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Disease Progression in Charcot-Marie-Tooth Disease Type 4B (CMT4B) Associated With Mutations in Myotubularin-Related Proteins 2 and 13

Alessandro Bertini[1] | Mary M. Reilly[2] | Chiara Pisciotta[1] | Stefano C. Previtali[3,4] | Yesim Parman[5] | Esra Battaloglu[6] | Matilde Laurà[2] | Julian Blake[2,7] | Sabrina Sacconi[8] | Shahram Attarian[9] | Tanya Stojkovic[10] | Mounia Bellatache[11] | Sonia Nouioua[11] | Meriem Tazir[11] | Arman Cakar[5] | Antonio Gambardella[12] | Paola Valentino[12] | Richard A. Lewis[13] | Rita Horvath[14] | Alberto A. Zambon[3,4] | Mario Sabatelli[15] | Marco Luigetti[16,17] | Stefano Tozza[18] | Fiore Manganelli[18] | David N. Herrmann[19] | Steven S. Scherer[20] | Nicole Kressin[21] | Kailee Ward[21] | Alessandra Bolino[3,22] | Michael E. Shy[21] | Davide Pareyson[1] | CMT4B Study Group | Inherited Neuropathy Consortium

[1]Unit of Rare Neurological Diseases, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy | [2]Centre for Neuromuscular Diseases, Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, England | [3]Institute of Experimental Neurology (InSpe), Division of Neuroscience, IRCCS Ospedale San Raffaele, Milan, Italy | [4]Neurology Unit, IRCCS Ospedale San Raffaele, Milan, Italy | [5]Neuromuscular Unit, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey | [6]Bogazici University, Department of Molecular Biology and Genetics, Istanbul, Turkey | [7]Department of Clinical Neurophysiology, Norfolk and Norwich University Hospital, Norfolk, UK | [8]Université Côte d'Azur, Service Système Nerveux Périphérique, Muscle et SLA, Centre Hospitalier Universitaire de Nice, Nice, France | [9]Reference Center for Neuromuscular Disorders and ALS, CHU la Timone, Aix-Marseille University, Marseille, France | [10]APHP, Sorbonne Université, Hôpital Pitié-Salpêtrière, Centre de référence Des Maladies Neuromusculaires Nord/Est/Ile de France, Paris, France | [11]Department of Neurology, Neuroscience Research Laboratory, Benyoucef Benkheda University, Algiers, Algeria | [12]Department of Neurology, Università Magna Graecia di Catanzaro, Catanzaro, Italy | [13]Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, California, USA | [14]Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK | [15]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Centro Clinico Nemo Adulti Rome, Rome, Italy | [16]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, UOC Neurologia, Rome, Italy | [17]Università Cattolica del Sacro Cuore, Sede di Roma, Rome, Italy | [18]Department of Neurosciences, Reproductive Sciences and Odontostomatology, University Federico II of Naples, Naples, Italy | [19]Department of Neurology, University of Rochester, Rochester, New York, USA | [20]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA | [21]Department of Neurology, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA | [22]Vita-Salute San Raffaele University, Milan, Italy

Correspondence: Davide Pareyson (davide.pareyson@istituto-besta.it)

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Keywords: Charcot-Marie-Tooth disease | CMT4B | neuromuscular

ABSTRACT

Background and Aims: In 2019, we conducted a cross-sectional study, collecting information on 50 patients with CMT4B, an ultrarare CMT subtype, to better define the clinical phenotype. We now aimed at investigating disease progression in 26 patients with CMT4B1/CMT4B2, recruited from the previous study and among the Inherited Neuropathy Consortium.

Materials and Methods: We retrospectively analysed disease progression in patients with CMT4B1/CMT4B2, collecting MRC scores from nine muscle pairs, Charcot-Marie-Tooth Examination Score (CMTES), and a minimal dataset of clinical information

CMT4B Study Group members are in Appendix A.

(walking difficulties, aids dependency, upper limb impairment, cranial nerves involvement) at baseline and follow-up visits. Thirteen centres from four continents were involved.

