenotypes, much like *BSCL2*- and *REEP1*-related disorders (9), as well as the recently described *KIF5A* (10), on either case there might be a combination of dHMN and pyramidal tract signs.

The rarity of dHMN and the even more rare dHMN caused by mutations of the *SIGMAR1* gene, with the few clinical cases described in the literature, make it difficult to be certain about the phenotypes that are associated with mutations of the *SIGMAR1* gene.

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