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-
ing, clumsier with increasing falls. By the same time, she
developed progressive distal muscle wasting and weak-
ess of the lower limbs, more evident on the right foot. Her medical records from the pediatric orthopedic ap-
pointments 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 up-
per motor neuron signs, nor signs of bulbar involvement.
Muscle stretch reflexes were abolished throughout. Sen-
sory examination was normal.

Neurophysiologic study showed normal sensory
responses and unobtainable motor responses when re-
corded over the intrinsic muscles of the hands and feet.
Muscle needle examination showed a few fibrillations
potentials and positive sharp waves in the intrinsic mus-
cles of the hands and feet, and in the tibialis anterior bi-
laterally. These muscles were not voluntarily activated
and motor unit potentials of increased duration and
amplitude were recorded in the arm and forearm mus-
cles, and in the vastus medialis muscles, together with a
significantly reduced muscle recruitment pattern. Ven-
tilatory parameters were all normal, as well the cardiac
evaluation. The parents had a normal clinical and neuro-
physiologic 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 muta-
tion, variant c.561_576del on exon 4 (p.Asp188Profs*69),
and a macrodeletion encompassing all exon 4. These al-
terations 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 trun-
cated protein.

**Discussion**

The s1R plays an important role in cell mainte-
nance and survival and its loss or malfunction causes
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.

**References**

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