Results: Thirteen CMT4B1 and 13 CMT4B2 patients were followed up for 7.1 ± 4.9 and 7.9 ± 4.5 years, respectively. During follow-up, walking aid dependency increased: two CMT4B1 patients adopted AFOs (overall 11/12 at follow-up), and one started using wheelchair (6/12 at follow-up) at the age of 19; among CMT4B2 patients, two more required unilateral support in walking (4/11 at follow-up) by the age of 33 and 49 years, respectively. We found that disease progression, as measured by CMTES, was faster in CMT4B1 as compared to CMT4B2 patients (ΔCMTES/year 0.7 vs. 0.3, $p = 0.037$) but tended to slow down over time as burden of disease increased. At the end of follow-up, CMT4B1 was associated to higher disability.

Conclusions: This international collective effort enabled collection of relevant data for characterizing natural history and estimating disease progression of CMT4B1/CMT4B2 ultrarare diseases, aiming at improving their management and paving the way for designing future clinical trials.

1 | Introduction

Charcot-Marie-Tooth (CMT) disease, a heterogenous group of hereditary neuropathies, includes ultrarare subtypes [1]. Among demyelinating recessive forms (CMT4), CMT4B is characterized by focal hypermyelination on nerve biopsy, with myelin outfoldings constituted by redundant loops of myelin lamellae in several nerve fibers [2]. CMT4B1 and CMT4B2 are associated with recessive variants in the myotubularin-related proteins 2 (*MTMR2*) and 13 (*MTMR13/SBF2*) genes, respectively [3–5]. Most mutations imply a complete loss-of-function mechanism [6]. Shared features are early onset and disabling progression which may be complicated by vocal cord palsy and respiratory involvement; early-onset glaucoma may occur in CMT4B2 [3, 6]. Less than 150 cases have been reported in the literature.

In 2019, Pareyson and colleagues [6] conducted a multicenter retrospective cross-sectional study, collecting information on 50 CMT4B patients' to better define the clinical phenotypes. However, longitudinal data, critical for trial readiness, are needed, as there are promising potential treatments under investigation for CMT4B, including niacin and PIKfyve kinase inhibitors [7–10].

In this multicenter longitudinal study, we investigated disease progression in a cohort of CMT4B1/CMT4B2 patients.

2 | Materials and Methods

We retrospectively analyzed data from follow-up visits for patients collected in our previous study [6]. Further prospectively evaluated patients carrying homozygous/compound heterozygous pathogenic mutations in MTMR2/13 were recruited through the Inherited Neuropathy Consortium (INC, NCT01193075/NCT01193088/NCT01203085) at one of 21 INC sites between 2009 and 2023. Inclusion criteria required data at baseline (= first available visit) and from at least one follow-up (f-up) visit. We gathered a minimal dataset of clinical/genetic information, as described [6]. MRC scores were collected from nine muscle pairs (first dorsal interosseous, abductor pollicis brevis, wrist extensors, accounting for MRC-distal upper limb score; biceps, deltoid, accounting for MRC-proximal upper limb score; foot dorsiflexors, foot plantar flexors, accounting for MRC-distal lower limb score; knee extensors, hip flexors, accounting for MRC-proximal lower limb score). Disease progression was expressed as Charcot-Marie-Tooth Examination Score-Version2 [11] (CMTES) variation from baseline to the last available visit/time elapsed (ΔCMTES/year); the CMTPedS [12], scale for children, was employed only for one patient, as most centers assessing children were not trained for administering it. Thirteen centers collected data from at least one patient. Data were pseudo-anonymized. Patients gave informed consent. The study was approved by Fondazione IRCCS Istituto Neurologico C.Besta (58.7,01/16/2019; 90.8,12/15/2021) and INC centers (832955,01/10/2024) Ethics Committees.

