Phenotypic correlations in a large single-center cohort of patients with BSCL2 nerve disorders: a clinical, neurophysiological and muscle magnetic resonance imaging study

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Background and purpose: BSCL2 heterozygote mutations are a common cause of distal hereditary motor neuropathies (dHMNs). A series of BSCL2 patients is presented and clinical, neurophysiological and muscle magnetic resonance imaging (MRI) findings are correlated.

Methods: Twenty-six patients from five families carrying the p.N88S mutation were identified. Age of onset, clinical phenotype (dHMN, Charcot–Marie–Tooth, spastic paraplegia), physical examination, disability measured as a modified Rankin Scale score and neurophysiological findings were collected. A whole body muscle MRI had been performed in 18 patients. The pattern of muscle involvement on T1-weighted and short time inversion recovery sequences was analysed. Hierarchical analysis using heatmaps and an MRI Composite Score were generated. Statistical analysis was carried out with STATA SE v.15 (TX, USA).

Results: The mean age was 51.54 ± 19.94 years and 14 patients were men. dHMN was the most common phenotype (50%) and five patients (19.23%) showed no findings on examination. Disease onset was commonly in childhood and disability was low (modified Rankin Scale score 1.34 ± 1.13) although median time since onset of disease was 32 years (range 10–47). Charcot–Marie–Tooth-like patients were more disabled and disability correlated with age. On muscle MRI, thenar eminence, soleus and tibialis anterior were most frequently involved, irrespective of clinical phenotype. MRI Composite Score was strongly correlated with disability.

Conclusion: Patients with the p.N88S BSCL2 gene mutation are phenotypically variable, although dHMN is most frequent and generally slowly progressive. Muscle MRI pattern is consistent regardless of phenotype and correlates with disease severity, probably serving as a reliable outcome measure for future clinical trials.
Introduction
Distal hereditary motor neuropathies (dHMNs) are a genetically heterogeneous group of neurodegenerative secondary motoneuron disorders. Heterozygous mutations in the Berardinelli–Seip congenital lipodystrophy 2 (BSCL2) gene are a common cause of dHMN if intrinsic hand muscle involvement is present (dHMN-V) [1]. In 1966 Silver described the classic association of distal motor neuropathy of upper and lower limbs combined with spasticity, known as the Silver syndrome [2]. However, BSCL2 mutations cause a wide spectrum of nerve disorders, such as a pure dHMN with or without hand involvement (dHMN-V and dHMN-II respectively), an axonal Charcot–Marie–Tooth (CMT-2) associated with sensory disturbances or a pure spastic paraplegia (SPG-17) [3-5]. A few families have been described [2-3,5-7] and show a broad phenotypic variability, complicating diagnosis.

The p.N88S and p.S90L mutations account for the majority of BSCL2 patients [3,6,8], whilst the p.S90W and p.R96H mutations have been exceptionally documented [9-11]. The p.N88S missense mutation is located in exon 3 of the BSCL2 gene on chromosome 11q13. BSCL2 encodes the integral membrane protein named Seipin, with different putative functions ranging from phospholipid metabolism to fat droplet formation [12,13]. The p.N88S mutation leads to an abnormal N-glycosylation site and unfolded protein aggregation leading to endoplasmic reticulum stress and possible secondary motoneuron degeneration [8,12].

Muscle magnetic resonance imaging (MRI) is a powerful tool in the assessment of muscular disorders [14-17], but studies in motoneuron disorders are scarce. In the past years, muscle atrophy on MRI has been shown to correlate with muscle testing in CMT and dHMN and to document the severity and pattern of muscle atrophy [18]. Quantitative muscle MRI is a biomarker that can detect early changes and assess therapeutic responses in hereditary neuropathies [19-21].

The aim of this study was to describe the full phenotypic spectrum of BSCL2 disease in a series of patients carrying the common p.N88S, with special detail to clinical and neurophysiological findings. Furthermore, the muscle MRI findings of these patients are presented in order to provide a recognizable radiological pattern and correlates with clinical data.

