CASE STUDY

Charcot–Marie–Tooth disease type 2F associated with biallelic HSPB1 mutations

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Abstract

Objective: This work aims to expand knowledge regarding the genetic spectrum of HSPB1-related diseases. HSPB1 is a gene encoding heat shock protein 27, and mutations in HSPB1 have been identified as the cause of axonal Charcot–Marie–Tooth (CMT) disease type 2F and distal hereditary motor neuropathy (dHMN). Methods: Two patients with axonal sensorimotor neuropathy underwent detailed clinical examinations, neurophysiological studies, and next-generation sequencing with subsequent bioinformatic prioritization of genetic variants and in silico analysis of the likely causal mutation. Results: The HSPB1 p.S135F and p.R136L mutations were identified in homozygosis in the two affected individuals. Both mutations affect the highly conserved alpha-crystallin domain and have been previously described as the cause of severe CMT2F/dHMN, showing a strictly dominant inheritance pattern. Interpretation: Thus, we report for the first time two cases of biallelic HSPB1 p.S135F and p.R136L mutations in two families.

Introduction

Charcot–Marie–Tooth (CMT) disease is a spectrum of primary hereditary sensorimotor neuropathies with an overall prevalence of 1/1,200–2,500, making it the most common genetic neuromuscular disorder.1 CMTs are classified according to their neurophysiological properties and inheritance pattern.1 Motor nerve conduction velocity (MNCV) allows to distinguish demyelinating CMT type 1 (slow MNCV) from axonal CMT type 2 (preserved MNCV).1 Both these forms mainly display autosomal dominant transmission, although recessive inheritance.

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have been described in several demyelinating and axonal CMT subtypes. Moreover, six types of X-linked CMT have been described. While the link between CMT1 forms and mutations in genes affecting myelination is clear, the specific disease-causing mechanisms underlying mutations in genes associated with axonal forms is not.

Distal hereditary motor neuropathy (dHMN), presenting as a pure length-dependent motor nerve syndrome with no sensory involvement, might overlap CMT. Both diseases are characterized by wide clinical and genetic heterogeneity. As an example, mutations in HSPB1 are associated with both CMT type 2F presentation and distal HMN2B phenotype. HSPB1 encodes heat shock protein 27 (HSP27), a member of the small HSP family, which act as molecular chaperones, binding partially denatured proteins and preventing irreversible aggregation under stressful conditions. HSP27 shares with other HSPs a highly conserved alpha-crystallin domain of approximately 90 amino acids near the C-terminus, and its beta-sheets conformation guarantees stable dimerization. HSP27 has a role in thermotolerance, stress response, and activation of the proteasome. Moreover, HSP27 plays a role in several cellular processes, such as the modulation of intracellular redox state, cellular differentiation, apoptosis inhibition, and assembly of cytoskeletal structures such as microfilaments, neurofilaments (NFLs), and microtubules (MTs). Its interactions with NFLs are important in order to maintain the integrity of cytoskeletal networks, which can be disrupted by disease-causing mutations in HSPB1.

Forty-four HSPB1 mutations have been reported thus far, distributed along the whole gene sequence (Figure 1). Most HSPB1 mutations are missense, although sporadic frameshift, nonsense, and splicing mutations have been described (Figure 1). The vast majority of cases show autosomal-dominant (AD) inheritance, while recessive inheritance has been reported in very few cases (Table 1).

Both the p.S135F and the p.R136L missense mutations have been previously reported as the cause of CMT2F or hereditary motor neuropathy 2B (dHMN2B). The mutations affect the highly conserved alpha-crystallin domain and in silico analyses and functional studies support their pathogenic role. The p.S135F mutation is by far the most frequent cause of HSPB1-related neuropathy, with 40 patients reported, while the p.R136L has been observed in 10 patients. Notably, both mutations seem to segregate with disease according to a strictly dominant pattern of inheritance.