3 | Statistical Analysis

Data were expressed as mean ± standard deviation (range). Mann–Whitney *U*-test/age-adjusted Quade test were used for comparison between CMT4B1 and CMT4B2, as appropriate. Spearman's rank correlation coefficient was performed to assess significant associations between both age and CMTES-total score at baseline, and disease progression (ΔCMTES/year) for CMT4B1 and CMT4B2 separately. Statistical tests were two-tailed; significance was set at $p < 0.05$.

4 | Results

Of the original 45 CMT4B1/CMT4B2 patients previously reported [6], we have information on follow-up visits of 22, while four others were known to have died because of the disease and seven were lost to follow up; we recruited four additional patients through the INC. Overall, there were 13 CMT4B1 (six females, mean age at baseline 17.6 ± 12.2 years, range 1–40) and 13 CMT4B2 (five females, mean age at baseline 26.2 ± 14.5, range 8–55) patients. Seven CMT4B1 and five CMT4B2 patients were < 18-year-old (all but two > 7-year-old). Overall, we collected 44 (range 2–10) visits for CMT4B1 and 51 (range 2–10) for CMT4B2, with a similar mean follow-up time of 7.1 ± 4.9 (2–18) and 7.9 ± 4.5 (2–17) years, respectively.

Clinical features at baseline and changes during follow-up period are shown in Table 1.

In brief, all patients with CMT4B1 and CMT4B2 had walking difficulties at baseline. Among them, respectively, 75% (9/12) and 62% (8/13) used AFOs, 14% (1/7) and 18% (2/11) required

TABLE 1 | Clinical features changes in CMT4B1 and CMT4B2 during follow-up period (from baseline to last available visit).

	CMT4B1 baseline (12pts)[a]	CMT4B1 f-up (12pts)[a]	CMT4B2 baseline (13pts)	CMT4B2 f-up (13pts)
Follow-up period mean ± sd (range)	7.1 ± 4.9 (2–18)		7.9 ± 4.5 (2–17)	
Age of symptoms onset Mean ± sd (range)	2.3 ± 1.6 (0–5)[e] Onset p.Arg628Profs*18 hom = 13 years		5.8 ± 5.9 (1–20)	
Walking difficulties	12/12 (100%)	12/12 (100%)	13/13 (100%)	13/13 (100%)
Walking difficulties onset Mean ± sd (range)	4.6 ± 3.4 (1–13)		5.8 ± 6.3 (1–20)	
AFOs	9/12 (75%)	**11/12 (92%)**	8/13 (62%)	8/13 (62%)
Unilateral/bilateral support need (crutches)	1/7 (14%)[b]	1/7 (14%)[b]	2/11 (18%)[d]	**4/11 (36%)**[d]
Unilateral/bilateral support use onset (age)	16 yrs	16 yrs	38 and 58 yrs	**33**/38/**49**/58 yrs
Wheelchair	5/12 (42%)	**6/12 (50%)**	2/13 (15%)	2/13 (15%)
Wheelchair use onset (age)	14/17/22/29/39 yrs	14/17/**19**/22/29/39 yrs	10 and 16 yrs	10 and 16 yrs
Difficulties with buttons/eating utensils	12/12 (100%)	12/12 (100%)	13/13 (100%)	13/13 (100%)
Vocal cord palsy	6/11 (55%)	6/11 (55%)	3/10 (30%)	**5/10 (50%)**
Unilateral	1/11 (9%)	0	1/10 (10%)	1/10 (10%)
Bilateral	5/11 (46%)	**6/11 (55%)**	2/10 (20%)	**4/10 (40%)**
Stridor	4/11 (36%)	4/11 (36%)	0	0
Hoarse voice	2/11 (18%)	2/11 (18%)	3/10 (30%)	**4/10 (40%)**
Respiratory insufficiency	4/11 (36%)	**5/11 (46%)**	1/10 (10%)	1/10 (10%)
NIV	0	0	0	0
Invasive ventilation	0	**1/11 (9%)**	0	0
Positive sensory symptoms[c]	1/12 (8%)	**5/12 (42%)**	2/12 (17%)	**4/12 (33%)**
Sensory loss	2/12 (17%)	**6/12 (50%)**	8/12 (67%)	**9/12 (75%)**
Optic nerve atrophy	0	0	1/10 (10%)	1/10 (10%)
Hearing loss	0	0	3/10 (30%)	3/10 (30%)
Glaucoma	0	0	2/10 (20%)	**4/10 (40%)**
Facial weakness	6/11 (55%)	6/11 (55%)	1/10 (10%)	**2/10 (20%)**
Ptosis	2/11 (18%)	2/11 (18%)	1/10 (10%)	1/10 (10%)