Methods
BSCL2 population
A total of 26 patients from five families carrying the p.N88S heterozygote mutations were identified. Clinical data were obtained cross-sectionally from electronic clinical records. The following variables were registered: gender, date of birth, age of onset (childhood 0–14 years; youth 15–24 years; adult onset ≥25 years), age at diagnosis, mutation, phenotype (SPG, dHMN, CMT, asymptomatic) and limb onset. Distal muscle weakness at last visit was scored using the Medical Research Council (MRC) scale for leg dorsiflexion and hand interosseous [22]. Other features like osteotendinous reflexes, Babinski sign, spasticity, sensory signs, and bladder, osseous, hearing and respiratory problems were documented. Disability at last visit was measured with the modified Rankin Scale (mRS) score [23].

Molecular analysis
Whole-exome sequencing
Individuals from family 2 (n = 2) were diagnosed in the context of whole-exome sequencing and were negative for molecular screening of common causes of dominant CMT. Index singleton cases was carried out on exon targets isolated by capture using the SeqCap Exome V3.0 64 Mb kit (NimbleGen, Roche, USA) with 100-bp paired-end read sequences, generated on a HiSeq2000 Platform (Illumina Inc., USA) at the Centre Nacional d’Anàlisi Genòmica (Barcelona, Spain). The sequencing methodology and variant analysis protocol followed the Genome Analysis Tool Kit pipeline [24].

Sanger sequencing and putative mutations assignment
The other four families were diagnosed by Sanger sequencing of exon 3 of the BSCL2 gene. For the identification of mutation carriers, the corresponding DNAs of the pools were individually amplified and sequenced with BigDye chemistry in an ABI3130 equipment (Life Technologies) to identify the mutation carrier. All the DNA sequence variants were named following the guidelines of the American College of Medical Genetics [25].

Ancillary tests
Nerve conduction studies in 19 patients were carried out. Compound motor action potentials (CMAPs) and sensory nerve action potentials as well as conduction velocity (CV, m/s) from the median, cubital, peroneal, sural and tibial nerves were registered. The presence of dispersed potentials was noted as well as a neurogenic trace on electromyogram. Cervical MRI was described when available.

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Whole body muscle MRI

From June 2018, 18 patients underwent a whole body muscle MRI (1.5 T, Siemens, Germany) with axial T1-weighted and short time inversion recovery (STIR) sequences. The scan lasted 45 min, covering hand and feet. Fat replacement was evaluated using the Mercuri score modified by Fischer [26] and assessed by a clinically blind neurologist (RFT) and a radiologist (AG), both experienced in muscle MRI analysis. A mean value was given bilaterally for each muscle as well as a description of muscle atrophy on axial T1-weighted sequences. A heatmap was generated in R software for hierarchical analysis of muscle involvement.

Data analysis

Data analysis was carried out using STATA SE v.15. The mean and standard deviation of symmetric quantitative variables, the median and interquartile range of asymmetric quantitative variables, and absolute or relative frequencies of categorical variables were assessed. Statistical significance was considered at $P \leq 0.05$ and parametric tests or non-parametric tests were applied when necessary (Table S1).

This study was approved by the Ethics Committee of the Donostia University Hospital (FER-BSC-2019-01).

Results

Demographic and phenotypic presentation

All individuals were molecularly confirmed carriers of the p.N88S mutation (exon 3) and came from a small region on the coast of the Basque Country. There was a slight male predominance (53.85%). Mean age at onset of disease was 24.44 ± 21.96 years; however, age at diagnosis was 51.54 ± 19.94 years, and therefore median time since onset was 32 years (range 10–47 years) (Table 1).