![Figure 1](image_url). Domain architecture of HSPB1 and localization of known HSPB1 mutations. α-crystallin domain is shown in green. Sites of phosphorylation by MAPKAPK-2 are shown as red rectangles. All currently known mutations are listed. Biallelic HSPB1 mutations are indicated in bold.
Here, we report the first description of biallelic HSPB1 p.S135F and p.R136L mutations underlying CMT type 2F phenotype in two patients.

Materials and Methods

All the attendees provided written informed consent. The probands and assessed relatives (three asymptomatic sisters of Patient 1 and the patient’s son) received a complete neurological evaluation and underwent neurophysiological assessment. The parents and one asymptomatic brother of Patient 1, who were unavailable for clinical review, were asked to complete a questionnaire in Portuguese language regarding the presence of motor and/or sensory symptoms suggesting the presence of neuropathy. The questionnaire was reviewed by a native Portuguese speaker. Personal and family history of the probands was obtained, and common causes of acquired axonal neuropathy were excluded. Patients’ DNA was extracted from peripheral blood leukocytes and used to generate a library for the next-generation sequencing (NGS) of a panel of genes causing hereditary neuropathies. NGS was run on an Illumina MiSeq platform, according to the manufacturer instruction. Sanger sequencing was used to validate candidate variants and to test segregation in available family members.

Case Description and Results

Case 1

The first proband is a 44-year-old woman, born in the Republic of Cabo Verde, a small African archipelago with approximately 550,000 inhabitants. Her parents were referred to be nonconsanguineous but originated from two nearby villages. They are asymptomatic, and their past medical history is unremarkable. The proband is the last of eight healthy siblings and has an asymptomatic 9-year-old son (Figure 2). She has no other relevant medical conditions. She had a normal psychomotor development. Her neurological symptoms started at the age of 25 with muscle cramps and progressive distal motor impairment in lower limbs, for which she was prescribed ankle foot orthoses (AFOs) at the age of 34. Distal upper limb muscle wasting and weakness occurred in the following years. She also complained of slight sensory loss and paresthesia in her feet. Neurological examination revealed severe distal muscle wasting and weakness in upper (intrinsic hand muscle MRC 1/5 on the left, 2–3/5 on the right) and lower limbs (MRC 0/5 for feet movements). Deep tendon reflexes (DTRs) were symmetrically reduced at upper limbs and absent at lower limbs. Light touch and pain sensations were slightly reduced up to mid-calf. CMTES was 12/28, and CMTNS was 13/36. Ambulation was possible with steppage gait, and the patient needed unilateral support when standing and occasionally when walking. The remaining neurological examination was normal, and she showed no foot deformity.

Nerve conduction studies (NCS), at age 42 years, showed normal sensory conduction velocities, preservation of sensory action potentials (SAPs), markedly decreased or absent compound muscle action potentials (CMAPs) in lower limbs (with greater involvement of posterior tibial than peroneal nerve) and left upper limb (Table 2). Needle EMG examination showed moderate signs of chronic and active denervation in distal limb muscles with complex repetitive discharges in lower limb muscles. Motor evoked potentials were normal. Sural nerve biopsy showed mild

| Nucleotide change | Amino acid change | Domain | Clinical features | Parents’ clinical features | Ref. |
|-------------------|-------------------|--------|-------------------|--------------------------|------|
| c.158G>A          | p.G53D            | N-terminal | dHMN + Cerebellar ataxia | Asymptomatic | Echaniz-Laguna et al. (2017) |
| c.250G>C          | p.G84R            | N-terminal | CMT2F             | Mother: hyporeflexia (LLLL) | Fischer et al. (2011) |
| c.295C>A          | p.L99M            | α-Crystallin domain | CMT2F | Asymptomatic | Houlden et al. (2008) |
| c.404C>T          | p.S135F           | α-Crystallin domain | CMT2F | Asymptomatic | This study |
| c.407G>T          | p.R136L           | α-Crystallin domain | CMT2F | Asymptomatic | This study |
| c.418C>G          | p.R140G           | α-Crystallin domain | dHMN + distal vacuolar myopathy | Mild distal weakness and areflexia (UULL + LLLL), mild hypoesthesia/hypopallestesia (LLLL) | Bugiardini et al. (2017) |

Abbreviations: CMT2F, Charcot-Marie-Tooth type 2F; dHMN, distal hereditary motor neuropathy; LLLL, lower limbs; NCV, nerve conduction velocities; UULL, upper limbs.
reduction of myelinated fiber density, suggestive of slight sensory nerve damage. Cerebrospinal fluid (CSF) analysis was performed to exclude immune causes of axonal neuropathy, yielding normal results.