(Continues)

TABLE 1 | (Continued)

	CMT4B1 baseline (12pts)[a]	CMT4B1 f-up (12pts)[a]	CMT4B2 baseline (13pts)	CMT4B2 f-up (13pts)
Tongue involvement	3/11 (27%)	3/11 (27%)	0	**1/10 (10%)**
Dysphagia	1/11 (9%)	1/11 (9%)	0	**1/10 (10%)**

Note: Clinical feature changes in the follow-up period in bold.
Abbreviations: AFOs = ankle–foot orthoses; NIV=non-invasive ventilation.
[a]Clinical information not available for one patient with CMT4B1.
[b]Five wheelchair-bound patients excluded.
[c]For example, burning, tingling.
[d]Two wheelchair-bound patients excluded.
[e]Patient carrying p.Arg628Profs*18 variant in homozygosity excluded.

unilateral/bilateral support (crutches), and 42% (5/12) and 15% (2/13) were wheelchair-bound. During the follow-up period, walking aid dependency increased both in CMT4B1 and CMT4B2: two CMT4B1 patients adopted AFOs (overall 11/12 at f-up), and one started using wheelchair (6/12 at f-up) at the age of 19 (disease duration 17 years); among CMT4B2 patients, two more required unilateral support in walking (4/11 at f-up) by the age of 33 (disease duration 28 years) and 49 (disease duration 35 years) years, respectively.

As disease progressed, sensory involvement became more prominent: 5 of 12 (versus 1/12 at baseline) and 6 of 12 (vs. 2/12 at baseline) CMT4B1, and 4 of 12 (vs. 2/12 at baseline) and 9 of 12 (vs. 8/12 at baseline) CMT4B2 patients reported positive sensory symptoms and hypoesthesia, respectively, at the end of follow-up period.

At baseline, bilateral vocal cord palsy was observed in 5 of 11 (46%) of CMT4B1 and 2 of 10 (20%) CMT4B2 patients, and respiratory insufficiency in 4 of 11 (36%) and 1 of 10 (10%) cases. One CMT4B1 patient with neonatal onset and hypotonia at birth developed bilateral (from unilateral) vocal cord palsy and related respiratory insufficiency by the age of 2, and subsequently underwent tracheostomy by the age of 3. Among CMT4B2, two further patients developed bilateral vocal cord palsy (4/10 at f-up, in one patient vocal cord palsy remained unilateral), although respiratory insufficiency did not occur. None of the CMT4B2 patients required non-invasive/invasive ventilation.

As far as other cranial nerve involvement is concerned, 55% of CMT4B1 patients had facial weakness, 18% ptosis, 27% tongue involvement, and 9% dysphagia, with no changes during follow-up evaluations. Concerning CMT4B2, one patient (2/10 at f-up) developed facial weakness at age 21 years, one (1/10 at f-up) tongue weakness at age 20, and another one (1/10 at f-up) dysphagia at age 59. In addition, bilateral glaucoma, a common feature of CMT4B2, was diagnosed in two patients (overall 4/10 at f-up), at age 10 and 26 years, respectively.

At baseline, we found that CMT4B1 patients showed similar CMTES-total (11.8 vs. 14.7, $p = 0.883$) and -motor (9.5 vs. 8.0, $p = 0.134$) scores but milder sensory (CMTES-sensory score 2.5 vs. 6.5, $p = 0.021$) involvement as compared to CMT4B2. However, when evaluating muscular strength (Table S1), CMT4B1 patients displayed worse global weakness (= lower scores) (MRC-total score 50.1/90 vs. 63.7/90, $p = 0.043$), particularly in hands (MRC-distal upper limbs 12.3/30 vs. 18.1/30, $p = 0.037$) and thigh (MRC-proximal lower limbs 13.8/20 vs. 19.3/20, $p = 0.017$) (all comparisons adjusted for age, as CMT4B1 patients were younger).