A pure dHMN was the clinically defined phenotype in 13 patients (50%); although onset was frequently referred to the lower limbs (66.7%), at presentation it normally involved lower and upper limbs distally (dHMN-V) (nine patients, 34.61%). Whilst pes cavus and pyramidal features were frequent (46.15% and 50% respectively), sensory symptoms were rare (three patients, 11.54%). Five individuals (19.23%) remain to the last visit completely asymptomatic. Proximal weakness was anecdotal (patient 2.II.1) and only two patients had respiratory insufficiency: patient 5.I.1 (70 years) with a restrictive respiratory insufficiency and patient 1.II.1 (75 years) with a mixed respiratory insufficiency and elevated left hemidiaphragm. Both patients were males, showed a dHMN-V phenotype and had significant disability (mRS 4 and mRS 3 respectively). The typical p.N88S BSCL2 clinical phenotypes observed have been highlighted in Table 2.

Table 1 Demographic description of the cohort

| BSCL2 cohort          |            |
|----------------------|------------|
| Age (years)          | 51.54 (SD ± 19.94) |
| Time since onset (years) | 32 (range 10–47) |
| Age onset            |            |
| No symptoms          | 8 (30.77%)  |
| Childhood (0–14 years) | 9 (34.62%)  |
| Youth (15–24 years)  | 3 (11.54%)  |
| Adulthood (≥25 years) | 6 (23.08%)  |
| Gender (male)        | 14 (53.85%) |
| Phenotypic classification |          |
| dHMN                 | 13 (50%)    |
| type V               | 9 (34.61%)  |
| type II              | 4 (15.38%)  |
| SPG-17               | 5 (19.23%)  |
| CMT2                 | 3 (11.54%)  |
| Asymptomatic         | 5 (19.23%)  |
| Distal muscle atrophy|            |
| None                 | 6 (23.07%)  |
| Thenar eminence      | 1(3.85%)    |
| Tibialis anterior    | 6 (23.07%)  |
| Tibialis anterior and thenar eminence | 13 (50%) |
| Distal weakness (MRC) |          |
| Hand                 | 3.96 (SD ± 1.49) |
| Tibialis anterior    | 3.42 (SD ± 1.28) |
| Sensory symptoms     | 3 (11.54%)  |
| Spasticity           | 5 (19.23%)  |
| Reflexes (n = 24)$^b$|            |
| Abolished            | 1 (4.17%)   |
| Normal               | 10 (41.67%) |
| Brisk or Babinski sign| 13 (50%)   |
| Osseous changes (n = 21)$^b$|         |
| Pes cavus ± hammer toes | 12 (57.14%) |
| Only hammer toes     | 1 (4.76%)   |
| Achilles retraction  | 2 (9.52%)   |
| Scoliosis            | 1 (4.76%)   |
| Neurosensorial hypoacusia | 3 (11.54%) |
| Disability (mRS)     | 1.34 (SD ± 1.23) |
| Neurophysiology (n = 19) |        |
| Motor axonal neuronopathy | 10 (52.63%) |
| Mixed polyneuropathy | 7 (36.84%)  |
| Normal               | 2 (10.53%)  |
| Whole body muscle MRI (n = 18) | 15 (83.33%) |
| Altered              |            |
| Normal               | 3 (16.67%)  |

CMT2, Charcot–Marie–Tooth type 2; dHMN, distal hereditary motor neuropathy; MRC, Medical Research Council; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; SPG-17, spastic paraplegia 17; $^a$Eight patients do not report symptoms, but three show distal weakness on examination (dHMN); thus five patients are completely unaffected (asymptomatic); $^b$Reflexes and osseous changes missing from n = 2 and n = 5 patients respectively.
Mean disability was also low (mRS 1.34 ± 1.13). Two patients walked with aid (mRS 3), and one patient required help with activities of daily living (mRS 4). No patient is to this day wheelchair-bound. The disease was slowly progressive in all 26 patients and there was a non-significant tendency for female patients to be less disabled than men (mRS 0.92 ± 0.99 vs. 1.71 ± 1.14; \( P = 0.0716 \)). No association between gender and phenotype, age or time since onset was found. Disability was higher in CMT2-like and SPG-17 than dHMN-V (mRS 2.33 ± 0.58, 2 ± 0, 1.15 ± 1.14 respectively; \( P = 0.0000 \)). There was a moderate correlation between mRS and age (\( r = 0.6711, P = 0.0002 \)), whilst this was not clear with time since onset (\( r = 0.2533, P = 0.3106 \)) (Fig. 1).

Ancillary tests

Nerve conduction studies were pathological in 17 out of 19 individuals (89.47%) showing a predominantly axonal motor neuropathy. Two patients had no electrical signs of polyneuropathy (one clinically asymptomatic patient and one with pure paraparesis) (Table S1). Dispersed CMAPs were found in the lower limbs in seven patients (36.84%). These dispersed potentials were in both tibial and peroneal nerves and were described in one patient (1.III.16) as proximally located. However, slowing of CV was very rare and mild (Table S1).

Eight patients had undergone a cervical MRI. Patient 05.II.01 (SPG phenotype) showed a protruding C4–C5 and C5–C6 discal hernia and secondary signs of myelopathy, resolving in a subsequent MRI after undergoing cervical surgery. All other patients showed no evidence of myelopathy or anterior horn degeneration.

Muscle MRI

For the 18 patients who underwent a whole body muscle MRI, their clinical characteristics were similar to the whole series. Mean age at scan was 50 years and 11 patients were male (61.11%). Mean duration of the disease was 26.43 years and mean disability was mRS score 1.28. Ten patients showed a dHMN phenotype (55.56%), four SPG-17, two CMT2, and the remaining two were completely asymptomatic. Fifteen out of 18 individuals (83.33%) had an abnormal muscle MRI. The pattern of involvement was generally symmetric, with a proximal-to-distal gradient fat replacement within each muscle (Fig. 2). Hyperintensities on STIR were seen in six patients (33.33%).

The most frequently affected muscles on axial T1-weighted scans were the soleus, tibialis anterior and thenar eminence (61.11%, 55.56% and 50% respectively). Other commonly affected muscles were the extensor digitorum longus, medial gastrocnemius, peroneus and flexor digitorum longus (44.44%, 38.89%, 33.33% and 33.33% respectively). Axial or proximal limb muscle abnormalities were very uncommon, and this chronology and general pattern of muscle involvement was irrespective of the clinical phenotype (dHMN, SPG-17 or CMT2) on hierarchical analysis (Fig. 3). Even one asymptomatic patient (1.III.07) even showed mild bilateral soleus fat replacement with medial gastrocnemius hyperintensities on STIR (Fig. 2).

Three patients (16.67%), all females, had no muscle abnormalities on whole body muscle MRI: patient 1.II.04 (67 years) with a pure paraparesis (SPG-17), patient 1.III.03 (22 years) asymptomatic with normal

| Table 2 Typical p.N88S BSCL2 clinically defined phenotypes |
|---------------------------------|---------------|---------------|--------------|---------------|----------------|
|                                | dHMN-V        | dHMN-II       | SPG-17       | CMT2          | Asymptomatic   |
| Number (% of total)            | 9 (34.61%)    | 4 (15.38%)    | 5 (19.23%)   | 3 (11.54%)    | 5 (19.23%)     |
| Age, years                     | 47 ± 18 SD    | 47 ± 17.15 SD | 63.8 ± 12.64 SD | 54.67 ± 16.26 SD | 49.2 ± 31.22 SD |
| Gender (male)                  | 4             | 3             | 3            | 3             | 1              |
| mRS                            | 1.33 ± 1.32 SD| 0.75 ± 0.5 SD | 2 ± 0        | 2.33 ± 0.57 SD | 0              |
| Distal muscle atrophy and weakness | Always upper and lower limb atrophy | Only lower limb atrophy | Any (lower limb, upper and lower or none) | Always upper and lower limb atrophy | |
| Brisk reflexes or Babinski sign | 5             | 2             | 5            | 2             | 0              |
| Pes cavus/hammer toes/Achilles retraction | 6             | 2             | 2            | 3             | 1              |
| Others                         | + Spasticity  | + Sensory symptoms or sensorimotor neuropathy | |
| Respiratory insufficiency      | 2             | 0             | 0            | 0             | 0              |

CMT2, Charcot–Marie–Tooth type 2; dHMN, distal hereditary motor neuropathy; mRS, modified Rankin Scale; SPG-17, spastic paraplegia 17.
clinical examination, and patient 3.II.02 (41 years) asymptomatic with mild upper and lower limb amyotrophy and tibialis anterior weakness on examination (dHMN). The clinical versus muscle MRI correlations can be seen in Fig. 1.

The MRI Composite Score (MRI CS) was positively correlated with disability measured by mRS ($r = 0.7119$, $P = 0.0009$). Males had a higher MRI CS than females (13.92/C6 vs. 2.67/C6, $P = 0.0209$). As for the phenotype, CMT patients were more severely affected than SPG or dHMN patients (24.33/C6 vs. 8.33/C6 vs. 8.4/C6, $P = 0.1473, P = 0.0441$ after grouping dHMN + SPG) and (3) male patients ($P = 0.0209$), and lastly (4) shows mild correlation with time since onset of symptoms ($r = 0.3435$). [Colour figure can be viewed at wileyonlinelibrary.com]

Discussion

The MRI Composite Score (MRI CS) was positively correlated with disability measured by mRS ($r = 0.7119$, $P = 0.0009$). Males had a higher MRI CS than females (13.92/C6 ± 13.77 vs. 2.67 ± 4.27 respectively; $P = 0.0209$). As for the phenotype, CMT patients were more severely affected than SPG or dHMN patients (24.33/C6 ± 15.27 vs. 8.33/C6 ± 11.93 vs. 8.4/C6 ± 11.06 respectively), although the difference only reached statistical significance when CMT was confronted with dHMN + SPG (similarly affected) and asymptomatic patients (Table S1). The MRI CS showed a moderate correlation with age ($r = 0.6680$) and a mild correlation with time since onset ($r = 0.3435$). Results did not vary when patient 03.I.01 (hands not visualized on MRI study) was removed.

Phenotypic variability and low grade of disability in BSCL2 disease

The most common presentation was a pure motor neuropathy. Upper limb involvement, a clinical hallmark of the disease, was not invariably present, and only 20% of patients presented with the characteristic upper and lower limb distal motor neuropathy with spasticity first described by Silver in 1966 [2], which has also been previously found to represent 15% of individuals [3]. The p.N88S mutation was identified in family 2 through whole-exome sequencing giving that patient 02.II.01 showed a paraparesis with a motor neuropathy without distal upper limb atrophy and patient 02.I.02 showed a mild (mRS 1) distal neuropathy of all four limbs without spasticity. However, in all other families, direct sequencing of exon 3 of the BSCL2 gene was undertaken given a more classical presentation in certain family members. Sensory symptoms are also rare (11.54%) and it is shown that they tend to occur in more severely affected patients (Table 1, Fig. 1) [3,4]. However, 95.83% of patients showed normal or brisk reflexes which is an uncommon finding in hereditary polyneuropathies, and therefore this could guide the diagnosis.
In our series, median time to diagnosis since onset of symptoms was 32 years. This could be partly explained by a very slow progression and overall low disability (mRS 1.34), as well as the almost 25% of non-penetrant or subclinically affected individuals carrying the p.N88S (19.23% in our series) [3]. There was a tendency for female patients to be less disabled, and females showed a significantly lower MRI CS than males. It is especially relevant that patient 1.I.02, a 99-year-old woman, remains unaffected by the disease. The above further emphasizes the variable penetrance of the p.N88S mutation, introducing a possible

Figure 2  Axial T1-weighted and STIR muscle MRI sequences in the spectrum of disease: 01.III.06, 38-year-old male, mRS 0, minimal TA weakness (dHMN-II), Mercuri grade 1 soleus fat replacement and STIR hyperintensities on medial gastrocnemius; 03.II.03, 41-year-old female hand and shin atrophy, mild TA weakness (dHMN-V); mRS 0, Mercuri 1 thenar eminence and soleus fat replacement; 05.I.02, 69-year-old female with predominant spasticity and minimal TA weakness (SPG-17), mRS 2, Mercuri 2–3 soleus, tibialis anterior, extensor digitorum longus and peroneus, and Mercuri 1 semitendinosus, gluteus (not shown) and axial muscles (not shown) fat replacement; 01.III.10, 37-year-old male with TA and TE weakness with an axonal sensorimotor neuropathy (CMT2), mRS 2, Mercuri 4 thenar eminence, Mercuri 2–3 soleus and tibialis anterior and Mercuri 1 extensor digitorum longus and flexor digitorum longus muscle fat replacement, as well as hyperintensities notably on soleus and thenar eminence muscles; 01.I.08, 58-year-old male with TA and TE muscle weakness and distal sensory disturbances (CMT2), mRS 3, Mercuri 3 thenar eminence and tibialis anterior, soleus and medial gastrocnemius as well as Mercuri 2 semimembranosus, extensor digitorum longus, flexor digitorum longus and peroneus muscle fat replacement, STIR hyperintensities on thenar eminence and semimembranosus muscles. The tibialis posterior is characteristically spared. TE, thenar eminence; SM, semimembranosus; ST, semitendinosus; TA, tibialis anterior; P, peroneus muscles; GAm, gastrocnemius medialis, So, soleus, EDL, extensor digitorum longus; FDL, flexor digitorum longus. [Colour figure can be viewed at wileyonlinelibrary.com]
differing penetrance of the disease by gender. Interestingly, females seem to be more severely affected by the congenital generalized lipodystrophy caused by homozygote/compound heterozygote mutations in the BSCL2 gene [27]. Female mice lacking BSCL2 specifically in adipose tissue develop metabolic dysfunction not apparent in the same male mice model [28] however, entirely null BSCL2 female and male mice models recapitulate the metabolic disturbances observed in humans, underpinning the importance of BSCL2 in tissues other than adipose tissue and the relationship with gender [29].

When comparing phenotypes, there was a tendency towards higher disability in ‘complex’ BSCL2 phenotypes, those associated with either sensory signs and symptoms (CMT2) or spasticity (SPG-17). Muscle MRI confirmed that CMT patients had more severe muscle fat replacement than SPG or dHMN patients, supporting the hypothesis that sensory damage appears later in the course of the disease. Only one previous case of respiratory insufficiency in a male patient with a rapidly evolving disease fulfilling El Escorial criteria for amyotrophic lateral sclerosis (ALS), who required noninvasive ventilation, had been previously reported [5]. Two further cases of restrictive or mixed respiratory insufficiency are presented, although this remains uncommon and seems to present in severe cases of BSCL2 disease.

**Predominance of an axonal motor neuronopathy but occasional dispersed CMAPs on nerve conduction studies**

Electrophysiological studies showed a predominantly motor axonal neuropathy, with peroneal and tibial nerves similarly affected in lower limbs and a predominant median nerve involvement in upper limbs, as originally described [3]. However, it was surprising to
find the presence of dispersed CMAPs in seven patients, mainly in tibial and sometimes peroneal nerves (Table S1). Although there is primary axonal damage, chronodispersion, CVs in the demyelination range and partial conduction blocks have been described in BSCL2 and other motoneuron disorders suggesting a demyelinating component in the disease pathogenesis [3,30,31]. These findings are in line with sural nerve biopsies previously described [10,31], which have revealed a predominant axonal neuropathy, with loss of large myelinated fibres and axonal regeneration clusters. Active axonal degeneration is exceptional and demyelinating features like small onion bulbs can be present, although rare [10,31]. Sural nerve compound sensory action potentials could be elicited in all cases, further supporting the later sensory involvement in the disease.

**Muscle involvement in muscle MRI is consistent across the clinical spectrum of the disease and the degree correlates with disease severity**

Muscle MRI was altered in the majority of cases (83.33%) and showed a distal symmetric pattern of muscle fat replacement in both upper and lower limbs. This proximal-to-distal gradient has been evidenced in other neuropathies and differs from the more homogeneous replacement across the muscle’s length seen in distal myopathies, a differential diagnosis of BSCL2 disease [32].

The most frequently affected muscles were the soleus, tibialis anterior and thenar eminence muscles, followed by extensor and flexor digitorum longus, medial gastrocnemius and peroneus. Following the Price et al. classification of muscle involvement by nerve territory [33], BSCL2 nerve disorders showed both an initial P-type (peroneal) and T-type (tibial) involvement, progressing to S-type (sciatic). The sparing of the deep posterior leg compartment (notably the tibialis posterior) seen in the present series of BSCL2 patients has also been described in CMT1A patients [34].

The fact that distal branches from peroneal and tibial nerves tended to be first and more severely affected irrespective of clinical phenotype supports the hypothesis of an associated mechanism of length-dependent motor axon degeneration in BSCL2 disease, similar to that described in CMT1A and other CMT2 and dHMN hereditary neuropathies [34,35]. However, a genotype–phenotype correlation may exist. Whilst a prominent superficial posterior compartment (T-type) muscle involvement has been described in 21 patients with PMP22 mutations, 12 patients with HSP27 mutations and eight patients with HSPB1 mutations [35-37], three patients with DNM2 mutations showed a predominant anterior and peroneal compartment (P-type) muscle involvement [38]. It is seen that in BSCL2 patients both T-type and P-type muscle involvement normally coexist.

These same muscles could present hyperintensities on STIR sequences, previous to any evidence of fat replacement in two patients, making denervation a plausible early event in the disease [39]. However, five patients showed STIR hyperintensities in partly fat-replaced muscles, which evidences ongoing denervation in later stages of the disease. As mentioned earlier, BSCL2 mutations may even present as an ALS-like phenotype [5]. There is no specific pattern of fat replacement in ALS, but marked STIR changes from rapid denervation have been reported [40]. Although no ALS-like phenotype was observed in our series, the predominantly distal involvement on MRI, notably tibialis anterior and soleus versus peroneal in ALS, and the more isolated STIR hyperintensities could help differentiate ambiguous cases.

Probably the most important finding is that this T-type and P-type muscle involvement on MRI was irrespective of the clinical phenotype, even if asymptomatic (Fig. 2), which could guide the genetic diagnosis of this clinically heterogeneous disease. Furthermore, there was a strong correlation of muscle fat replacement with disability, as well as a mild-to-moderate correlation with time since onset of disease, supporting the role of muscle MRI in future clinical trials development [41].

This study has some limitations. Although the number of patients identified (n = 26) and the total number of different families (n = 5) are relatively large for a rare disease, the fact that all families share the p.N88S heterozygote variant and came from a small area makes a shared underlying genetic background probable. Despite this, it is interesting to find such a wide phenotypic spectrum, resembling the series previously reported [2-3,5-7]. Mean disability was low; however, the real burden of BSCL2 disease may be underestimated by the mRS. Thirdly, not all patients underwent a muscle MRI; however, the distributions of age, gender, duration of disease and mean disability were similar, and all phenotypes were represented.

The p.N88S BSCL2 mutation commonly presents as a pure dHMN; nevertheless, there is a variety of other presentations. Generally, the disease is slowly progressive and patients maintain autonomy until late stages. Muscle MRI shows a consistent proximal-to-distal and symmetric fat replacement in the soleus, tibialis anterior and thenar eminence muscles, with frequent changes on STIR sequences, regardless of the
clinical phenotype. Furthermore, there is a strong correlation of muscle fat replacement and disability. Therefore, muscle MRI can offer a recognizable pattern of muscle involvement and can probably serve as a reliable outcome measure for future clinical trials.

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Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. NCS studies (n = 12). Values for each variable are shown as (Right/Left), and missing values are coded as a (-). Amplitude of action potentials are shown in (mV) and conduction velocities in (m/sec).

Appendix S1. Test used in the statistical analysis.

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