NGS analysis revealed homozygosity for the HSPB1 (NM_001540) nucleotide transition c.404C > T resulting in the amino acid change p.S135F, subsequently confirmed by Sanger sequencing (Figure 2). HSPB1 deletion was excluded by quantitative PCR. The affected residue is the highly conserved serine-135 within the alpha-crystallin domain (Figure 1). DNA of asymptomatic parents was not available.

Three asymptomatic sisters—aged 59, 55, and 48, respectively—resulted negative at molecular testing (Figure 2). The 9-year-old son, an obligate carrier, has remained asymptomatic so far. Short tandem repeat (STR) haplotyping in available DNA samples does not support parental consanguinity or the occurrence of uniparental disomy (Table S1).

**Table 2.** Electrophysiological findings.

|                     | Patient 1 (42 years) | Patient 2 (49 years) |
|---------------------|----------------------|----------------------|
| **Motor conduction** |                      |                      |
| DML ms, MNCV m/s, dCMAP mV |                  |                      |
| R Median nerve      | 4.2, 53.2, 18.4      | 3.5, 58, 18.6        |
| L Median nerve      | 5.2, 48, 2.8         | 3.8, 62.5, 17        |
| R Ulnar nerve       | 3.5, 54.7, 6.7       |                      |
| L Ulnar nerve       | 2.8, 58.4, 13.2      |                      |
| L Peroneal nerve    | NA, NA, 0            | 5, 50.7, 2.8         |
| R Tibial nerve      | NA, NA, 0            | 5, 44.3, 0.1         |
| **Sensory conduction** |                      |                      |
| SNCV m/s, SNAP µV   |                      |                      |
| L Median nerve      | 58.3, 7.3            |                      |
| R Radial nerve      | 62.9, 24             |                      |
| R Sural nerve       | 43.5, 22             | 54.5, 6.5            |
| L Superficial peroneal nerve | 56.8, 12 |                      |

Note: Abnormal values are in bold. Abbreviations: dCMAP, distal compound muscular action potential amplitude; DML, distal motor latency; L, left; MNCV/SNCV, motor/sensory nerve conduction velocity; NA, not applicable; R, right; SNAP, sensory nerve action potential amplitude.

**Case 2**

The second proband is a 66-year-old man born to an Iranian family. His nonconsanguineous parents and his three sisters were reported to be asymptomatic (Figure 2). He had normal psychomotor development, and his past medical history is unremarkable. At the age of 48, he started complaining of gait disturbances, easy fatigability and muscle pain at lower limbs, which progressed slowly over the following years. When last seen in 2006, neurological examination revealed slight distal weakness, atrophy and fasciculations, and sensory loss in lower limbs. There was no muscle wasting nor weakness in upper limbs. Ankle jerks were absent.

NCS, performed at age 49 years in 2003, showed normal sensory conduction velocities, slightly reduced sural and median SAPs, markedly decreased or absent CMAPs in lower limbs (with greater involvement of posterior tibial than peroneal nerve) (Table 2). Needle EMG examination showed marked signs of chronic and active
denervation with complex repetitive discharges in lower limb muscles. Motor-evoked potentials were normal. Brain MRI was normal. Notably, CK levels were increased (699 U/l; n.v. <195). CSF analysis, performed to rule out immune causes of axonal neuropathy, showed moderately elevated proteins (83 mg/dl; n.v., 10–45).

NGS analysis showed homozygosity for the HSPB1 (NM_001540) nucleotide transversion c.407G > T, resulting in the p.R136L amino acid change, subsequently confirmed by Sanger sequencing (Figure 2). HSPB1 deletion was excluded by quantitative PCR. The affected residue is the highly conserved arginine-136 within the alpha-crystallin domain (Figure 1). DNA of parents was not available. STR haplotyping in this patient does not exclude parental consanguinity or segmental uniparental disomy (Table S1).

Discussion

HSPB1 pathogenic variants are responsible for both distal HMN and CMT type 2F. Although the vast majority of described mutations show dominant inheritance, four homozygous substitutions (p.G53D, p.G84R, p.L199M, and p.R140G) have been previously reported in patients with typical (dHMN/CMT2F) and atypical (distal vacuolar myopathy, cerebellar ataxia) presentations (Table 1). In two cases, parents were asymptomatic heterozygous carriers, while obligate carriers for p.G84R and p.R140G mutations displayed a subclinical phenotype with minor disturbances only detected by neurophysiological studies. The same mutations had been previously detected in several families with dHMN, displaying autosomal dominant inheritance with complete penetrance.6,9,31

In this manuscript, we describe the first reports of HSPB1-related neuropathy presenting p.S135F or p.R136L genotype in homozygosis. Heterozygous p.S135F change was previously associated with severe clinical presentations.6,26 Reported age at onset for this mutation spans from 9 to 26 years.6,26,31 Heterozygous p.R136L change was previously reported in 10 patients from four families with phenotypic variability and atypical signs. Reported age at onset for this mutation spans from 42 to 60 years.7,22,23

Several functional studies evaluated the impact of HSPB1 mutations on cytoskeletal organization, axonal viability, and mitochondrial transport. In particular, HSPB1S135F displays a dominant-negative effect on NFL assembly, inducing aggregation of wild-type NLs and subsequent motor neuron degeneration and death.4 Interestingly, the presence of NFL protein is essential to manifest mutant HSPB1 toxicity.4

In a subsequent study, chaperone activity was evaluated for several HSPB1 mutants, including the p.S135F and a different amino acid substitution affecting arginine 136 (p.R136W).33 Both mutants were associated with an abnormal increase in HSPB1 chaperone activity that might promote toxic MT stabilization, engaging a deacetylating response which impairs the integrity of the MT network and axonal transport leading to nerve degeneration.34

Finally, defects in axonal mitochondrial transport were observed in cellular and animal models expressing HSPB1S135F.36,37 Similar alterations were also observed in MFN2-related CMTs,38 suggesting the existence of common pathogenic pathways in axonal CMTs. Remarkably, in 2011 d’Ydewalle and colleagues discovered that the use of a selective HDAC6 inhibitor successfully reversed the clinical phenotype in HSPB1S135F rodent models.36 Further preclinical studies of these compounds in other models of axonal CMT have revealed promising results,39,40 thereby paving the way for future clinical trials in patients.

Our first patient showed typical features of a length-dependent predominantly motor neuropathy, with onset during early adulthood, severe involvement of distal limb muscles, and minor sensory signs and symptoms with preserved SAP amplitudes at NCS but mild loss of myelinated fibers at nerve biopsy. She showed some asymmetry of clinical and electrophysiological involvement, a feature already reported in other subjects carrying HSPB1 mutations.9,26,27 The second patient presented a later onset with distal motor and sensory involvement of lower limbs. In both cases, parents were asymptomatic but could be examined neither clinically nor electrophysiologically. Therefore, we cannot exclude subclinical abnormalities in obligate carriers. Nevertheless, it is puzzling that monoallelic p.S135F and p.R136L mutations are clinically silent in these families, considering the complete penetrance in the pedigrees reported so far. Moreover, the phenotype of the homozygous probands does not appear to be more severe than that previously reported in heterozygous patients.5,7,22,23,26 A limitation of the present study is the lack of DNA samples from the parents, that precludes the assessment of their actual genotype and a definite conclusion about the transmission pattern of the HSPB1 locus in these families. However, our discovery of biallelic inheritance of the two most frequent dominant HSPB1 mutations further expands the genetic complexity of HSPB1-associated neuropathies.

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**Conflict of Interest**
The authors declare that they have no conflict of interest.

**Data Availability Statement**
The data that support the findings of this study are available from authors FT, DP, and SC upon request.

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