Disease progression according to CMTES was faster in CMT4B1 as compared to CMT4B2 (ΔCMTES-total/year 0.7 vs. 0.3, $p = 0.037$; Figure 1), particularly on the sensory side (ΔCMTES-sensory/year 0.2 vs. 0.0, $p = 0.038$) (Table S2). Moreover, we found a trend supporting also faster motor worsening in CMT4B1, as far as ΔMRC-distal upper limb/year (−1.2 vs. −0.8, $p = 0.187$) and ΔMRC-distal lower limb/year (−1.1 vs. −0.7, $p = 0.214$) items are concerned. On the other hand, we found differences neither in the ΔCMTES-motor/year (0.4 vs. 0.3) nor in total muscles'

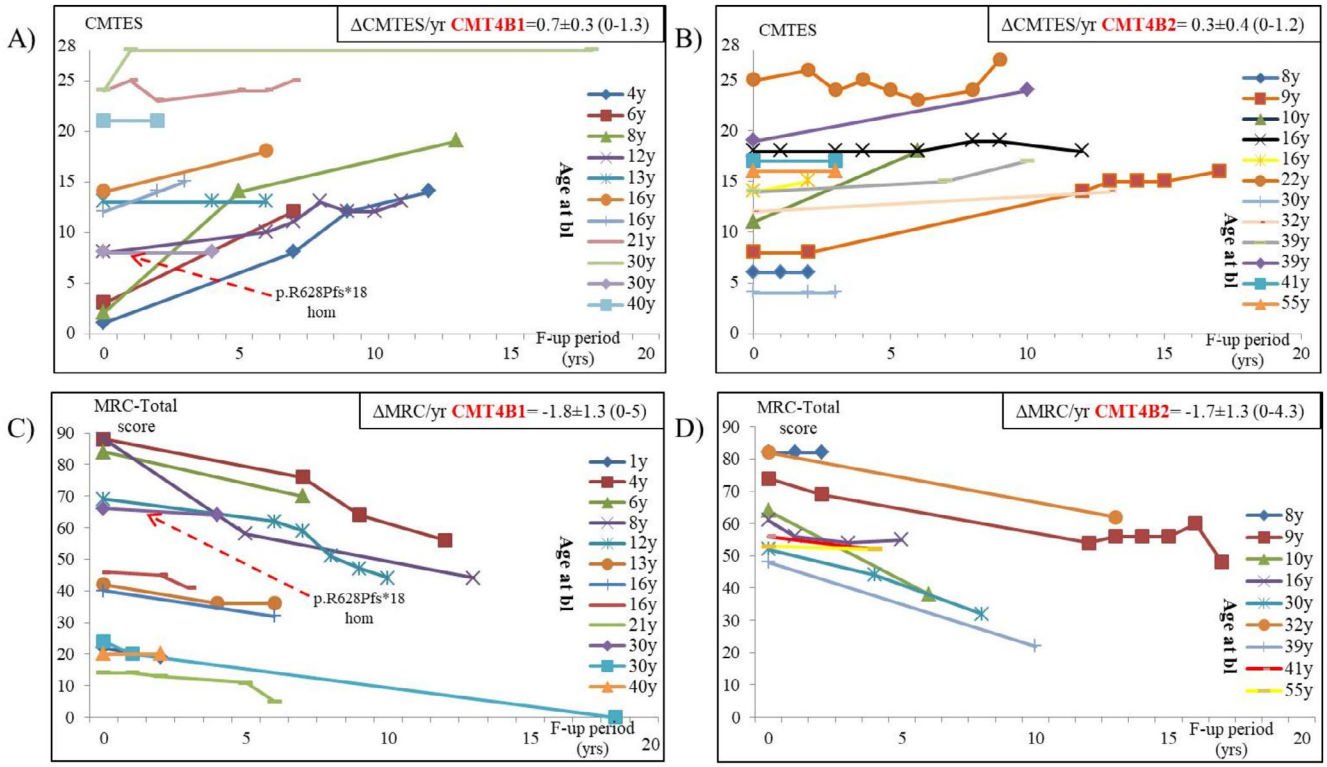

FIGURE 1 | Disease progression, assessed through CMTES (A, B) and MRC-Total score (C, D) variation over follow-up time in CMT4B1 ($n=11$ and $n=12$, respectively)* and CMT4B2 ($n=12$ and $n=9$, respectively)§ patients. bl = baseline; F-up = follow-up; hom = homozygous; yr. = year; yrs. = years; rs = Spearman rank correlation. *Data on CMTES progression missing for two patients with CMT4B1 and one with CMT4B2. §Data on MRC-Total score variation missing for one patient with CMT4B1 and four with CMT4B2. (Box A–D) Age at baseline is reported on the right side of each box. Red arrow indicates the CMT4B1 patient carrying homozygous p.R628Pfs*18 mutation, exhibiting milder phenotype and negligible progression (ΔCMTES/year = 0; ΔMRC-Total score/year = −0.5) over time.

ΔMRC/year (−1.8 vs. −1.7, Figure 1) or upper (−0.2 vs. −0.2) and lower (−0.1 vs. −0.1) proximal sites' ΔMRC/year between CMT4B1 and CMT4B2, respectively.

We found a moderate-to-strong inverse correlation between ΔCMTES-total/year, and both age (rs = −0.76, $p=0.007$) and CMTES (rs = −0.63, $p=0.037$) at baseline for CMT4B1, but not CMT4B2 (rs = −0.29, $p=0.382$; rs = −0.20; $p=0.540$, respectively) patients (Figure S1).

5 | Discussion

This international multicenter study involving 13 centers in four continents, stemmed from previous work [6] further strengthened by INC contribution, collected detailed longitudinal clinical information on 26 patients with the ultrarare CMT4B1/CMT4B2, followed for a mean time of ~7 years (up to 18 years) with a total of 95 evaluations, in the first study on CMT4B progression ever performed.

We confirmed the higher burden of disease of CMT4B1 patients [6] and found that disease progression was faster in CMT4B1, especially on the sensory side, as compared to CMT4B2. A trend supporting faster motor weakening of distal limb muscles in CMT4B1 was also detected. CMT4B1 is the CMT type showing the fastest progression to date (Table S2, legend).

Interestingly, differences in disease progression between the two forms might have been mitigated by the CMT4B1 patient carrying the homozygous p.R628Pfs*18 mutation, who showed a milder phenotype, and negligible progression over 4 years (Figure 1). Indeed, this variant is predicted to act with a partial loss-of-function mechanism, by retaining part of the protein function [6].

At the end of follow-up period, CMT4B1 patients clearly showed higher disability and more prominent bulbar and respiratory impairment compared to CM4B2, despite younger age: 50% of them were wheelchair-bound (vs. 15%), 46% had respiratory insufficiency (vs. 10%), 55% had facial involvement (vs. 20%), and 27% tongue weakness (vs. 10%).

These findings are noteworthy as "classic"-onset demyelinating (onset age CMT4B2 = 6.7 ± 5.0) [6] CMTs have been traditionally considered to display greater progression during later childhood/adulthood compared to infantile-onset dysmyelinating (onset age CMT4B1 = 2.8 ± 2.8) [6] forms, in which worsening is believed to take place mainly in the very first years of life [13].

However, in CMT4B1, disease progression tended to slow down with age and increase of disease burden (Figure S1), although this could in part reflect the intrinsic lack of sensitivity of CMTES (not measuring bulbar/respiratory involvement) in detecting progression in severe stages of disease [14].

This finding further strengthens the need for early treatment in CMT4B1 patients. Conversely, disease progression did not correlate with age/disease severity in CMT4B2 patients who showed slower worsening during childhood/adulthood.

The present study represents an international collective effort which enabled the collection of relevant data for characterizing natural history and estimating disease progression of ultrarare diseases such as CMT4B1 and CMT4B2, aiming at improving their management and paving the way for designing future clinical trials. The CMTES is not responsive enough especially in the late stages; the CMTPedS in children and the CMT-FOM [15] items in adults may be more responsive, but require specific centers training; measures of cranial nerve involvement, vocal cord motility, and respiratory capacity may be useful particularly for advanced disease stages. It will be important to test the responsiveness of paraclinical outcome measures, including quantitative muscle MRI, skin biopsy, and wet biomarkers.

Author Contributions

Alessandro Bertini: conceptualization, writing – review and editing, data curation, writing – original draft, formal analysis. **Mary M. Reilly:** writing – review and editing, data curation, writing – original draft. **Chiara Pisciotta:** data curation. **Stefano C. Previtali:** data curation. **Yesim Parman:** data curation. **Esra Battaloglu:** data curation. **Matilde Laurà:** data curation. **Julian Blake:** data curation. **Sabrina Sacconi:** data curation. **Shahram Attarian:** data curation. **Tanya Stojkovic:** data curation. **Mounia Bellatache:** data curation. **Sonia Nouioua:** data curation. **Meriem Tazir:** data curation. **Arman Cakar:** data curation. **Antonio Gambardella:** data curation. **Paola Valentino:** data curation. **Richard A. Lewis:** data curation. **Rita Horvath:** data curation. **Alberto A. Zambon:** data curation. **Mario Sabatelli:** data curation. **Marco Luigetti:** data curation. **Stefano Tozza:** data curation. **Fiore Manganelli:** data curation. **David N. Herrmann:** data curation. **Steven S. Scherer:** data curation. **Nicole Kressin:** data curation. **Kailee Ward:** data curation. **Alessandra Bolino:** data curation. **Michael E. Shy:** data curation, writing – original draft, writing – review and editing. **Davide Pareyson:** data curation, writing – review and editing, funding acquisition, conceptualization, writing – original draft.

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Conflicts of Interest

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Data Availability Statement

Data relevant to the study are included in the article. Data supporting study results are deposited in an ad hoc repository and are available from the principal investigator (D.P.) to be shared anonymously on request from any qualified investigator.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix A

Sarah Leonard-Louis (Hôpital Pitié-Salpêtrière, AP-HP, Centre de Référence des Maladies Neuromusculaires Nord/Est/Ile de France, Paris, France), Nathalie Bonello-Palot (Department of Medical Genetics, Timone Hospital, Marseille, France), Nicolas Lévy (Department of Medical Genetics, Timone Hospital, Marseille, France), Raquel Guimarães-Costa (Hôpital Pitié-Salpêtrière, AP-HP, Centre de Référence des Maladies Neuromusculaires Nord/Est/Ile de France, Paris, France), Philippe Latour (Center of Biology and Pathology Laboratory of Molecular Neurogenetics, Hospices Civils, Lyon, France), Guilhem Solé (Reference Center for Neuromuscular Disorders AOC (Atlantique Occitanie Caraibes), CHU de Bordeaux, Bordeaux, France), André Megarbane (Institut Jérôme Lejeune, Paris, France; INOVIE, Beirut, Lebanon), Byung-Ok Choi (Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea), Angelo Schenone (Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and MATERNAL Infantile Sciences, University of Genoa, and IRCCS Policlinico San Martino, Genoa, Italy), Chiara Gemelli (Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and MATERNAL Infantile Sciences, University of Genoa, and IRCCS Policlinico San Martino, Genoa, Italy), Alessandro Geroldi (Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and MATERNAL Infantile Sciences, University of Genoa, and IRCCS Policlinico San Martino, Genoa, Italy), Lois Dankwa (Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA), Tatsufumi Murakami. (Department of Neurology, Kawasaki Medical School, Kurashiki, Japan), Paola Saveri (Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy), Luca Crivellari (Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy).