Underestimated associated features in CMT neuropathies: clinical indicators for the causative gene?

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Underestimated associated features in CMT neuropathies: clinical indicators for the causative gene?

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Abstract

Introduction: Charcot–Marie–Tooth neuropathy (CMT) is a genetically heterogeneous group of peripheral neuropathies. In addition to the classical clinical phenotype, additional features can occur. Methods: We studied a wide range of additional features in a cohort of 49 genetically confirmed CMT patients and performed a systematic literature revision. Results: Patients harbored a PMP22 gene alteration (n = 28) or a mutation in MPZ (n = 11), GJB1 (n = 4), LITAF (n = 2), MFN2 (n = 2), INF2 (n = 1), NEFL (n = 1). We identified four novel mutations (3 MPZ, 1 GJB1). A total of 88% presented at least one additional feature. In MPZ patients, we detected hypertrophic nerve roots in 3/4 cases that underwent spinal MRI, and pupillary abnormalities in 27%. In our cohort, restless legs syndrome (RLS) was present in 18%. We describe for the first time RLS associated with LITAF or MFN2 and predominant upper limb involvement with LITAF. Cold-induced hand cramps occurred in 10% (PMP22, MPZ, MFN2), and autonomous nervous system involvement in 18% (PMP22, MPZ, LITAF, MFN2). RLS and respiratory insufficiency were mostly associated with severe neuropathy, and pupillary abnormalities with mild to moderate neuropathy. Conclusions: In CMT patients, additional features occur frequently. Some of them might be helpful in orienting genetic diagnosis. Our data broaden the clinical spectrum and genotype–phenotype associations with CMT.

Introduction

Charcot–Marie–Tooth (CMT) neuropathy (also called hereditary motor and sensory neuropathy or HMSN) is a rare disorder with a prevalence of one in 2500 (Skre 1974). CMT is clinically characterized by muscle wasting and weakness in the distal limbs resulting in steppage gait as well as distal sensory loss. Foot deformities such as pes cavus and hammer toes are frequently present (Rossor et al. 2013; Timmerman et al. 2014). Usually, the disease course is slowly progressive and in some cases, the use of a walker or wheelchair is necessary later in life (Timmerman et al. 2014). Besides the classical clinical appearance of CMT patients, additional symptoms have been described in association with mutations in certain genes, such as pupillary abnormalities with mutations in the myelin protein zero (MPZ) gene (De Jonghe et al. 1999; Hattori et al. 2003; Stojkovic et al. 2003), hearing impairment in association with pathogenic variants in the gap junction protein beta 1 (GJB1) gene (Hattori et al. 2003), or focal...
segmental glomerular sclerosis (FSGS) with mutations in the inverted formin 2 (INF2) gene (Boyer et al. 2011; Mademan et al. 2013).

CMT has been subdivided into three forms by nerve conduction velocity (NCV) studies: a demyelinating form with motor NCV in the upper limbs below 38 m/sec (CMT1), an axonal form with NCV above 38 m/sec (CMT2) (Harding and Thomas 1980), and an intermediate form with NCV between 25 and 45 m/sec (Davis et al. 1978). The neuropathological hallmark of CMT1 is segmental de- and remyelination and onion bulb formations. In CMT2 patients, nerve biopsies typically show axonal loss and regenerative sprouting (Schröder 2001). Both histopathological abnormalities are present in intermediate CMT. At the molecular genetic level, CMT is very heterogeneous with mutations in over 80 causative genes known so far and all possible modes of inheritance (Azzedine et al. 2012; Timmerman et al. 2014). The most frequently mutated gene is peripheral myelin protein 22 (PMP22), leading to CMT1A (duplication or point mutation) or hereditary neuropathy with liability to pressure palsies (HNPP, deletion or point mutation) (van Paassen et al. 2014). Novel parallel gene sequencing techniques (next-generation sequencing (NGS), whole-exome sequencing (WES)) are nowadays available (Rosor et al. 2013); however, the costs for WES in a diagnostic setting are still high and not (yet) covered by health insurances in many countries. Furthermore, the novel genetic techniques usually lead to a large number of variants of which the causative relation with the disease is often unclear.

Here, we studied the occurrence of additional features in a large cohort of genetically defined CMT patients and performed a systematic revision of the literature. We explored whether the presence of diverse associated clinical features, such as hypertrophic nerve roots or pupil abnormalities, might contribute to identify the causative gene in CMT patients. We also examined whether the occurrence of additional features correlated with the CMTNS2 neuropathy severity score.

**Patients and Methods**

**Patient selection**

We included 49 patients with genetically confirmed CMT or HNPP that were followed in our neuromuscular outpatient clinic (Department of Neurology, University Hospital RWTH Aachen, Germany) from January 2010 to December 2014 (Table 1). In addition, we searched the database of the Department of Nephrology (University Hospital RWTH Aachen, Germany) for patients born after 1970 presenting focal segmental glomerular sclerosis (FSGS) diagnosed on kidney biopsy. We identified 20 FSGS patients and screened them for an additional polyneuropathy, using a questionnaire on neuropathy symptoms and a clinical neurological examination. The study was approved by the ethical committee of the RWTH University Aachen, Germany.

**Clinical and paraclinical examinations**

In all patients, we performed a detailed history taking, and general clinical and neurological examination with particular attention for additional features (Table 2). The feature cold-induced hand cramps was asked for anamnestically and the presence of scoliosis was derived from the patients’ medical reports in a retrospective manner. We applied the CMT neuropathy score version 2 (CMTNS2) in 37 patients, in order to evaluate the severity of neuropathy: mild (range 0–10), moderate (range 11–20), or severe (≥20, maximum 36) (Table 1) (Murphy et al. 2011). We systematically performed motor and sensory nerve conduction velocities (NCV) at the upper limbs in all patients and additionally at the lower limbs in some. Prior to this study, a lumbar puncture was performed in two CMT patients (patients 2 and 6), a magnetic resonance imaging (MRI) of the thoraco-lumbo-sacral spine (Philips Intera, 1.5 Tesla, Andover, MA) in patients 2, 4, 6, 7, and 13, a MRI of the cervical spine in patient 12 and a MRI of the brain in patients 1, 2, 5, 6, 12, and 22 for diagnostic purposes. Sural nerve biopsies were obtained previous to the study for diagnostic reasons in patients 1, 2, 6, 23, 24, and 47, after written informed consent. The biopsies were processed following standard procedures (Weis et al. 2012). Semithin sections were stained with toluidine blue and both light and electron microscopic studies were performed.

**Molecular genetic analyses**

The molecular genetic tests were performed using genomic DNA from total peripheral blood samples following standard procedures, after obtaining patients’ written informed consent. Sanger sequencing or multiplex ligation-dependent probe amplification (MLPA) combined with microsatellite marker method was performed in 46 CMT patients. A molecular genetic analysis of INF2 was conducted in two patients with a polyneuropathy and histologically proven FSGS (from the initial cohort of 20 patients with FSGS, see above). NGS-based panel diagnostics for mutations in 71 CMT-causing genes was done in three patients (patients 6, 10, and 46; Tables 1 and 2), in whom previous single-gene analyses had not revealed a causative mutation. In addition, a segregation analysis was performed in two families (patient 1 with healthy mother and healthy sister; patients 7, 8, 9 with healthy mother and
| Patient (Family) | Gender/AAE | CMTNS2/ at AAE | Gene | CMT subtype | Mutation | Protein change | SIFT | PolyPhen-2 | Provean | Sift | References |
|-----------------|------------|----------------|------|-------------|----------|----------------|------|------------|--------|------|------------|
| 1 (S)           | M/27       | 25              | MPZ  | CMT1B       | c.678delC| p.S226fs      | na   | na         | na     | na   | Novel     |
| 2 (F1)          | M/51       | 16              | MPZ  | CMT1B       | c.487G>A | p.G163R       | Not tolerated | Probably damaging | Deleterious |
| 3 (F1)          | M/78       | ND              | MPZ  | CMT1B       | c.487G>A | p.G163R       | Not tolerated | Probably damaging | Deleterious |
| 4 (F1)          | F/46       | 10              | MPZ  | CMT1B       | c.487G>A | p.G163R       | Not tolerated | Probably damaging | Deleterious |
| 5               | F/30       | 2               | MPZ  | CMT2-I/J    | c.368G>C | p.G123A       | Not tolerated | Probably damaging | Deleterious |
| 6               | M/68       | 14              | MPZ  | CMT1B       | c.293G>A | p.R98H        | Not tolerated | Probably damaging | Deleterious |
| 7 (F2)(S)       | F/44       | 29              | MPZ  | CMT1B       | c.103_104insA | p.L35fsX66 | na   | na         | na     | na   | Novel     |
| 8 (F2)(S)       | M/70       | 4               | MPZ  | CMT1B       | c.103_104insA | p.L35fsX66 | na   | na         | na     | na   | Novel     |
| 9 (F2)(S)       | M/41       | 0               | MPZ  | CMT1B       | c.103_104insA | p.L35fsX66 | na   | na         | na     | na   | Novel     |
| 10              | F/48       | 27              | MPZ  | CMT2-I/J    | c.293G>A | p.R98H        | Not tolerated | Probably damaging | Deleterious |
| 11              | M/64       | 22              | MPZ  | CMT1B       | c.670G>T | p.D224Y       | Not tolerated | Probably damaging | Deleterious |
| 12 (F3)         | M/33       | 6               | LITAF | CMT1C     | c.430G>A | p.V144M       | Not tolerated | Probably damaging | Damaging |
| 13 (F3)         | F/54       | 22              | LITAF | CMT1C     | c.430G>A | p.V144M       | Not tolerated | Probably damaging | Damaging |
| 14              | M/51       | 21              | GJB1 | CMTX1      | c.547C>A | p.R183S       | Not tolerated | Probably damaging | Deleterious |
| 15              | F/38       | 18              | GJB1 | CMTX1      | c.8G>A    | p.W3X         | na   | na         | na     | na   | Ananth U (1999), private data |
| 16 (F4)         | F/45       | 15              | GJB1 | CMTX1      | c.303dup  | p.E102Rfs*8  | na   | na         | na     | na   | Novel     |
| 17 (F4)         | M/39       | 18              | GJB1 | CMTX1      | c.303dup  | p.E102Rfs*8  | na   | na         | na     | na   | Novel     |
| 18              | M/48       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 19              | M/37       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 20              | F/26       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 21              | F/27       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 22              | F/33       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 23              | M/51       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 24 (F5)         | F/65       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 25 (F5)         | F/40       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 26              | F/56       | na              | PMP22| HNPP       | Deletion   | Deletion      | na   | na         | na     | na   | Chance et al. (1993) |
| 27 (F6)         | F/49       | 21              | PMP22| CMT1A      | Duplication| Duplication   | na   | na         | na     | na   | Lupski et al. (1991); Raemaekers et al. (1991) |

(Continued)
| Patient (Family) | Gender/AAE | CMTNS2/AAE | Gene   | CMT subtype | Mutation    | Protein change | SIFT   | PolyPhen-2 | Provean Sift | References                                                                 |
|-----------------|------------|------------|--------|-------------|-------------|----------------|--------|------------|--------------|--------------------------------------------------------------------------|
| 28 (F6)         | F/70       | 18         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 29              | M/23       | 11         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 30              | F/26       | 24         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 31              | M/30       | 25         | PMP22  | CMT1A       | c.256C>T    | p.Q86X         | na     | na         | na           | Numakura et al. (2002)                                                    |
| 32              | M/62       | 7          | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 33              | M/42       | 14         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 34              | M/59       | 26         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 35              | F/49       | 31         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 36              | F/56       | 21         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 37 (F7)         | F/66       | 24         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 38 (F7)         | M/45       | 19         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 39              | F/51       | 20         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 40              | M/63       | 27         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 41              | F/46       | 16         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 42              | F/34       | ND         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 43 (F8)         | F/8        | 5          | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 44 (F8)         | F/45       | 24         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 45              | F/51       | 26         | PMP22  | CMT1A       | Duplication | Duplication    | na     | na         | na           | Lupski et al. (1991); Raeymaekers et al. (1991)                           |
| 46              | M/45       | 13         | NEFL   | CMT1F       | c.995A>C    | p.Q332P        | Not tolerated | Probably damaging | Deleterious | Mersiyanova et al. (2000)                                                  |

(Continued)
affected father – family 2; Table 1). We used the prediction programs SIFT (sorting intolerant from tolerant algorithm), PolyPhen2 (polymorphism phenotyping version 2), and Provean Sift (protein variation effect analyzer) to verify pathogenicity of the identified variants (Table 1).

**Literature search and meta-analysis**

In order to study the additional features reported in CMT patients so far, we conducted a systematic review in PubMed from 1985 to 2014. We included published CMT patients in whom a genetic defect was identified, and excluded patients with other hereditary neuropathies, such as hereditary motor neuropathies (HMN) or hereditary sensory (and autonomic) neuropathies (HSN, HSAN). CMT patients with compound heterozygous mutations in two different genes were also excluded, since no unequivocal genotype–phenotype correlation could be made. These criteria led to 280 publications that have been included in this study (Appendix S1).

**Results**

**Patient cohort**

Our study cohort included 49 patients with a genetically confirmed diagnosis of CMT or HNPP (Table 1). Nineteen patients belonged to eight different families and 30 patients were isolated cases. Six distinct mutations have been identified in the MPZ gene, of which three were novel (patients 1, 5; and patients 7, 8, 9 belonging to family 2) and predicted to be pathogenic by the three prediction programs applied (Table 1). Furthermore, the variants co-segregated with the disease status in the healthy mother and sister of patient 1, as well as in the healthy mother, affected father (patient 8) and brother (patient 9) of index patient 7. The two patients carrying the same c.293G>A, p.R98H mutation in MPZ (patients 6 and 10) were not related. Eighteen patients carried a PMP22 duplication, nine had a PMP22 deletion, and one harbored a point mutation in the PMP22 gene. In four patients, a pathogenic variant in the GJB1 gene was identified, of which the c.303dup, p.E102Rfs*8 mutation in GJB1 in the related patients 16 and 17 was novel (brother and sister, family 4, Table 1). Two patients belonging to the same family (mother and son) carried a mutation in the lipopolysaccharide-induced tumor necrosis factor-α factor (LITAF) gene, one in the neurofilament protein light polypeptide (NEFL) gene, one in INF2, and two in the mitofusin 2 (MFN2) gene. The patient with INF2 mutation has been described previously (Roos et al. 2015). Neuropathy severity, measured using the CMTNS2 score, was mild in seven patients (range 0–10), moderate

| Patient (Family) | Gender | AAE | CMT subtype | Gene | Mutation | Protein change | SIFT | PolyPhen-2 | Provean Sift | References |
|-----------------|--------|-----|-------------|------|----------|---------------|------|------------|-------------|------------|
| 47              | F      | 12  | CMTDIE      | INF2 | c.230T>G | p.L77R        | Not tolerated | Not tolerated | Not tolerated | Mademan et al. (2013) |
| 48              | F      | 32  | CMT2A2      | MFN2 | c.839G>A | p.R280H       | Not tolerated | Not tolerated | Not tolerated | Zuchner et al. (2004); Chung et al. (2006); Verhoeven et al. (2006) |
| 49              | M      | 42  | CMT2A2      | MFN2 | c.281G>A | p.R94Q        | Not tolerated | Not tolerated | Not tolerated | Zuchner et al. (2004); Chung et al. (2006); Verhoeven et al. (2006) |
| 47              | F      | 21  | CMT2A2      | MFN2 | c.281G>A | p.R94Q        | Not tolerated | Not tolerated | Not tolerated | Zuchner et al. (2004); Chung et al. (2006); Verhoeven et al. (2006) |

AAE, age at examination; CMTNS2, Charcot-Marie-Tooth neuropathy score version 2 (score ranging from 0 to 36; mild: 0–10; moderate: 11–20; severe: >20); CMT, Charcot-Marie-Tooth neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies. In bold, the novel mutations are indicated. SIFT, sorting intolerant from tolerant algorithm; PolyPhen-2, polymorphism phenotyping version 2; Provean Sift, protein variation effect analyzer; S, segregation analysis was performed in the patient’s family. Families are marked with F followed by the family number.
Table 2. Additional symptoms and features identified in our CMT cohort (N = 49).

| Mutated gene | MPZ | PMP22 (CMT1A) | PMP22 (HNPP) | GJB1 | NEFL | INF2 | LITAF | MFN2 |
|--------------|-----|----------------|--------------|------|------|------|-------|------|
| Number of patients | 11  | 19             | 9            | 4    | 1    | 1    | 2     | 2    |
| Tremor       | + (P3) | + (P30, 35, 38, 41, 45) | + (P19, 22, 24) | + (P14, 17) | –    | –    | + (P13) | + (P49) |
| UL predominant | –  | –             | –            | –    | –    | –    | –     | –    |
| Scoliosis    | + (P1, 2, 4) | + (P29, 31, 35, 39, 41, 42, 43, 45) | + (P25) | + (P15) | –    | –    | + (P12*) | –    |
| Hand deformities | + (P1, 10) | + (P40) | –    | –    | –    | –    | –     | –    |
| Skeletal deformities | –  | Hip dysplasia bilat. (P33, 42, 45) | –    | –    | –    | –    | –     | –    |
| Deafness     | –  | + (P35) | –    | –    | –    | –    | –     | –    |
| Cognitive impairment | + (P1, 7) | + (P30) | –    | –    | –    | –    | –     | + (P13) |
| Bulbar       | –  | Dysphagia (P35) | –    | –    | –    | –    | –     | –    |
| Fasciculations | + (P10) | –    | + (P19) | –    | –    | –    | –     | –    |
| Facial weakness | –  | + (P28, 30, 32, 45) | + (P18) | –    | –    | –    | –     | –    |
| Pain         | + (P1, 7) | + (P31, 34, 35, 36, 39, 40, 41, 45) | + (P22) | + (P14, 15) | –    | –    | + (P12*, 13) | + (P48) |
| Paresthesia  | + (P1, 5, 6, 7) | + (P27, 32, 35, 38, 40, 41) | + (P19, 26) | + (P14, 17) | + (P46) | –    | + (P12*, 13) | + (P48) |
| Early onset  | + (P1) | –    | –    | –    | –    | –    | –     | –    |
| Eye involvement | Pupillary (P2, 4, 5) | –    | –    | –    | –    | –    | –     | –    |
| CTS          | + (P4, 7) | + (P40, 45) | + (P24) | –    | –    | –    | –     | + (P13) |
| Respiratory insufficiency | Restrictive + (P10) | + (P30), elevated daphagm (P37) | –    | –    | –    | –    | –     | –    |
| Autonomic    | Bladder urgency (P1), postural hypotension (P7), urinary incon-tinence (P7), hyperhidrosis (P11) | Incontinence (P36), hyperhidrosis (P38), postural hypotension (P34) | Slowed emptying of stomach (P20) | –    | –    | –    | Postural hypotension (P13) | Bladder urgency (P49) |
| Brain MRI    | Vascular leuencecephalopathy and plump lateral ventricles (P6, MRI at age 65y) | –    | –    | –    | –    | –    | –     | –    |
| Hypertrophic nerve roots | + (P2, 4, 6) | –    | –    | –    | –    | –    | –     | –    |
| RLS          | + (P1) | + (P40, 45) | + (P24, 26) | + (P17) | –    | –    | –     | + (P12*, 13) |
| Cold-induced hand cramps | + (P7) | + (P39, 40) | + (P24) | –    | –    | –    | –     | + (P48) |
| ESRD, proteinuria, GS | –    | –    | –    | –    | –    | –    | –     | + (P48) |

CMT1A, Charcot–Marie–Tooth neuropathy type 1A; HNPP, hereditary neuropathy with liability to pressure palsies; P, patient; UL, upper limb; bilat., bilateral; CTS, carpal tunnel syndrome; MRI, magnetic resonance imaging; RLS, restless legs syndrome; ESRD, end-stage renal disease; GS, glomerular sclerosis.

*Multiple sclerosis as additional disease in this patient. For abbreviations of genes, see text and Table 1.
in 13 (range 11–20), and severe in 17 cases (>20). Genetic data, CMTNS2 scores, and CMT subtype of the patients are summarized in Table 1.

**Associated symptoms and signs**

The additional features that were ascertained in our CMT patient cohort are listed in Table 2. A total of 65% (32/49) of the patients presented two or more additional symptoms, 23% (11/49) had one, and 12% (6/49) expressed no additional features (Table 2).

**Hypertrophic cauda equina or nerve roots**

MRI of the spine revealed a hypertrophic cauda equina in three patients with a mutation in MPZ (CMT1B): in a brother and sister (patients 2 and 4) belonging to family 1 and in a third unrelated patient with a distinct MPZ mutation (patient 6) (Tables 1 and 2; Fig. 1). The affected father of patients 2 and 4 (patient 3) was not available for MRI examination and patient 10, who harbored the same MPZ mutation as patient 6, could not undergo the examination due to marked respiratory insufficiency. We did not find hypertrophic nerve roots or cauda fascicles in the two patients with a mutation in LITAF (CMT1C), who underwent a cervical (patient 12) or lumbar MRI (patient 13). In the other study patients, a spinal MRI was not performed. Hypertrophy of cranial nerves was not additionally revealed on brain MRI in patients 2 and 6, neither in the other patients (patients 1, 5 12, 22) in whom a brain MRI was available (Table 2).

**Clinical presentation of the three patients with MPZ mutation and hypertrophic nerve roots**

Patients 2 and 4 (brother and sister) had disease onset in childhood (patient 2) and at 38 years of age (patient 4) and patient 6 at 62 years (Table 1). They presented typical symptoms and signs of CMT. Additional symptoms were scoliosis, anisocoric, and tonic pupils in patient 2, bilateral carpal tunnel syndrome (CTS), tonic pupils, and scoliosis in patient 4, and a sleep apnea syndrome in…

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**Figure 1.** Thoraco-lumbo-sacral MRI and sural nerve biopsies in three CMT1B patients with MPZ-mutation and hypertrophic cauda equina/nerve roots. (A–C) T2-weighted sagittal sections of the thoracal, lumbar, and sacral spinal column in patients 6 (A), 4 (B), and 2 (C), indicating the thickened nerve roots of the cauda equina (arrows). This is also shown for patient 2 at a T1-weighted sagittal section (D) and a T1-weighted coronal section (E). Arrow heads show congested intraspinal vessels. (F–H) T2-weighted axial sections at the level of the fourth lumbar vertebral body (L4) of patients 6 (F), 4 (G) and 2 (H), showing extensive hypertrophic nerve roots of the cauda equina inside the spinal column. (I–K) Nerve Biopsy pictures of patients 6 (I, J) and 2 (K) with (J) being a magnification of (I). Arrow heads show onion bulb formations, the arrow points toward a remaining hypomyelinated nerve fiber. Notice the extensive loss of the large myelinated fibers.
patient 6. Pupils could not be evaluated in patient 6 due to previous bilateral cataract surgery. Patient 4 complained of lower back pains and patient 6 of occasional lumbar pain radiating in the legs, which can be explained by the hypertrophic lumbar nerve roots.

NCVs were within the range of demyelinating CMT with motor NCV in the upper limbs of 19 m/sec (patient 2), 26 m/sec (patient 4), and 18 m/sec (patient 6). Liquor analysis in patients 2 and 6 revealed elevated protein levels (1.45 g/L and 0.46 g/L, respectively, normal value 0.15–0.45 g/L), and was not performed in patient 4. Spinal MRI in the three patients demonstrated bilaterally multiple enlarged nerve roots within the spinal column at the lumbar and sacral level (Fig. 1A–H), leading to congested intraspinal vessels (Fig. 1A–C and E). Sural nerve biopsies showed a prominent loss of large myelinated fibers (Fig. 1I–K), as well as Schwann cells forming multiple layers of myelin sheaths around lost fibers leading to onion bulb formations (Fig. 1J and K).

Our revision of the literature revealed the occurrence of hypertrophic nerve roots at the cervical and/or lumbar spine in association with MPZ mutations: c.306delA in two patients and c.167G>A in another two cases, as well as PMP22 gene alterations in five cases, of which three patients with PMP22 duplication, one with a homozygous PMP22 duplication, and one carrying a PMP22 point mutation (Appendix S1). In our study, we added two distinct MPZ mutations associated with this feature (Table 1). Furthermore, hypertrophy of the cranial nerves has also been described in two patients with a MPZ mutation and in another two with a PMP22 gene deletion (Appendix S1).

Restless legs syndrome

Restless legs syndrome (RLS) was present in nine patients of our cohort (18%), five females and four males, aged 27, 32, 33, 39, 51, 54, 56, 63, and 65 years. They carried a mutation in the MPZ, GJB1, or MFN2 gene (one patient each), in LITAF (two patients), or a PMP22 duplication (two patients) or deletion (two patients). CMT patients with RLS had CMTNS2 scores ranging from mainly severe (patient 1, 40, 45, 13), to moderate (patient 17) or mild neuropathy (patient 12) (Table 1).

In the literature, RLS has been associated with three different CMT genes (Appendix S1), among them also the genes that we have identified in our patient group, except for the LITAF and MFN2 genes that were novel findings in our study.

Respiratory insufficiency and scoliosis

In patient 10 with CMT2-I/J caused by a MPZ mutation, a severe restrictive respiratory insufficiency with vital capacity of 1.2 L (36.8% of the theoretical value) leading to severe dyspnea and orthopnea was diagnosed at the age of 48 years. Respiratory symptoms started at least 6 years before. Neurological examination at 48 years revealed distally pronounced weakness and sensory loss, pes cavus, clawed hands, and fasciculations at the extremities. She reported onset of CMT symptoms between 20 and 25 years of age. Due to pronounced orthopnea, the patient was not able to lie down, slept in sitting position, and needed a CPAP mask for sufficient oxygenation. Interestingly, patient 6 with the same R98H mutation in MPZ showed no signs of respiratory compromise (Table 2). Furthermore, we diagnosed respiratory insufficiency with a vital capacity of 1.91 L (54% of the theoretical value) at 25 years of age in patient 30 harboring a PMP22 duplication. CMTNS2 scores were severe in both patients (Table 1). They did not have a scoliosis as a possible cause of respiratory problems.

Mild scoliosis was noted in 14 patients and in one patient (patient 41, CMT1A), scoliosis was severe, necessitating a surgical correction. Three had a mutation in MPZ (CMT1B), eight had a PMP22 duplication, one a PMP22 point mutation, one a PMP22 deletion, one carried a GJB1 mutation, and one patient had a mutation in LITAF (Table 2).

Literature findings revealed that respiratory insufficiency and scoliosis are frequent additional features in many different CMT subtypes including those that we have detected (Appendix S1).

Pupillary abnormalities

Pupillary abnormalities were noticed in three of our patients with a MPZ mutation. Two of them had the CMT1B phenotype (patients 2 and 4) and showed tonic pupils and/or anisocoria. The third patient, with CMT2 I/J (patient 5), presented tonic pupils, anisocoria, and mydriasis (Table 2). In patients 3 and 6, reactions to light were not measurable because of a previous bilateral cataract surgery. CMTNS2 scores in our patients with pupillary abnormalities were in the range of mild (patients 4 and 5) or moderate (patient 2) neuropathy severity (Table 1).

Our literature review revealed that pupillary abnormalities have been reported with mutations in 10 different CMT-causing genes (Appendix S1). Most frequently occurring abnormalities are tonic pupils [PMP22, MPZ, GJB1, SH3 domain, and tetrameric peptide repeat domain 2 (SH3TC2) gene, set-binding factor 1 (SBFI) gene], or an impaired pupillary reaction [transient receptor potential cation channel subfamily V, member 4 (TRPV4) gene, NMYC downstream-regulated gene 1 (NDRG1) gene]. Furthermore, anisocoria [PMP22, MPZ, MFN2, SH3TC2;
FYVE, RhoGEF, and PH domain-containing protein 4 (FGD4) gene, miosis (PMP22, MPZ) and mydriasis (MPZ) have been described previously.

Cold-induced hand cramps

In our cohort, cold-induced hand cramps were indicated during history taking by one patient with MPZ mutation (CMT1B, patient 7), two cases with PMP22 duplication (patients 39, 40), one patient with PMP22 deletion (patient 24), and one with a mutation in MFN2 (patient 48) (Table 2).

In contrast to our findings, literature data revealed this symptom only in association with a mutation in the glycyl-tRNA synthetase (GARS) gene (Appendix S1).

Focal segmental glomerular sclerosis

In one of the two patients with histologically proven FSGS and a polyneuropathy, we identified a pathogenic mutation in the INF2 gene (patient 47). Literature findings confirmed that renal problems and FSGS in particular in CMT patients occur so far exclusively in association with mutations in INF2. In addition, deafness, cerebral white matter hyperintensities, and enlarged ventricles have been described in association with INF2 mutations (Appendix S1). These features were, however, not present in our patient.

Summary of associated features in CMT

Considering our study cohort and literature data, we detected more than 80 different additional symptoms or signs associated with CMT (Appendix S1, Table 3). Table 3 summarizes the new findings in our cohort compared to the literature (Table 3).

Regarding the additional features of all CMT-causing genes described in the literature, many additional features were reported in association with many distinct CMT-causing genes, for example, vocal cord involvement, tremor, scoliosis, hand deformities (claw hands and/or finger contractures), deafness, cognitive impairment, bulbar symptoms, fasciculations, facial weakness, early proximal weakness, pain, paresthesias, early onset CMT, pupillary abnormality, ophthalmoparesis, respiratory failure/distress, SAS, dysmorphic features, central nervous system/cranial nerve involvement, brain imaging abnormality, white matter involvement, severe slow NCV, and kyphosis/lordosis (Table 3, Appendix S1).

On the contrary, other additional symptoms were described in a single patient or family only and in association with only one gene, such as optic neuritis, chronic vomiting, bowel dysfunction, mutilating arthropathy, nocturnal vomiting, hyperkeratosis, myokymia, cardiac insufficiency and cardiomyopathy, involuntary movements, edema, self-abusive behavior, acrocyanosis, lactic acidosis under fasting conditions, and slowed emptying of stomach (Appendix S1).

Link between additional features and gene function?

We studied whether the occurrence of certain additional symptoms might be related to mutations in genes that express a similar function. We considered as distinct functional groups (Azzedine et al. 2012; Timmerman et al. 2013): genes expressing a role in myelination, mitochondrial functioning, cytoskeletal stability and motor proteins, RNA and protein metabolism, protein folding, membrane traffic, transcription regulation, channel or transporter and other/unknown (Appendix S1). However, we did not find a correlation between the additional features and the function of the causative genes.

Mutations identified in our cohort compared with the same mutations reported in the literature

We compared the clinical phenotype and in particular the associated features related to the mutations identified in our cohort with literature findings on the same mutations (Appendix S2). If clinical data were not available in addition to the mutation in the literature, the respective publication was not included in the Appendix S2.

Discussion

We showed that the majority of CMT patients presented one or more feature in addition to the classical CMT phenotype. Several additional features revealed by our study, such as hypertrophic nerve roots and RLS, seem to be underestimated. Their occurrence broaden the clinical spectrum and genotype–phenotype associations in CMT.

Methodological issues of our study and future perspectives

Due to the partly retrospective nature of our study, some data such as MRI images or nerve biopsies were lacking in some patients. Furthermore, although our overall patient cohort was large considering the rarity of the disease, some of the subgroups, such as CMT1F and CMT2A2, were small. However, we additionally included in our study all data of the currently available literature (in total 280 papers, Table 3, Appendices S1 and S2), in order to obtain more data and larger subgroups. Our
results are very interesting, but prospective larger multicenter studies will be necessary in the future to confirm our findings.

**Hypertrophic nerve roots as additional finding in patients with CMT**

Hypertrophic nerve roots can occur in hereditary disorders (e.g., CMT1, CMT3, neurofibromatosis), infectious or inflammatory neuropathies, neoplastic nerve disorders, and diverse acquired diseases such as amyloidosis (Ginsberg et al. 1995). Hypertrophied nerve roots in CMT have been reported previously by using pathological, ultrasonographic, and MRI examinations (Andermann et al. 1962; Symonds and Blackwood 1962; Marchini et al. 2009; Sugimoto et al. 2013). Thus, the presence of hypertrophic nerve roots in CMT is not new, and is probably often not reported since there is rarely a compelling reason to perform MRI in patients with CMT. So far, two CMT-causing genes, PMP22 and MPZ, have been related to this feature (Butefisch et al. 1999; Kleopa et al. 2002; Simonati et al. 2002; Marchini et al. 2009) (Table 3, Appendix S1). Also in our cohort, three CMT1B patients with a MPZ mutation presented a hypertrophic cauda equina. In contrast to another case in which the hypertrophic nerve roots and cauda resulted in a compression with severe symptoms and improvement by surgery (Kleopa et al. 2002), our patients did not show signs of medullar compression. Interestingly, we observed hypertrophic nerve roots in two relatives with CMT1B (brother and sister, family 1) as well as in a third unrelated individual. The two mutations in the MPZ gene that were associated with this feature in our study (Table 1), have been described in the literature before; however, in those cases,

### Table 3. Additional features identified in our CMT cohort and occurrence in the literature.

| Category                        | Associated Genes                      |
|---------------------------------|---------------------------------------|
| **Autonomous**                  | PMP22, MPZ, FN2, LRSAM1, TRPV4, SBF1  |
| **Urgency/incontinence**        | PMP22, MPZ, LITAF                     |
| **Postural hypotension**        | PMP22, MPZ, FN2, GARS                 |
| **Hyperhidrosis**               | PMP22, MPZ, FN2, GARS                 |
| **Cold-induced hand cramps**    | PMP22, MPZ, FN2, GARS                 |
| **Carpal tunnel syndrome**      | PMP22, MPZ, PRX, LITAF, FIG, TRPV4, FBLN5 |
| **Deafness**                    | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Early onset**                 | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Eye: Pupillary**              | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Facial weakness**             | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Fasciculations**              | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Hand deformities**            | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **MRI, brain: White matter involvement** | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **MRI, spinal: Hypertrophic nerve roots** | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Pain**                        | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Paresthesia**                 | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Renal problems**              | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Respiratory insufficiency**   | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Restless legs syndrome**      | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Skeletal: Congenital hip dysplasia** | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Skeletal: Hyperkyphosis**     | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Skeletal: Scoliosis**         | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Skeletal: Ulnar deviation of hands** | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Tremor**                      | PMP22, MPZ, FN2, GDN1, GARS, SLC12A6, AIFM1 |
| **Upper limb predominant**      | LITAF, GARS                           |

Bold: new findings in current patient cohort; italics and underlined: findings in current study that have been reported previously; not underlined, not italics and not bold: literature findings. CMT, Charcot-Marie-Tooth neuropathy; U, urinary. Additional features are listed in alphabetical order.
hypertrophic nerve roots were not reported (Appendix S2). Hypertrophic nerve roots in CMT1B-patients were mainly described in isolated cases (Kleopa et al. 2002; Simonati et al. 2002) and in only one family comprising a father and his two affected daughters carrying the Val102 fs mutation in MPZ (Marchini et al. 2009). Hypertrophic nerve roots caused by mutations in MPZ were not only found in association with the CMT1B phenotype, but also with congenital hypomyelinating neuropathy (CHN) (Simonati et al. 2002) and Dejerine-Sottas neuropathy (DSS) (Kleopa et al. 2002). Most authors presume that the thickening of nerve roots is due to a Schwann cell proliferation in the context of consistent demyelination over the years (Kleopa et al. 2002; Simonati et al. 2002). This explanation is further strengthened by the finding that the number of onion bulb formations in sural nerve biopsies, indicating active de- and remyelination, correlated with the occurrence of spinal nerve root enhancement and thickening on lumbosacral MRI in CMT patients (Cellerini et al. 2000).

**RLS as additional symptom in CMT**

RLS was present in 18% of our cohort, which was higher compared to the prevalence of 9.8% in the general population above 65 years of age (Rothdach et al. 2000). In our cohort, five females (19% of all females, aged 32, 51, 54, 56, and 65 years) and four males (18% of all males, aged 27, 33, 39, and 63 years) were affected. In contrast to these quite similar numbers, women in the general population were found to be affected twice as often as men (13.9% vs. 6.1%) (Rothdach et al. 2000) and also female CMT patients showed RLS more frequently than male CMT patients in previous studies (Boentert et al. 2010, 2014). The prevalence of RLS has previously been shown to be significantly increased in hereditary neuropathies, including CMT1, CMT2, CMTX, and HNPP (Hattan et al. 2009). Since RLS is frequently associated with peripheral neuropathy in general, our findings were, however, to be expected (Hattan et al. 2009). In our cohort, eight out of nine patients with RLS harbored demyelinating subtypes with mutations in the MPZ (n = 1), GJB1 (n = 1), or LITAF gene (n = 2) or a PMP22 duplication (n = 2) or deletion (n = 2) and one patient with RLS displayed an axonal neuropathy with MFN2 gene mutation (Table 2). In the literature, RLS was described in cohorts consisting of CMT patients with PMP22 duplication and MPZ or GJB1 gene mutation (Appendix S1). Female CMT patients were also found to be more severely affected by RLS than men (Boentert et al. 2010, 2014). In our cohort, four patients suffering from RLS had severe (two male and two female, patient 1, 40, 45, 13), one moderate (male, patient 17), and one mild neuropathy (male, patient 12) (Table 1). One hypothesis is that axonal atrophy increases axonal excitability in primary sensory units of leg muscles which results in creeping sensations (Iannaccone et al. 1995). As a consequence, this sensory input in the central nervous system may lead to the oscillatory leg movements typical for RLS (Iannaccone et al. 1995). This hypothesis links axonal atrophy with RLS. In CMT patients, axonal damage may occur in axonal subtypes as well as in demyelinating subtypes, where it develops consequently to the loss of myelin (Boentert et al. 2010). This might explain how CMT may predispose to RLS.

**Pupillary abnormalities as additional feature in CMT patients**

In our cohort, pupillary abnormalities were seen in three out of 11 patients with a MPZ gene mutation (27%): two CMT1B patients belonging to one family (patients 2 and 4) and one isolated CMT2-I/J patient (patient 5) (Tables 1 and 2). Their pupil changes became apparent at 51, 41, and 23 years of age, respectively. In another eight patients with MPZ gene mutation, one CMT2 and seven CMT1, we did not detect pupil changes (Tables 1 and 2). Families and isolated CMT patients have been described with pupillary abnormalities harboring mutations in 10 different CMT-causing genes, including the MPZ gene (Table 3, Appendix S1). Certain MPZ mutations were found to be particularly associated with pupil abnormalities, such as the Thr124Met mutation leading to CMT2-I/J in most patients. This mutation is associated with a distinct clinical phenotype including late onset in the fourth or fifth decade, pupillary abnormalities, shooting pains, deafness, explicit sensory disturbances, rapid progression, various autonomic system involvement, and respiratory insufficiency (De Jonghe et al. 1999; Stojkovic et al. 2003). Patient 5 of our cohort also showed the CMT2-I/J phenotype with pupillary abnormalities associated with the novel MPZ mutation Gly123Ala (Table 1). She complained of painful paresthesia in the lower limbs, hands, and face, compatible with the lancinating pains described in patients with the Thr124Met mutation. In contrast, her disease symptoms already began in the third decade, disease progression was rather slow, and no further associated features such as deafness or autonomic system involvement were present (Table 2).

**Conclusions**

We conclude that additional features are present in the majority of CMT patients. In case of rather specific features, occurring in association with only one (e.g., renal problems) or a few different CMT genes (e.g.,
hypertrophic nerve roots, Table 3), they might be used to guide genetic diagnosis by performing one or only a few single-gene analyses. However, many other additional symptoms, such as hearing impairment or cognitive involvement, can present in association with a large number of distinct genes (Table 3, Appendix S1), which hampers a gene search based on the additional features. Therefore, in these cases, it might diagnostically be more efficient to directly perform novel genetic techniques (WES), in which a large number of genes can be tested at the same time. However, aside from additional clinical features, the mode of inheritance, NCVs, and pathological examination of nerve biopsies also remain important clues to molecular diagnosis in CMT.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

References

Ananth, U., Athena Diagnostics Inc. 1999. Personal data. http://www.molgen.ua.ac.be/cmtmutations/Mutations/Mutations.cfm
Andermann, F., D. L. Lloyd-Smith, H. Mavor, and G. Mathieson. 1962. Observations on hypertrophic neuropathy of Dejerine and Sottas. Neurology 12:712–724.
Azedine, H., J. Senderek, C. Rivolta, and R. Chrast. 2012. Molecular genetics of charcot-marie-tooth disease: from genes to genomes. Mol. Syndromol. 3:204–214.
Boentert, M., R. Dwiesaw, A. Heidbreder, S. Happe, I. Kleffner, S. Evers, et al. 2010. Fatigue, reduced sleep quality and restless legs syndrome in Charcot-Marie-Tooth disease: a web-based survey. J. Neurol. 257:646–652.
Boentert, M., K. Knop, C. Schuhmacher, B. Gess, A. Okegov, and P. Young. 2014. Sleep disorders in Charcot-Marie-Tooth disease type I. J. Neurol. Neurosurg. Psychiatry 85:319–325.
Bort, S., E. Nelis, V. Timmerman, T. Sevilla, A. Cruz-Martinez, F. Martinez, et al. 1997. Mutational analysis of the MPZ, PMP22 and Cx32 genes in patients of Spanish ancestry with Charcot-Marie-Tooth disease and hereditary neuropathy with liability to pressure palsies. Hum. Genet. 99: 746–754.
Boyer, O., F. Nevo, E. Plaisier, B. Funalot, O. Gribouval, G. Benoit, et al. 2011. INF2 mutations in Charcot-Marie-Tooth disease with glomerulopathy. N. Engl. J. Med. 365: 2377–2388.
Butefisch, C., L. Gutmann, and L. Gutmann. 1999. Compression of spinal cord and cauda equina in Charcot-Marie-Tooth disease type 1A. Neurology 52:890–891.
Cellerini, M., S. Salti, V. Desideri, and G. Marconi. 2000. MR imaging of the cauda equina in hereditary motor sensory neuropathies: correlations with sural nerve biopsy. AJNR Am. J. Neuroradiol. 21:1793–1798.
Chance, P. F., M. K. Alderson, K. A. Leppig, M. W. Lensch, N. Matsunami, B. Smith, et al. 1993. DNA deletion associated with hereditary neuropathy with liability to pressure palsies. Cell 72:143–151.
Chung, K. W., S. B. Kim, K. D. Park, K. G. Choi, J. H. Lee, H. W. Eun, et al. 2006. Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. Brain 129:2103–2118.
Davis, C. J., W. G. Bradley, and R. Madrid. 1978. The peroneal muscular atrophy syndrome: clinical, genetic, electrophysiological and nerve biopsy studies. I. Clinical, genetic and electrophysiological findings and classification. J. Genet. Hum. 26:311–349.
De Jonghe, P., V. Timmerman, C. Ceuterick, E. Nelis, E. De Vriendt, A. Lofgren, et al. 1999. The Thr124Met mutation in the peripheral myelin protein zero (MPZ) gene is associated with a clinically distinct Charcot-Marie-Tooth phenotype. Brain 122(Pt 2):281–290.
Eggars, S. D., S. C. Keswani, G. Melli, and D. R. Cornblath. 2004. Clinical and genetic description of a family with Charcot-Marie-Tooth disease type 1B from a transmembrane MPZ mutation. Muscle Nerve 29:867–869.
Fabrizi, G. M., M. Pellegrini, C. Angiari, T. Cavallaro, A. Morini, F. Taioli, et al. 2006. Gene dosage sensitivity of a novel mutation in the intracellular domain of P0 associated with Charcot-Marie-Tooth disease type 1B. Neuromuscul. Disord. 16:183–187.
Gabreels-Festen, A. A., J. E. Hoogendijk, P. H. Meijerink, F. J. Gabreels, P. A. Bolhuis, S. van Beersum, et al. 1996. Two divergent types of nerve pathology in patients with different P0 mutations in Charcot-Marie-Tooth disease type 1B. Neuromuscul. Disord. 6:761–765.
Gerding, W. M., J. Koetting, J. T. Epplen, and C. Neusch. 2009. Hereditary motor and sensory neuropathy caused by a novel mutation in LITAF. Neuromuscul. Disord. 19:701–703.
Ginsberg, L. A. D. Platts, and P. K. Thomas. 1995. Chronic inflammatory demyelinating polyneuropathy mimicking a lumbar spinal stenosis syndrome. J. Neurol. Neurosurg. Psychiatry 59:189–191.
Harding, A. E., and P. K. Thomas. 1980. The clinical features of hereditary motor and sensory neuropathy types I and II. Brain 103:259–280.
Hattan, E., C. Chalk, and R. B. Postuma. 2009. Is there a higher risk of restless legs syndrome in peripheral neuropathy? Neurology 72:955–960.

Hattori, N., M. Yamamoto, T. Yoshihara, H. Koike, M. Nakagawa, H. Yoshikawa, et al. 2003. Demyelinating and axonal features of Charcot-Marie-Tooth disease with mutations of myelin-related proteins (PMP22, MPZ and Cx32): a clinicopathological study of 205 Japanese patients. Brain 126:134–151.

Iannaccone, S., M. Zucconi, P. Marchetti, L. Ferini-Strambri, R. Nemni, A. Quattrini, et al. 1995. Evidence of peripheral axonal neuropathy in primary restless legs syndrome. Mov. Disord. 10:2–9.

Kleopa, K. A., L. N. Sutton, J. Ong, G. Tennekoon, and A. E. Telféian. 2002. Conus medulla-cauda compression from nerve root hypertrophy in a child with Dejerine-Sottas syndrome: improvement with laminectomy and duraplasty. Case report. J. Neurosurg. 97:244–247.

Lupski, J., R. M. de Oca-Luna, S. Slaugenhaupt, L. Pentao, V. Guzzetta, B. J. Trask, et al. 1991. DNA duplication associated with Charcot-Marie-Tooth disease type 1A. Cell 66:219–232.

Mademan, I., T. Deconinck, A. Dinopoulos, T. Voit, U. Schara, K. Devriendt, et al. 2013. De novo IN2 mutations expand the genetic spectrum of hereditary neuropathy with glomerulopathy. Neurology 81:1953–1958.

Marchini, C., S. Z. Marsala, M. Bendini, F. Taioli, G. Damante, I. R. Lonigro, et al. 2009. Myelin protein zero Val102 fs mutation manifesting with isolated spinal root hypertrophy. Neumusculos. Disord. 19:849–852.

Mersiyanova, I. V., A. V. Perepelov, A. V. Polyakov, V. F. Sinitikov, E. L. Dadali, R. B. Oparin, et al. 2000. A new variant of Charcot-Marie-Tooth disease type 2 is probably the result of a mutation in the neurofilament-light gene. Am. J. Hum. Genet. 67:37–46.

Murphy, S. M., D. N. Herrmann, M. P. McDermott, S. S. Scherer, M. E. Shy, M. M. Reilly, et al. 2011. Reliability of the CMT neuropathy score (second version) in Charcot-Marie-Tooth disease. J. Peripher. Nerv. Syst. 16:191–198.

Numakura, C., C. Lin, T. Ikegami, P. Guldberg, and K. Hayasaka. 2002. Molecular analysis in Japanese patients with Charcot-Marie-Tooth disease: DGGE analysis for PMP22, MPZ, and Cx32/GJB1 mutations. Hum. Mutat. 20:392–398.

van Paassen, B. W., A. J. van der Kooi, K. Y. van Spanenook-Zwartz, C. Verhamme, F. Baas, and M. de Visser. 2014. PMP22 related neuropathies: Charcot-Marie-Tooth disease type 1A and hereditary neuropathy with liability to pressure palsies. Orphanet J. Rare Dis. 9:38.

Raeymeekers, P., V. Timmerman, E. Nelis, P. De Jonghe, J. E. Hoogendijk, F. Baas, et al. 1991. Duplication in chromosome 17p11.2 in Charcot-Marie-Tooth neuropathy type 1a (CMT 1a). The HMSN Collaborative Research Group. Neuromuscul. Disord. 1:93–97.

Roos, A., J. Weis, R. Korinthenbergh, H. Fehrenbach, M. Hauser, S. Zuchner, et al. 2015. Inverted formin 2-related Charcot-Marie-Tooth disease: extension of the mutational spectrum and pathological findings in Schwann cells and axons. J. Peripher. Nerv. Syst. 20:52–59.

Rossor, A. M., J. M. Polke, H. Houlden, and M. M. Reilly. 2013. Clinical implications of genetic advances in Charcot-Marie-Tooth disease. Nat. Rev. Neuro. 9:562–571.

Rothdach, A. J., C. Trenkwalder, J. Haberstock, U. Keil, and K. Berger. 2000. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and morbidity in Augsburg elderly. Neurology 54:1064–1068.

Schroder, J. M. 2001. Pathology of peripheral nerves. An atlas of structural and molecular pathological changes.

Simonati, A., G. M. Fabrizi, F. Taioli, A. Polo, R. Cerini, and N. Rizzuto. 2002. Dejerine-Sottas neuropathy with multiple nerve roots enlargement and hypomyelination associated with a missense mutation of the transmembrane domain of MPZ/P0. J. Neurol. 249:1298–1302.

Skre, H. 1974. Genetic and clinical aspects of Charcot-Marie-Tooth’s disease. Clin. Genet. 6:98–118.

Stojkovic, T., J. de Seze, O. Dubourg, M. C. Arne-Bes, S. Tardieu, J. C. Hache, et al. 2003. Autonomic and respiratory dysfunction in Charcot-Marie-Tooth disease due to Thr124Met mutation in the myelin protein zero gene. Clin. Neurophysiol. 114:1609–1614.

Street, V. A., G. Meekins, H. P. Lipe, W. K. Seltzer, G. T. Carter, G. H. Kraft, et al. 2002. Charcot-Marie-Tooth neuropathy: clinical phenotypes of four novel mutations in the MPZ and Cx 32 genes. Neuromuscul. Disord. 12:643–650.

Sugimoto, T., K. Ochi, N. Hosomi, T. Takahashi, H. Ueno, T. Nakamura, et al. 2013. Ultrasonographic nerve enlargement of the median and ulnar nerves and the cervical nerve roots in patients with demyelinating Charcot-Marie-Tooth disease: distinction from patients with chronic inflammatory demyelinating polyneuropathy. J. Neurol. 260:2580–2587.

Symonds, C. P., and W. Blackwood. 1962. Spinal cord compression in hypertrophic neuritis. Brain 85:251–260.

Timmerman, V., E. C. Clowes, and E. Reid. 2013. Overlapping molecular pathological themes link Charcot-Marie-Tooth neuropathies and hereditary spastic paraplegias. Exp. Neurol. 246:14–25.

Timmerman, V., A. V. Strickland, and S. Zuchner. 2014. Genetics of Charcot-Marie-Tooth (CMT) disease within the frame of the human genome project success. Genes 5:13–32.

Verhoeven, K., K. G. Claeyys, S. Zuchner, J. M. Schroder, J. Weis, C. Ceuterick, et al. 2006. MFN2 mutation distribution frame of the human genome project success. Genes 5:13–32.

Watanabe, M., N. Yamamoto, N. Ohkoshi, H. Nagata, Y. Kohno, A. Hayashi, et al. 2002. Corticosteroid-responsive asymmetric neuropathy with a myelin protein zero gene mutation. Neurology 59:767–769.
Weis, J., S. Brandner, M. Lammens, C. Sommer, and J. M. Vallat. 2012. Processing of nerve biopsies: a practical guide for neuropathologists. Clin. Neuropathol. 31:7–23.

Zuchner, S., I. V. Mersiyanova, M. Muglia, N. Bissar-Tadmouri, J. Rochelle, E. L. Dadali, et al. 2004. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat. Genet. 36:449–451.

Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1. Additional symptoms and features in patients with CMT reported in the literature.

Appendix S2. Phenotypic comparison of mutations found in our cohort with the literature.
## Appendix S1: Additional symptoms and features in patients with CMT reported in the literature.

| Mutated gene | Severe sensory | Vocal cords | Tremor | UL-predominant | Contrac-tures | Scoliosis | Hand deformities | Skeletal | Deafness | Cognitive impairment | Bulbar |
|--------------|----------------|-------------|--------|----------------|--------------|----------|------------------|----------|----------|---------------------|--------|
| PMF2         | -              | -           | +[1,2] | -              | +[5]         | +[1,2,4] | +[1,2]          | cong. hip dysplasia, ulnar deviated hand, lordosis[5], chest deformation[6] | +[1,2] | +[7]     | +[3,4]              |        |
| MF2          | +[8]           | +[9]        | +[10]  | -              | +[11]        | +[12,8,11] | +[8]             | chest deformity[13] | +[12,14] | +         | +[15,11]            |        |
| GJB1         | -              | -           | -[20]  | -              | -            | -         | -                | -        | +[12]    | +[21]               | +[21]  |
| PRK        | -              | -           | +[46]  | -              | +[46,47]     | +[48]     | kyphosis[49]     | +[47]    | -         | -                   |        |
| TFG2         | -              | +[25,26]    | +[27]  | -              | +[28]        | +[29,30]  | +[31,30]        | hip dysplasia[32] | +[25]    | +         | +[32,26]            |        |
| FLEXHGS      | -              | -           | -      | -              | -            | -         | -                | -        | -         | -                   | -       |
| MFN2         | -              | +[16]       | +[16]  | -              | +[16]        | -         | hyperlordosis, kyphosis[52] | +[16]    | +[18]    | +[168]              |        |
| GDAP1        | -              | +[51]       | -      | -              | +[51]        | -         | +[52]            | joint laxity[52], ulnar deviated hands, kyphosis[53] | -       | +[52]    | -                   |        |
| DHTKD1       | -              | -           | -      | -              | -            | -         | -                | -        | -         | -                   | -       |
| NFE2         | -              | -           | +[65]  | -              | -            | -         | +[65]            | partial syndactyly[56], ulnar deviated hands, kyphosis[57] | -       | -        | +[66]              | -       |
| NF1          | -              | -           | -      | -              | -            | -         | -                | -        | -         | -                   | -       |
| NF1          | -              | -           | -      | -              | -            | -         | -                | -        | -         | -                   | -       |
| PRPS1        | -              | -           | -      | -              | -            | -         | -                | -        | -         | -                   | -       |
| SBF1         | -              | -           | -      | -              | -            | -         | -                | -        | -         | -                   | -       |
| Mutated gene | Upper motor neuron | Fasciculations | Facial weakness | Early proximal weakness | Pain | Paresthesia | Early onset | Eye involvement | CTS | Respiratory |
|--------------|--------------------|----------------|----------------|-------------------------|------|-------------|-------------|----------------|------|-------------|
| FMP22        |                    | -              | [5]            | [5,2]                   | -    | [5,3]       | [5,3]       | optic neuritis[93], pupil.[5,3] | +   | diaphragm weakness[5,2], respiratory failure, resp. distress at birth[3] |
| MPZ          |                    | -              | +[94,95]       | +[15,96]                | -    | +[97,98]    | [97,98]     | pupil[12,98], ophtalmoparesis[94], optic atrophy[167] | +   | respiratory failure[97,100,95], chronic cough[101], resp. distress neonatal[15,11], resp. obstruction, stridor[9] |
| GJB1         | +[21]              | -              | -              |                         | -    | -           | [21]        | pupil.[102] | -   | -           |
| PRX          | -                  | +[to][47]      | -              | +[47]                   | -    | +[48,109]   | [48]        | glaucoma[110] | +[46] | restr. resp. failure[110] |
| EGR2         | +[26]              | +[26]          | +[104]         | -                       | -    | -           | +[26]       | ophtalmoparesis[25,26], strabisinus[25,32,105], pupil.[26] | -   | restrictive pulmonary disease, resp. failure (with death)[26] |
| PLEKHG5      |                    | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| MNS2         | +[16]              | -              | +[17]          | +[16]                   | +[16]| -           | [17]        | bilat. optic atrophy[16], ophtalmoparesis[18], pupil.[102] | -   | resp. failure[103] |
| GADAP1       | -                  | -              | +[52]          | -                       | +[112]| -           | +[52]       | optic atrophy[112] | -   | diaphragm weakness, resp. failure[52] |
| PDK2         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| SURF1        | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| DHTKDH       | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| LEM2         | -                  | -              | -              | +[65]                   | -    | +[65]       | -           | -              | -   | -           |
| EFTB         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| DYNC1H1      | -                  | -              | +[77]          | +[77]                   | -    | -           | +[77]       | -              | -   | -           |
| LRRA1        | -                  | +[123]         | -              | -                       | -    | -           | -           | -              | -   | -           |
| LRR1         | +[24]              | +[23]          | +[22]          | -                       | -    | -           | [22]        | -              | -   | -           |
| KHRP         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| GARS         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| RARS         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| MARS         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| BROS         | -                  | -              | -              | +[129]                  | -    | -           | -           | -              | -   | -           |
| VAR1         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| HNF4A        | -                  | +[ext][32]     | -              | -                       | -    | -           | -           | -              | -   | -           |
| LRESA4       | -                  | +[ext][28]     | -              | -                       | -    | -           | -           | -              | -   | -           |
| SHH1C1       | -(to)[43]          | +[106]         | +[43]          | +[44]                   | -    | +[43]       | pupil.[106] | -              | -   | resp. failure[107], left diaphragm paralysis[108] |
| FAB1         | -                  | +(to)[111]     | -              | -                       | +[59]| -           | -           | -              | -   | -           |
| HG2          | -                  | +[60]          | +[61]          | +[60]                   | +[60]| +[60]       | ophtalmoparesis[60] | +     | [115] | death due to resp. failure[116], elevated hemi-diaphragm[60] |
| DNM2         | -                  | -              | +[107]         | -                       | +[108]| +[119]      | cataracts, ophtalmoparesis, strabisinus[117] | -     | -    | -           |
| H2R2         | -                  | -              | +[67]          | +[68]                   | -    | +[120]      | -           | -              | -   | death due to resp. failure[68], chronic stridor[67] |
| LEF8         | +(ext)[69]         | +[69]          | +[69]          | +[69]                   | +[122]| -           | -           | -              | -   | -           |
| HMGU1        | -                  | -              | -              | +[71]                   | +[123]| -           | -           | -              | -   | resp. failure[69] |
| HMGU2        | -                  | -              | -              | -                       | +[71]| -           | -           | -              | -   | -           |
| GOLR1        | -                  | -              | +[86]          | -                       | -    | -           | -           | early-onset glaucoma[130] | -   | -           |
| RDSN2        | -                  | -              | +[113]         | -                       | -    | -           | +[114]      | pupil.[56] | -   | -           |
| DIS1         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| INSM1        | -                  | +[ext][91]     | -              | -                       | +[91]| -           | -           | -              | -   | -           |
| RSL1         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| HSD1A1       | -                  | -              | +[134]         | -                       | -    | -           | -           | -              | -   | -           |
| GPR10A       | -                  | -              | +[124]         | -                       | -    | -           | -           | -              | -   | -           |
| TRPM2        | -                  | +[33]          | +[33]          | -                       | -    | +[33]       | strabisinus[36], ophtalmoparesis[33], pupil.[36] | +     | [36] | intercostal weakness, stridor, resp. failure[33] |
| HLA-B        | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| HLA-C        | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| HLA-DQA1     | -                  | -              | -              | -                       | -    | +[89]       | -           | -              | -   | -           |
| HLA-DQB1     | -                  | -              | -              | -                       | -    | +[89]       | -           | -              | -   | -           |
| AIFEM1       | -                  | +[58]          | +[59]          | -                       | -    | -           | -           | -              | -   | strabisinus[99] |
| PRPS1        | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| FBLN3        | -                  | -              | -              | +[73]                   | -    | -           | -           | macular degeneration[72] | +[72] | resp. failure[72] |
| GNR4         | -                  | -              | -              | -                       | -    | -           | -           | -              | -   | -           |
| SBF1         | -                  | -              | +[83]          | -                       | -    | -           | -           | strabisimus, pupil.[85] | -   | -           |
Appendix S1 (continued): Additional symptoms and features in patients with CMT reported in the literature.

| Mutated gene | SAS | Autonomous involvement | Dys- | CNS/ | Brain imaging | WM involvement (MRI) | Severe slow nerve roots | Hyper- | Hyper- | Low blood cells | Additional |
|---------------|-----|------------------------|------|-------|--------------|----------------------|------------------------|-------|-------|----------------|------------|
| PMP2         | +   | ulcers[5], U+D urgency[136], U+D incontinence[6], OH, hyperhidrosis | +  | nystagmus[5,3], abnormal eye pursuit[5] | [137] | [7] | [138, 2, 4] | [136,2] | - | - | RLS[135], calf hypertrophy[1], cold induced hand cramps |
| MPZ          | +   | ED, OH, U urgency[97], U incontinence, atonic bladder[101], hyperhidrosis | - | - | plump lateral ventricles | + [139] | [12, 15,11] | [140, 141,142] | [143, 142] | - | - | RLS[135], calf hypertrophy[12], asymmetric weakness[144], cold induced hand cramps |
| GJB1         | +   | - | transient leukencephalopathy[151], stroke-like episodes[152], ataxia[21], tremor, dysdiadochokinesia, saccadic pursuit, nystagmus, dysmetria[148] | cerebellar/spinal cord atrophy [148] | +[151] | - | - | - | - | - | RLS[135], asymmetric weakness[153] |
| PRX          | -   | - | dysemetria, nystagmus, hypidiadokinesia, [46] | large cisterna magna[48] | - | [46, 109] | - | - | - | cardiac insufficiency+ cardiomyopathy [47] |
| EGR2         | -   | - | nystagmus[105] | - | - | +[104, 105] | - | - | - | - |
| PLEXHGS      | -   | - | - | - | - | - | - | - | - | - |
| MFN2         | -   | ED, hyperhidrosis [145], bladder urgency | +  | fatal subacute encephalopathy[147], dysemetria, dysdiadochokinesia, saccadic pursuit, nystagmus[148] | [146] | [16] | - | - | - | scapular winging [103], RLS, cold induced hand cramps |
| GDAP1        | +[52] | D incontinence D urgency[52], hyperhidrosis[54] | - | - | - | - | +[159] | - | - | - | - |
| FDNB         | -   | - | - | - | - | - | - | - | - | - |
| SURF1        | -   | - | nystagmus, cerebellar ataxia[90] | hyperintense lesions putamen+periaqueductal [90] | - | - | - | - | - | lactic acidosis under fasting conditions[90] |
| DHTKD1       | -   | - | - | - | - | - | - | - | - | - |
| NEF          | -   | - | - | - | enlarged ventricles [66] | [65] | - | - | - | nephrotic syndrome/ proteinuria, FSGS, ESRD[65] |
| KIF14        | -   | - | - | - | - | - | - | - | - | - | proximal > distal weakness, periscapular atrophy + weakness[77] |
| DYNCH1       | -   | - | - | - | - | - | - | - | - | - |
| LMNA         | -   | - | - | - | - | - | - | - | - | - |
| VEL1         | -   | chronic vomiting[22] | - | nystagmus, cerebellar ataxia[23] | enlarged ventricles, cerebellar atrophy[24] | - | - | - | - | hyperkeratosis [154], calf hypertrophy [155] |
| TRIM38       | -   | - | - | - | - | - | - | - | - | - |
| GARS         | -   | - | - | - | - | - | - | - | - | cold induced hand cramps[40] |
| GARS         | -   | - | - | - | - | - | - | - | - | - | self-abusive behavior, developmental delay[127] |
| KARS         | -   | - | - | - | - | - | - | - | - | - |
| MARS         | -   | - | - | - | - | - | - | - | - | - | proximal = distal weakness in LL[129] |
| HARS         | -   | - | - | - | - | - | - | - | - | - |
| HINT1        | -   | - | - | - | - | - | - | - | - | - | myokymia, neuromyotonia [132] |
| GRSAMA       | -   | U urgency, ED[128], mutilating arthropathy | - | - | - | - | - | - | - | - | - |
| Gene | # of References | Function | Symptoms | Other Findings |
|------|-----------------|----------|----------|---------------|
| HNPP  | [107]           | VII-X + XII cranial nerve involvement,[45], tongue atrophy + weakness[106] | unilateral brain atrophy[106] | +[43] +[107] |
| LADB  | -               | nystagmus[50] | cerebellar degeneration [50] | - |
| LHC  | +[60]           | tongue weakness[60] | cerebellar/brain atrophy[60] | - +[60] |
| DRSP  | -               | facial synkinesis[68], tongue atrophy, masticatory weakness[2] | - +[163] | acrocyanosis [164] |
| TFG   | -               | constipation [69] | myelin pallor in spinal cord columns [121] | - +[165] |
| ITDAR | -               | OH        | -        | RLS           |
| GLIA  | -               | + [126]  | myotonia, hyperlipidemia, acrocyanosis[164], myelination, hyperelastic skin[34] |
| NERF  | -               | cranial nerve involvement[87] | - | |
| NMHC  | -               | ulcer[s][113], bowel dysfunction[55] | nystagmus[160], tongue atrophy[113] | - +[114] +[161] |
| UMPK  | -               | coordination deficits, dysmetria, dyssodiaochokinesia, nystagmus[92] | cerebellar atrophy[92] | - +[114] |
| FBN1  | +[33]           | U incontinence + urgency[39] | abducens nerve palsy[156] | - |
| LCP2A | -               | nocturnal vomiting[88] | coordination deficits[88] | - +[89] |
| HR1   | -               | -        | corpus callosum agenesis, enlarged ventricles, brain atrophy[89] | +[89] |
| AIFM1 | -               | -        | -        | - |
| PRPS1 | -               | -        | -        | - |
| FBNL5 | -               | chronic diarrhea[72] | corneal nerves,[72] | - - - |
| GNB4  | -               | incontinence [85] | brain atrophy[85] | - |

Concerning PMP22: HNPP data are not included; cong. = congenital, CTS = carpal tunnel syndrome, pupill. = pupillary abnormality, resp. = respiratory, bilateral, to = tongue, restr. = restrictive, ext = extremities, tr = trunk, SAS = sleep apnea syndrome, CNS = central nervous system, WM = white matter, MRI = magnetic resonance imaging, NCV = nerve conduction velocity, RLS = restless legs syndrome, ED = erectile dysfunction, OH = orthostatic hypotension, U = urinary, D = defecatory, FSGS = focal segmental glomerular sclerosis, ESRD = end stage renal disease, LL = lower limbs. Bold: new findings in current patient cohort; underlined: findings in current study that have been reported previously; not underlined and not bold: literature findings. Colors of the genes indicate their function within the peripheral nervous system. Yellow: myelination; light blue: mitochondrial; green: cytoskeletal stability and motor proteins; pink: RNA and protein metabolism; dark blue: protein folding; red: membrane traffic; grey: other/unknown. Violet: Transcription regulation. Brown: Channel/Transporter. Severe slow NCV < 10 m/s. Early onset < 18 month of age. Chest deformity = other than scoliosis.
References:

1. van Paasen BW, van der Kooi AJ, van Spaendonck-ZwARTS KY, Verhamme C, Baas F, de Visser M (2014) PMP22 related neuropathies: Charcot-Marie-Tooth disease type 1A and Hereditary Neuropathy with liability to Pressure Palsies. Orphanet J Rare Dis 9:38.

2. Tyson J, Ellis D, Fairbrother U, King RH, Muntoni F, Jacobs J et al. (1997) Hereditary demyelinating neuropathy of infancy. A genetically complex syndrome. Brain 120 (Pt 1):47-63.

3. Hui-Chou HG, Hashemi SS, Hoke A, Dellon AL (2011) Clinical implications of peripheral myelin protein 22 for nerve compression and neural regeneration: a review. J Reconstr Microsurg 27 (1):67-74.

4. Simonati A, Fabrizi GM, Pasquinnelli A, Taïoli F, Cavallaro T, Morbin M et al. (1999) Congenital hypomyelination neuropathy with Ser72Leu substitution in PMP22. Neuromuscul Disord 9 (4):257-261.

5. Marques W, Jr., Freitas MR, Nascimento OJ, Oliveira AB, Calia L, Melo A et al. (2005) 17p duplicated Charcot-Marie-Tooth 1A: characteristics of a new population. J Neurol 252 (8):972-979.

6. Thomas PK, Marques W, Jr., Davis MB, Sweeney MG, King RH, Bradley JL et al. (1997) The phenotypic manifestations of chromosome 17p11.2 duplication. Brain 120 (Pt 3):465-478.

7. Chanson JB, Echaniz-Laguna A, Blanc F, Lacour A, Ballonzoli L, Kremer S et al. (2013) Central nervous system abnormalities in patients with PMP22 gene mutations: a prospective study. J Neurol Neurosurg Psychiatry 84 (4):392-397.

8. Warner LE, Hilz MJ, Appel SH, Killian JM, Kolody EH, Karpati G et al. (1996) Clinical phenotypes of different MPZ (P0) mutations may include Charcot-Marie-Tooth type 1B, Dejerine-Sottas, and congenital hypomyelination. Neuron 17 (3):451-460.

9. Benson B, Sulica L, Guss J, Blitzer A (2010) Laryngeal neuropathy of Charcot-Marie-Tooth disease: further observations and novel mutations associated with vocal fold paresis. Laryngoscope 120 (2):291-296.

10. Choi BO, Kim SB, Kanwal S, Hyun YS, Park SW, Koo H et al. (2011) MPZ mutation in an early-onset Charcot-Marie-Tooth disease type 1B family by genome-wide linkage analysis. Int J Mol Med 28 (3):389-396.

11. Smit LS, Rooftfoort D, van Ruissen F, Baas F, van Doorn PA (2008) Congenital hypomyelinating neuropathy, a long term follow-up study in an affected family. Neuro muscular Disord 18 (1):59-62.

12. Hattori N, Yamamoto M, Yoshihara T, Koike H, Nakagawa M, Yoshikawa H et al. (2003) Demyelinating and axonal features of Charcot-Marie-Tooth disease with mutations of myelin-related proteins (PMP22, MPZ and Cx32): a clinicopathological study of 205 Japanese patients. Brain 126 (Pt 1):134-151.

13. Kochanski A, Drac H, Kabzinska D, Ryniewicz B, Rowinska R, Barankova L, Vyhnalek M et al. (2004) A novel MPZ gene mutation in congenital neuropathy with hypomyelination. Neurology 62 (11):2122-2123.

14. Gabreels-Festen A (2002) Dejerine-Sottas syndrome grown to maturity: overview of genetic and morphological heterogeneity and follow-up of 25 patients. J Anat 200 (4):341-356.

15. Tachi N, Kozuka N, Ohya K, Chiba S, Yamashita S (1998) A small direct tandem duplication of the myelin protein zero gene in a patient with Dejerine-Sottas disease phenotype. J Neurol Sci 152 (2):167-171.

16. Choi BO, Lee MS, Shin SH, Hwang JH, Choi KG, Kim WK et al. (2004) Mutational analysis of PMP22, MPZ, GJB1, EGR2 and NEFL in Korean Charcot-Marie-Tooth neuropathy patients. Hum Mutat 24 (2):185-186.

17. Polke JM, Laura M, Pareyson D, Taroni F, Milani M, Bergamin G et al. (2011) Recessive axonal Charcot-Marie-Tooth disease due to compound heterozygous mitofusin 2 mutations. Neurology 77 (2):168-173.

18. Casasnovas C, Banchs I, Cassereau J, Gueguen N, Chevrollier A, Martinez-Matos JA et al. (2010) Phenotypic spectrum of MFN2 mutations in the Spanish population. J Med Genet 47 (4):249-256.

19. Li QH, Liu XX, Feng JL, Zeng AY, Li H, Wu L et al. (2010) [A new mutation in the GJB1 gene of a Chinese family with Charcot-Marie-Tooth disease associated with vocal cord paresis]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 27 (5):497-500.

20. Yuan MM, Geevainga N, Nicholson GA, Fagan ER, Ryan MM, Ouvrier RA (2011) A retrospective review of X-linked Charcot-Marie-Tooth disease in childhood. Neurology 76 (5):461-466.

21. Kleopa KA, Scherer SS (2006) Molecular genetics of X-linked Charcot-Marie-Tooth disease. NeuroMolecular Medicine 8 (1-2):107-122.

22. Jordanova A, Thomas FP, Guergueltcheva V, Tournev I, Gondim FA, Ishpekova B et al. (2003) Dominant intermediate Charcot-Marie-Tooth type C maps to chromosome 1p34-p35. Am J Hum Genet 73 (6):1423-1430.

23. Milettenberger-Milenyi G, Janecke AR, Wanschitz JV, Timmerman V, Windpassinger C, Auer-Grumbach M et al. (2007) Clinical and electrophysiological features in Charcot-Marie-Tooth disease with mutations in the NEFL gene. Arch Neurol 64 (7):966-970.

24. Abe A, Numakura C, Saito K, Koide H, Oka N, Honma A et al. (2009) Neurofilament light chain polypeptide gene mutations in Charcot-Marie-Tooth disease: nonsense mutation probably causes a recessive phenotype. J Hum Genet 54 (2):94-97.

25. Pareyson D, Taroni F, Botti S, Morbin M, Baratta S, Lauria G et al. (2000) Cranial nerve involvement in CMT disease type 1 due to early growth response 2 gene mutation. Neurology 54 (8):1696-1698.

26. SzigiT K, Wiszniewski W, Saifi GM, Sherman DL, Sule N, Adesina AM et al. (2007) Functional, histopathologic and natural history study of neuropathy associated with EGR2 mutations. Neurogenetics 8 (4):257-262.

27. Yoshihara T, Kanda F, Yamamoto M, Ishihara H, Misu K, Hattori N et al. (2001) A novel missense mutation in the early growth response 2 gene associated with late-onset Charcot–Marie–Tooth disease type 1. J Neurosci 18 (2):149-153.

28. Funalot B, Topilko P, Arroyo MA, Sfeiani A, Hedley-Whyte ET, Yoldi ME et al. (2012) Homozygous deletion of an EGR2 enhancer in congenital amyelinating neuropathy. Ann Neurol 71 (5):719-723.

29. Mikesova E, Huhne K, Rautenstrauss B, Mazanec R, Barankova L, Vyhnanek M et al. (2005) Novel EGR2 mutation R359Q is associated with CMT type 1 and progressive scoliosis. Neuro muscular Disord 15 (11):764-767.

30. Numakura C, Shirahata E, Yamashita S, Kanai M, Kijima K, Matsuki T et al. (2003) Screening of the early growth response 2 gene in Japanese patients with Charcot–Marie–Tooth disease type 1. Journal of the Neurological Sciences 210 (1-2):61-64.

31. Safka Brozkova D, Nevsimalova S, Mazanae R, Rautenstrauss B, Seenman P (2012) Charcot-Marie-Tooth neuropathy due to a novel EGR2 gene mutation with mild phenotype: usefulness of human mapping chip linkage analysis in a Czech family. Neuro muscular Disord 22 (8):742-746.

32. Boerkoel CF, Takashima H, Bacino CA, Daentl D, Lupski JR (2001) EGR2 mutation R359W causes a spectrum of Dejerine-Sottas neuropathy. Neurogenetics 3 (3):153-157.
33. McEntagart ME, Reid SL, Irrthum A, Douglas JB, Eyre KE, Donaghy MJ et al. (2005) Confirmation of a hereditary motor and sensory neuropathy IIC locus at chromosome 12q23-q24. Ann Neurol 57 (2):293-297.

34. Echaniz-Laguna A, Dubourg O, Carlier P, Carlier RY, Sabouraud P, Percey V et al. (2014) Phenotypic spectrum and incidence of TRPV4 mutations in patients with inherited axonal neuropathy. Neurology 82 (21):1919-1926.

35. Auer-Grumbach M, Olschewski A, Papic L, Kremer H, McEntagart ME, Uhrig S et al. (2010) Alterations in the ankyrin domain of TRPV4 cause congenital distal SMA, scaropuloeroneal SMA and HMSN2C. Nat Genet 42 (2):160-164.

36. Chen DH, Sul Y, Weiss M, Hille A, Lipe H, Wolff J et al. (2010) CMT2C with vocal cord paresis associated with short stature and mutations in the TRPV4 gene. Neurology 75 (22):1968-1975.

37. Dyck PJ, Litchy WJ, Minnerrath S, Bird TD, Chance PF, Schaid DJ et al. (1994) Hereditary motor and sensory neuropathy with diaphragm and vocal cord paresis. Ann Neurol 35 (5):608-615.

38. Aharoni S, Harlalka G, Offiah A, Shuper A, Crosby AH, McEntagart M (2011) Striking phenotypic variability in familial TRPV4-axonal neuropathy spectrum disorder. Am J Med Genet A 155A (12):3153-3156.

39. Landoue G, Zdebik AA, Martinez TL, Burnett BG, Stanescu HC, Inada H et al. (2010) Mutations in TRPV4 cause Charcot-Marie-Tooth disease type 2C. Nat Genet 42 (2):170-174.

40. Sambhughin N, Sivakumar K, Selenge B, Lee HS, Friedlich D, Baasanjav D et al. (1998) Autosomal dominant distal spinal muscular atrophy type V (dSMaV) and Charcot-Marie-Tooth disease type 2D (CMT2D) segregate within a single large kindred and map to a refined region on chromosome 7p15. J Neurol Sci 161 (1):23-28.

41. Ionesescu V, Searby C, Sheffield VC, Roklina T, Nishimura D, Ionescusa R (1996) Autosomal dominant Charcot-Marie-Tooth axonal neuropathy mapped on chromosome 7p (CMT7). Hum Mol Genet 5 (9):1373-1375.

42. Nakrho K, Park JM, Kim YJ, Yoon BR, Yoo HJ, Koo H et al. (2013) A novel Lys141Thr mutation in small heat shock protein 22 (HSPB8) gene in Charcot-Marie-Tooth disease type 2L. Neuromuscul Disord 23 (8):655-663.

43. Colomer J, Gooding R, Angelicheva D, King RH, Guillen-Navarro P, Parman Y et al. (2006) Clinical spectrum of CMT4C disease in patients homozygous for the p.Arg1109X mutation in SH3TC2. Neuromuscul Disord 16 (7):449-455.

44. Iguchi M, Hashiguchi A, Ito E, Toda K, Urano M, Shimizu Y et al. (2013) Charcot-Marie-Tooth disease type 4C in Japan: report of a case. Muscle Nerve 47 (2):283-286.

45. Yger M, Stojkovic T, Tardieu S, Maisonobe T, Brice A, Echaniz-Laguna A et al. (2012) Characteristics of clinical and electrophysiological pattern of Charcot-Marie-Tooth 4C. J Peripher Nerv Syst 17 (1):112-122.

46. Marchesi C, Milani M, Morbin M, Cesani M, Lauria G, Scaioli V et al. (2010) Four novel cases of periaxin-related neuropathy and review of the literature. Neurology 75 (20):1830-1838.

47. Takashima H, Boerkoel CF, De Jonghe P, Ceuterick C, Martin JJ, Vooi T et al. (2002) Periaxin mutations cause a broad spectrum of demyelinating neuropathies. Ann Neurol 51 (6):709-715.

48. Delagve V, Bareil C, Tuffery S, Bouvagnet P, Chouery E, Koussa S et al. (2000) Mapping of a new locus for autosomal recessive demyelinating Charcot-Marie-Tooth disease to 1q9.3-13.3 in a large consanguineous Lebanese family: exclusion of MAG as a candidate gene. Am J Hum Genet 67 (1):236-243.

49. Auer-Grumbach M, Fischer C, Papic L, John E, Plecko B, Bittner RE et al. (2008) Two novel mutations in the GDAP1 and PRX genes in early onset Charcot-Marie-Tooth syndrome. Neuropediatrics 39 (3):33-38.

50. Houlden H, King RH, Muddle JR, Werner TT, Reilly MM, Orrell RW et al. (2004) A novel RAB7 mutation associated with ulceromutilating neuropathy. Ann Neurol 56 (4):586-590.

51. Azzedine H, Ruberg M, Ente D, Giraldeau C, Perie S, Wechsler B et al. (2003) Variability of disease progression in a family with autosomal recessive CMT associated with a S194X and new R310Q mutation in the GDAP1 gene. Neuromuscul Disord 13 (4):341-346.

52. Sevilla T, Jaijo T, Naufal D, Collado D, Chumillas MJ, Vilchez JJ et al. (2008) Vocal cord paresis and diaphragmatic dysfunction are severe and frequent symptoms of GDAP1-associated neuropathy. Brain 131 (Pt 11):3051-3061.

53. Baxter RV, Ben Othmane K, Rochelle JM, Stajich JE, Hulett C, Dew-Knight S et al. (2002) Ganglioside-induced differentiation-associated protein-I is mutant in Charcot-Marie-Tooth disease type 4A/4q21. Nat Genet 30 (1):21-22.

54. Kabzinska D, Niemann A, Drac H, Huber N, Potulskas-Chromik A, Hausmanowa-Petrusequicz I et al. (2011) A new missense GDAP1 mutation disturbing targeting to the mitochondrial membrane causes a severe form of AR-CMT2C disease. Neurogenetics 12 (2):145-153.

55. Hunter M, Bernard R, Freitas E, Boyer A, Morar B, Martins IU et al. (2003) Mutation screening of the N-myc downstream-regulated gene 1 (NDRG1) in patients with Charcot-Marie-Tooth Disease. Hum Mutat 22 (2):129-132.

56. Kalaydjieva L, Nikolova A, Turnev I, Petrova J, Hristova A, Ishpekova B et al. (1998) Hereditary motor and sensory neuropathy-Lom, a novel demyelinating neuropathy associated with deafness in gypsies. Clinical, electrophysiological and nerve biopsy findings. Brain 121 (Pt 3):393-408.

57. Dackovic J, Keckarevic-Markovic M, Komazec Z, Rakovevic-Stojanovic V, Lavrnic D, Stivic Z et al. (2008) Hereditary motor and sensory neuropathy Lom type in a Serbian family. Acta Myol 27:59-62.

58. Thomas PK, Kalaydjieva L, Youl B, Rogers T, Angelicheva D, King RHM et al. (2001) Hereditary motor and sensory neuropathy-russe: New autosomal recessive neuropathy in balkan gypsies. Annals of Neurology 50 (4):452-457.

59. Sevilla T, Martinez-Rubido D, Marquez C, Paradas C, Colomer J, Jaijo T et al. (2013) Genetics of the Charcot-Marie-Tooth disease in the Spanish Gypsy population: the hereditary motor and sensory neuropathy-Russe in depth. Clin Genet 83 (6):565-570.

60. Nicholson G, Lenk GM, Reddel SW, Grant AE, Towne CJ, Ferguson CJ et al. (2011) Distinctive genetic and clinical features of CMT4J: A severe neuropathy caused by mutations in the PI(3,5)P(2) phosphatase FIG4. Brain 134 (Pt 7):1959-1971.

61. Cottenie E, Menezes MP, Rossor AM, Morrow J, Yousry TA, Dick DJ et al. (2013) Rapidly progressive asymmetrical weakness in Charcot-Marie-Tooth disease type 4J resembles chronic inflammatory demyelinating polyneuropathy. Neuromuscul Disord 23 (5):399-403.

62. Cowchock FS, Duckett SW, Streletz LJ, Graziani LJ, Jackson LG (1985) X-linked motor-sensory neuropathy type II with deafness and mental retardation: a new disorder. Am J Med Genet 20 (2):307-315.

63. Kim JH, Sohn KM, Shy ME, Krajewski KM, Hwang M, Park JH et al. (2007) Mutations in PRPS1, which encodes the phosphoribosyl pyrophosphate synthetase enzyme critical for nucleotide biosynthesis, cause hereditary peripheral neuropathy with hearing loss and optic neuropathy (cmts5). Am J Hum Genet 83 (3):552-558.

64. Saint-Lezer A, Sole G, Ribeiro E, Latour P, Mercie P, Longy-Boursier M (2012) [Non-fortuitous dynamin II mutation-related association: neuropenia and Charcot-Marie-Tooth disease]. Rev Neurol (Paris) 168 (4):367-370.
65. Boyer O, Nevo F, Plaisier E, Funalot B, Gribouval O, Benoît G et al. (2011) INF2 mutations in Charcot-Marie-Tooth disease with glomerulopathy. N Engl J Med 365 (25):2377-2388.

66. Mademan I, Deconinck T, Dinopoulos A, Voit T, Schara U, Devriendt K et al. (2013) De novo INF2 mutations expand the genetic spectrum of hereditary neuropathy with glomerulopathy. Neurology 81 (22):1953-1958.

67. Nouriou S, Hamadouchi T, Funalot B, Bernard R, Bellatache N, Bouderba R et al. (2011) Novel mutations in the PRX and the MTRMR2 genes are responsible for unusual Charcot-Marie-Tooth disease phenotypes. Neuromuscul Disord 21 (8):543-550.

68. Quattrone A, Gambardella A, Bono F, Aguglia U, Bolino A, Bruni AC et al. (1996) Autosomal recessive hereditary motor and sensory neuropathy with focally folded myelin sheaths: clinical, electrophysiologic, and genetic aspects of a large family. Neurology 46 (5):1318-1324.

69. Takashima H, Nakagawa M, Nakahara K, Suehara M, Matsuizaki T, Higuchi I et al. (1997) A new type of hereditary motor and sensory neuropathy linked to chromosome 3. Ann Neurol 41 (6):771-780.

70. Bennett CL, Shirk AJ, Huynh HM, Street VA, Nelis E, Van Maldergem L et al. (2004) SIMPLE mutation in demyelinating neuropathy and distribution in sciatric nerve. Ann Neurol 55 (5):713-720.

71. Saïfi GM, Szigeti K, Wuyts L, Wuyts L, Sottas syndrome. J Neurol Neurosurg Psychiatry 66 (3):389-393.

72. Auer JM, Kressel HU, Coronado RA, Barinaga M, Wijdicks EFM et al. (1993) Charcot-Marie-Tooth disease (CMTX6) is caused by mutations in the pyruvate dehydrogenase kinase isozyme 3 (PDK3) gene. Hum Mol Genet 22 (7):1404-1416.

73. Saito M, Hayashi Y, Suzuki T, Tanaka H, Hozumi I, Tsuji S (1997) Linkage mapping of the gene for Charcot-Marie-Tooth disease type 2c to chromosome 1p (CMT2A) and the clinical features of CMT2A. Neurology 49 (6):1630-1635.

74. McLaughlin HM, Sakaguchi R, Gitlin W, Program NCS, Wilson TE, Biessker L et al. (2012) A recurrent loss-of-function alanine-rNA synthetase (AARS) mutation in patients with Charcot-Marie-Tooth disease type 2N (CMT2N). Hum Mutat 33 (1):244-253.

75. Weeden MN, Campeas R, Caswell R, Xie W, Paszkiewicz K, Antoniadi T et al. (2011) Exome sequencing identifies a DYNC1H1 mutation in a large pedigree with dominant axonal Charcot-Marie-Tooth disease. Am J Hum Genet 89 (2):308-312.

76. Bouhouche A, Birouk N, Azzedine H, Benomar A, Durosier G, Ente D et al. (2007) Autosomal recessive axonal Charcot-Marie-Tooth disease (ARCMT2): phenotype-genotype correlations in 13 Moroccan families. Brain 130 (Pt 4):1062-1075.

77. Tajiri M, Azzeddine H, Assami S, Sindou P, Nouriou S, Zemmourri R et al. (2004) Phenotypic variability in autosomal recessive axonal Charcot-Marie-Tooth disease linked to the R298C mutation in lamin A/C. Brain 127 (Pt 1):154-163.

78. Houlden H, Hamman S, Katifhi H, Reilly MM (2009) A novel Frabin (FGD4) nonsense mutation p.R275X associated with Charcot-Marie-Tooth disease type 4B3. Neurology 72 (6):617-620.

79. Facrizi GM, Taioi F, Cavallaro T, Ferrari S, Bertolasi L, Casarotto M et al. (2009) Further evidence that mutations in FGD4/frabin cause Charcot-Marie-Tooth disease type 4H. Hum Mol Genet 18 (3):1159-1164.

80. Weterman MA, Sorrentino V, Kasher PR, Jakobs ME, van Engelen BG, Fluiter MJ et al. (2011) Charcot-Marie-Tooth disease type 2N (CMT2N). Hum Mutat 22 (11):168-173.

81. Bohleba S, Alalzabi AM, Cudler E, Al-Hindi H, Ibrahim E, Alkarkaya FS (2011) A novel syndromic form of sensory-motor polyneuropathy is linked to chromosome 22q13.31-q13.33. Clin Genet 79 (2):193-195.

82. Othmane KB, Johnson E, Menold M, Graham FL, Hamida MB, Hasegawa O et al. (1999) Identification of a new locus for autosomal recessive Charcot-Marie-Tooth disease with focally folded myelin on chromosome 11p15. Genomics 62 (3):344-349.

83. Gambardella A, Boloio A, Muglia M, Valentino P, Bono F, Oliveri RL et al. (1998) Genetic heterogeneity in autosomal recessive Charcot-Marie-Tooth disease. Hum Mol Genet 22 (20):4224-4232.

84. Nakhoro K, Park JM, Hong YB, Park JH, Nam SH, Yoon BR et al. (2013) SET binding factor 1 (SBF1) mutation causes Charcot-Marie-Tooth disease type 4B3. Neurology 81 (2):165-173.

85. Bohleba S, Alalzabi AM, Cudler E, Al-Hindi H, Ibrahim E, Alkarkaya FS (2011) A novel syndromic form of sensory-motor polyneuropathy is linked to chromosome 22q13.31-q13.33. Clin Genet 79 (2):193-195.

86. Othmane KB, Johnson E, Menold M, Graham FL, Hamida MB, Hasegawa O et al. (1999) Identification of a new locus for autosomal recessive Charcot-Marie-Tooth disease with focally folded myelin on chromosome 11p15. Genomics 62 (3):344-349.

87. Gambardella A, Bolino A, Muglia M, Valentino P, Bono F, Oliveri RL et al. (1998) Genetic heterogeneity in autosomal recessive Charcot-Marie-Tooth disease with focally folded myelin sheaths (CMT4B). Neurology 50 (3):799-801.

88. Rudnik-Schoneborn S, Hehr U, von Kalle T, Bornemann A, Winkler J, Zerres K (2009) Andermann syndrome can be a phenotype of hereditary motor and sensory neuropathy—report of a discordant sibship with a compound heterozygous mutation of the KCC3 gene. Neuropediatrics 40 (5):129-133.

89. Uyanik G, Elcigloiu N, Penzien J, Gross C, Yilmaz Y, Olmez A et al. (2006) Novel truncating and missense mutations of the KCC3 gene associated with Andermann syndrome. Neurology 66 (7):1044-1048.

90. Echaniz-Laguna A, Ghezzi D, Chassagne M, Mayencon M, Padet S, Melchionda L et al. (2013) SURF1 deficiency causes demyelinating Charcot-Marie-Tooth disease. Neurology 81 (17):1523-1530.

91. Tang B, Liu X, Zhao G, Luo W, Xia K, Pan Q et al. (2005) Mutation analysis of the small heat shock protein 27 gene in Chinese patients with Charcot-Marie-Tooth disease. Asian J Neurol 62 (8):1201-1207.

92. Brkanac Z, Spencer D, Shendure J, Robertson PD, Matsushita M, Vu T et al. (2009) IFRD1 is a candidate gene for SMN2 on chromosome 17q22-q23. Am J Hum Genet 84 (5):692-697.

93. Wackerley BR, Hanman ME, Altmann DM, Malik O (2011) Charcot-Marie-Tooth disease associated with recurrent optic neuritis. J Clin Neurosci 18 (10):1422-1423.

94. Facrizi GM, Cavallaro T, Morbin M, Simonati A, Taioi F, Rizzuto N (1999) Novel mutation of the P0 extracellular domain causes a Dejerine-Sottas syndrome. J Neurol Neurosurg Psychiatry 66 (3):386-389.

95. Szigeti K, Saifi GM, Armstrong D, Belmont JW, Miller G, Lupski JR (2003) Disturbance of muscle fiber differentiation in congenital hypomyelinating neuropathy caused by a novel myelin protein zero mutation. Ann Neurol 54 (3):398-402.

96. McMillan HJ, Santos-Garcia S, Shapiro F, Batish SD, Couchon L, Donnelly S et al. (2010) Novel MPZ mutations and congenital hypomyelinating neuropathy. Neuromuscul Disord 20 (11):725-729.

97. Stojkovic T, de Seze J, Dubour O, Arne-Bes MC, Tardieu S, Hache JC et al. (2003) Autosomatic and respiratory dysfunction in Charcot–Marie–Tooth disease due to Thr124Met mutation in the myelin protein zero gene. Clinical Neurophysiology 114 (9):1609-1614.
98. Floroskufi P, Panas M, Karadima G, Vassilopoulos D (2007) New mutation of the MPZ gene in a family with the Dejerine-Sottas disease phenotype. Muscle Nerve 35 (5):667-669.

99. Shy ME, Jani A, Krajewski K, Grandis M, Lewis RA, Li J et al. (2004) Phenotypic clustering in MPZ mutations. Brain 127 (Pt 2):371-384.

100. Taioli F, Cabrini I, Cavallaro T, Simonati A, Testi S, Fabrizi GM (2011) Dejerine-Sottas syndrome with a silent nucleotide change of myelin protein zero gene. J Peripher Nerv Syst 16 (1):59-64.

101. Nakamura N, Kawamura N, Tateishi T, Doi H, Ohyagi Y, Kira J (2009) [Predominant parasympathetic involvement in a patient with Charcot-Marie-Tooth disease caused by the MPZ Thr124Met mutation]. Rinsho Shinkeigaku 49 (9):582-585.

102. Houlden H, Reilly MM, Smith S (2009) Pupil abnormalities in 131 cases of genetically defined inherited peripheral neuropathy. Eye (Lond) 23 (4):966-974.

103. Zuchner S, De Jonghe P, Jordanova A, Claeyss KG, Guergueltcheva V, Cherninkova S et al. (2006) Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2. Ann Neurol 59 (2):276-281.

104. Timmerman V, De Jonghe P, Ceuterick C, De Vriendt E, Loefgren A, Nelis E et al. (1999) Novel missense mutation in the early growth response 2 gene associated with Dejerine-Sottas syndrome phenotype. Neurology 52 (9):1827-1827.

105. Vandenbergh N, Upadhyaya M, Gatignol A, Bourtad L, Boucherat M, Chazot G et al. (2002) Frequency of mutations in the early growth response 2 gene associated with peripheral demyelinating neuropathies. J Med Genet 39 (12):e81.

106. Houlden H, Laura M, Ginsberg L, Jungbluth H, Robb SA, Blake J et al. (2009) The phenotype of Charcot-Marie-Tooth disease type 4C due to SH3TC2 mutations and possible predisposition to an inflammatory neuropathy. Neuromuscul Disord 19 (4):264-269.

107. Senderik J, Bergmann C, Stendel C, Kirkel J, Verpoorten N, De Jonghe P et al. (2003) Mutations in a gene encoding a novel SH3/TPR domain protein cause autosomal recessive Charcot-Marie-Tooth type 4C neuropathy. Am J Hum Genet 73 (5):1106-1119.

108. Aboussouan LS, Lewis RA, Shy ME (2007) Disorders of pulmonary function, sleep, and the upper airway in Charcot-Marie-Tooth disease. Lung 185 (1):1-7.

109. Boerkoel CF, Takashima H, Stankiewicz P, Garcia CA, Leber SC, Tardieu S et al. (2003) A novel mutation of the dynamin 2 gene in a Slovenian Roma (Gypsy) kindred. Ann Neurol 54 (1):30-37.

110. Renouil M, Stojkovic T, Jacquemont ML, Lauret K, Boue P, Fournimtraux A et al. (2009) Phenotypic clustering in MPZ mutations. Brain 132 (Pt 7):1741-1752.

111. Meggouh F, Bienfait HM, Weterman MA, de Visser M, Baas F (2006) Charcot-Marie-Tooth disease due to a de novo mutation of the RAB7 gene. Neurology 67 (8):1476-1478.

112. Claramunt R, Pedrola L, Sevilla T, Lopez de Munain A, Berciano J, Cuesta A et al. (2005) Genetics of Charcot-Marie-Tooth disease type 4A: mutations, inheritance, phenotypic variability, and founder effect. J Med Genet 42 (4):358-365.

113. Butinar D, Zidar J, Leonardis L, Popovc M, Kalaydjieva L, Angelicheva D et al. (1999) Hereditary auditory, vestibular, motor, and sensory neuropathy in a Slovenian Roma (Gypsy) kindred. Ann Neurol 46 (1):36-44.

114. Echaniz-Laguna A, Degos B, Bonnet C, Latour P, Hamadouche T, Levy N et al. (2007) NDRG1-linked Charcot-Marie-Tooth disease (CMT4D) with central nervous system involvement. Neuromuscul Disord 17 (2):163-168.

115. Menezes MP, Waddell L, Lenk GM, Kaur S, MacArthur DG, Meisler MH et al. (2014) Whole exome sequencing identifies three recessive FIG4 mutations in an apparently dominant pedigree with Charcot-Marie-Tooth disease. Neuromuscul Disord 24 (8):666-670.

116. Zhang X, Chow CY, Sahenk Z, Shy ME, Meisler MH, Li J (2008) Mutation of FIG4 causes a rapidly progressive, asymmetric neuronal degeneration. Brain 131 (Pt 8):1990-2001.

117. Bitoun M, Stojkovic T, Prudhon B, Maurage CA, Latour P, Tooth disease. PLoS Genet 6 (8).

118. Fabrizi GM, Ferrarini M, Cavallaro T, Berciano J, Garcia A, Verhoeven K et al. (2009) Phenotypic spectrum of dynamin 2 mutations in Charcot-Marie-Tooth neuropathy. Brain 132 (Pt 7):1741-1752.

119. Verny C, Ravise N, Leutenegger AL, Pouplard F, Dubourg O, Tardieu S et al. (2004) Coincidence of two genetic forms of Charcot-Marie-Tooth disease in a single family. Neurology 63 (8):1527-1529.

120. Fujiita K, Yoshida M, Sako W, Maeda K, Hashizume Y, Goto S et al. (2011) Brainstem and spinal cord motor neuron involvement with optineurin inclusions in proximal-dominant hereditary motor and sensory neuropathy. J Neurol Neurosurg Psychiatry 82 (12):1403-1404.

121. Patroclo CB, Lino AM, Marchiori PE, Brotto MW, Hirata MT (2009) Autosomal dominant HMSN with proximal involvement: new Brazilian cases. Arq Neuropsiquiatr 67 (3b):892-896.

122. Gerding WM, Koetting J, Epplen JT, Neusch C (2009) Hereditary motor and sensory neuropathy caused by a novel mutation in LITAF. Neuromuscul Disord 19 (10):701-703.

123. Berghoff C, Berghoff M, Leal A, Morera B, Barrantes R, Reis A et al. (2004) Clinical and electrophysiological characteristics of autosomal recessive axonal Charcot-Marie-Tooth disease (ARCMT2B) that maps to chromosome 19q13.3. Neuromuscul Disord 14 (5):301-306.

124. Chaouf M, Allal Y, De Sandre-Giovannoli A, Vallat JM, Amer-el-Khedoud A, Kassouri N et al. (2003) The phenotypic manifestations of autosomal recessive axonal Charcot-Marie-Tooth disease due to a mutation in Lamin A/C gene. Neuromuscul Disord 13 (1):60-67.

125. De Sandre-Giovannoli A, Delague V, Hamadouche T, Chaouf M, Krahn M, Boccaccio I et al. (2005) Homozygosity mapping of autosomal recessive demyelinating Charcot-Marie-Tooth neuropathy (CMT4H) to a novel locus on chromosome 12p11.21-q13.11. J Med Genet 42 (3):260-265.

126. McLaughlin HM, Sakaguchi R, Liu C, Igarashi T, Pehlivan D, Chu K et al. (2010) Compound heterozygosity for loss-of-function lysyl-tRNA synthetase mutations in a patient with peripheral neuropathy. Am J Hum Genet 87 (4):560-566.

127. Guernsey DL, Jiang H, Bedard K, Evans SC, Ferguson M, Matsuoka M et al. (2010) Mutation in the gene encoding ubiquitin ligase LRAS1M in patients with Charcot-Marie-Tooth disease. PLoS Genet 6 (8).

128. Gonzalez M, McLaughlin H, Houlden H, Guo M, Yo-Tsen L, Hadjivassiliou M et al. (2013) Exome sequencing identifies a significant variant in methionyl-tRNA synthetase (MARS) in a family with late-onset CMT2. J Neurol Neurosurg Psychiatry 84 (11):1247-1249.
130. Azzedine H, Bolino A, Taiieb T, Birouk N, Di Duca M, Bhouhouce A et al. (2003) Mutations in MTMR13, a new pseudophosphatase homologue of MTMR2 and Sbf1, in two families with an autosomal recessive demyelinating form of Charcot-Marie-Tooth disease associated with early-onset glaucoma. Am J Hum Genet 72 (5):1141-1153.

131. Vester A, Velez Ruiz G, McLaughlin HM, Program NCS, Lupski JR, Talbot K et al. (2013) A loss-of-function variant in the human histidyl-tRNA synthetase (HARS) gene is neurotoxic in vivo. Hum Mutat 34 (1):191-199.

132. Hahn AF, Parkes AW, Bolton CF, Stewart SA (1991) Neuromyotonia in hereditary motor neuropathy. J Neurol Neurosurg Psychiatry 54 (3):230-235.

133. Ylikallio E, Poyhonen R, Zimon M, De Vriendt E, Hilander T, Paetau A et al. (2013) Deficiency of the E3 ubiquitin ligase Trim2 in early-onset axonal neuropathy. Hum Mol Genet 22 (15):2975-2983.

134. Gess B, Auer-Grumbach M, Schirmacher A, Strom T, Zitzelsberger M, Rudnik-Schoneborn S et al. (2014) HSJ1-related hereditary neuropathies: novel mutations and extended clinical spectrum. Neurology 83 (19):1726-1732.

135. Boentert M, Knop K, Schuhmacher C, Gess B, Okegwo A, Young P (2014) Sleep disorders in Charcot-Marie-Tooth disease type 1. J Neurol Neurosurg Psychiatry 85 (3):319-325.

136. Butefisch C, Gutmann L, Gutmann L (1999) Compression of spinal cord and cauda equina in Charcot-Marie-Tooth disease type 1A. Neurology 52 (4):890-891.

137. Moog U, Engelen JJ, Weber BW, Van Gelderen M, Steyaert J, Baas F et al. (2004) Hereditary motor and sensory neuropathy (HMSN) IA, developmental delay and autism related disorder in a boy with duplication (17)(p11.2p12). Genet Couns 15 (1):73-80.

138. Birouk N, Gouider R, Le Guern E, Gugenheim M, Tabrizian M, Zimon M, De Vriendt E, Hilander T, Paetau A et al. (1997) Charcot-Marie-Tooth disease type 1A with 17p11.2 duplication. Clinical and electrophysiological phenotype study and factors influencing disease severity in 119 cases. Brain 120 (Pt 5):813-823.

139. Speevak MD, Farrell SA (2013) Charcot-Marie-Tooth 1B caused by expansion of a familial myelin protein zero (MPZ) gene duplication. Eur J Med Genet 56 (10):566-569.

140. Marchini C, Marsala SZ, Bendini M, Taioli F, Damante G, Lonigro IR et al. (2009) Myelin protein zero Val102fs mutation manifesting with isolated spinal root hypomyelopathy. Neuromuscul Disord 19 (12):849-852.

141. Kleopa KA, Sutton LN, Ong J, Tennekoon G, Telfeian AE (2002) Conus medulla oblongata: a CMT2B family with refined 3q13-14 interval. J Neurol 249 (5):293-295.

142. Fabrizi GM, Cavallaro T, Angiari C, Bertolasi L, Cabrini I, Ferrarini M et al. (2004) Giant axon and neurofilament accumulation in a child with Dejerine-Sottas syndrome: Improvement with laminectomy and duraplasty. Case report. J Neurol 249 (5):433-438.

143. Shizuka M, Ikeda Y, Watanabe M, Shoji M, Ikegami T et al. (1999) A novel mutation of the myelin P0 gene in a Japanese family with diffuse demyelinating Charcot-Marie-Tooth disease type 2A. J Neurochem 72 (3):961-965.

144. Hayasaka K, Ohnishi A, Takaga G, Fukushima Y, Murai M, Sato S et al. (2004) Myelin protein zero mutation and Charcot-Marie-Tooth disease type 1A. J Neurol Neurosurg Psychiatry 75 (1):52-56.

145. Martikainen MH, Kytouvoori L, Majamaa K (2014) Novel mitofusin 2 splice-site mutation causes Charcot-Marie-Tooth disease type 2 with prominent sensory dysfunction. Neuromuscul Disord 24 (4):360-364.

146. Chung KW, Suh BC, Cho SY, Choi SK, Kang SH, Yoo JH et al. (2010) Early-onset Charcot-Marie-Tooth patients with mitofusin 2 mutations and brain involvement. J Neurol Neurosurg Psychiatry 81 (11):1203-1206.

147. Boaretto F, Vettori A, Casarin A, Vazza G, Muglia M, Rossetto MG et al. (2010) Severe CMT type 2 with fatal encephalopathy associated with a novel MFN2 splice silencing mutation. Neurology 74 (23):1919-1921.

148. Carammins M, Colebatch JG, Bainbridge MN, Scherer SS, Abrams CK, Hackett EL et al. (2013) Exome sequencing identification of a GIB1 missense mutation in a kindred with X-linked spinocerebellar ataxia (SCA-X1). Hum Mol Genet 22 (21):4329-4338.

149. Del Bo R, Moggio M, Rango M, Bonato S, D'Angelo MG, Ghezzi S et al. (2008) Mutated mitofusin 2 presents with intrafamilial variability and brain mitochondrial dysfunction. Neurology 71 (24):1959-1966.

150. Genari AB, Borghetti VH, Gouveia SP, Bueno KC, dos Santos PL, dos Santos AC et al. (2013) Deficiency of the E3 ubiquitin ligase TRIM24 in Charcot-Marie-Tooth disease type 2. Neuromuscul Disord 23 (6):428-432.

151. Hanemann CO, Bergmann C, Senderek J, Zerres K, Spierfeld AD (2003) Transient, recurrent, white matter lesions in X-linked Charcot-Marie-Tooth disease with novel connexin 32 mutation. Arch Neurol 60 (4):605-609.

152. Anand G, Maheshwari N, Roberts D, Padenya A, Hamilton-Ayers M, van der Knaap M et al. (2010) X-linked hereditary motor sensory neuropathy (type 1) presenting with a stroke-like episode. Dev Med Child Neurol 52 (7):677-679.

153. Tabaraud F, Lagrange E, Sindou P, Vandenberge A, Levy N, Vallat JM (1999) Demyelinating X-linked Charcot-Marie-Tooth disease: unusual electrophysiological findings. Muscle Nerve 22 (10):1442-1447.

154. Mersiyanova IV, Peregolov AV, Polyakov YV, Sitnikov VF, Dadali EL, Oparin RB et al. (2000) A new variant of Charcot-Marie-Tooth disease type 2 is probably caused by a point mutation within the neurofilament-light gene. Am J Hum Genet 67 (1):37-46.

155. Fabrizi GM, Cavallaro T, Angiari C, Bertolasi L, Cabrini I, Ferrarini M et al. (2004) Giant axon and neurofilament accumulation in Charcot-Marie-Tooth disease type 2E. Neurology 62 (8):1429-1431.

156. Donaghhy M, Kennett R (1999) Varying occurrence of vocal cord paralysis in a family with autosomal dominant hereditary motor and sensory neuropathy. J Neurol 246 (7):552-555.

157. Auer-Grumbach M, De Jonghe P, Wagner K, Verhoeven K, Hartung HP, Timmerman V (2000) Phenotype-genotype correlations in a CMT2B family with refined 3q13-q22 locus. Neurology 55 (10):1552-1557.

158. Manganelli F, Pisciotta C, Provitera V, Taioli F, iodice R, Topa A et al. (2012) Autonomic nervous system involvement in a new CMT2B family. J Peripher Nerv Syst 17 (3):316-326.

159. Fusco C, Ucchino V, Barbon G, Bonini E, Mostacciolo ML, Frattini D et al. (2011) The homoygous ganglioside-induced differentiation-associated protein 1 molecule c.373C > T causes a very early-onset neuropathy: case report and literature review. J Child Neurol 26 (1):49-57.

160. Kalaydjieva L, Hallmayer J, Chandler D, Savov A, Nikolova A, Angelicheva D et al. (1996) Gene mapping in Gypsies identifies a novel demyelinating neuropathy on chromosome 8q24. Nat Genet 14 (2):214-217.

161. Merlini L, Villanova M, Sabatelli P, Trogu A, Malandrini A, Yanakiev P et al. (1998) Hereditary motor and sensory neuropathy Lom type in an Italian Gypsy family. Neuromuscul Disord 8 (3-4):182-185.
162. Rinaldi C, Grunseich C, Sevrioukova IF, Schindler A, Horkayne-Szakaly I, Lamperti C et al. (2012) Cowchock syndrome is associated with a mutation in apoptosis-inducing factor. Am J Hum Genet 91 (6):1095-1102.

163. Parman Y, Battaloglu E, Baris I, Bilir B, Poyraz M, Bissar-Tadmouri N et al. (2004) Clinicopathological and genetic study of early-onset demyelinating neuropathy. Brain 127 (Pt 11):2540-2550.

164. Sabatelli M, Mignogna T, Lippi G, Servidei S, Manfredi G, Ricci E et al. (1994) Autosomal recessive hypermyelinating neuropathy. Acta Neuropathol 87 (4):337-342.

165. Chance PF, Matsunami N, Lensch W, Smith B, Bird TD (1992) Analysis of the DNA duplication 17p11.2 in Charcot-Marie-Tooth neuropathy type 1 pedigrees: additional evidence for a third autosomal CMT1 locus. Neurology 42 (10):2037-2041.

166. Nicolaou P, Cianchetti C, Minaidou A, Marrosu G, Zamba-Papanicolaou E, Middleton L et al. (2013) A novel LRSAM1 mutation is associated with autosomal dominant axonal Charcot-Marie-Tooth disease. Eur J Hum Genet 21 (2):190-194.

167. Sanmaneechai O, Feely S, Scherer SS, Herrmann DN, Burns J, Muntoni F et al. (2015) Genotype-phenotype characteristics and baseline natural history of heritable neuropathies caused by mutations in the MPZ gene. Brain.

168. Chung KW, Kim SB, Park KD, Choi KG, Lee JH, Eun HW et al. (2006) Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. Brain 129 (Pt 8):2103-2118.
Appendix S2. Phenotypic comparison of mutations found in our cohort with the literature.

| CMT type   | MPZ G163R | MPZ R98H | MPZ D224Y | LITAF V144M | GJB1 R183S | NEFL Q332P | INF2 L77R | MFN2 R208H | MFN2 R94Q |
|------------|-----------|----------|-----------|-------------|-----------|-----------|----------|-----------|-----------|
| Age of onset (y) | 39, childhood | 20-25, 62 | 40 | AAE 31,78 | 29,49 | 10-57 | childhood | na | 26 | 11-35 |

| Hypertrophic nerve roots | + | - | + | - | - | - | - | - | + | [9] |
| CSF protein elevation | + | - | + | - | - | - | - | - | - | - |
| Cataracts bilateral | + | - | + | - | - | - | - | - | + | [10] |
| Pain | + | - | [12] | - | [4] | + | - | na | - | - |
| Paresthesias | - | 1,2 | + | - | - | + | [5] | + | na | - |
| Tremor | + | - | - | - | - | [4] | + | - | na | - |
| Respiratory insufficiency | - | - | + | - | - | - | - | - | - | - |
| Scoliosis | + | - | - | - | - | - | - | - | - | - |
| Hip dysplasia | - | - | - | - | - | - | - | - | - | - |
| Fasciculations | - | - | + | - | - | - | - | - | - | - |
| FSFG | - | - | - | - | - | - | - | - | - | - |
| Pupillary abnormalities | + | - | - | - | - | - | - | - | - | - |
| RLS | - | - | - | - | - | - | - | - | - | - |
| Brain MRI abnormalities | - | - | + | - | - | - | - | - | - | - |
| Claw hands | - | - | + | - | - | - | - | - | - | - |
| Asymmetrical weakness | - | - | + | - | - | - | - | - | - | - |
| Autonomic | - | - | - | - | - | - | - | - | - | - |
| Severe slow NCV | - | - | - | - | - | - | - | - | - | - |
| UL predominant | - | - | - | - | - | - | - | - | - | - |
| Facial weakness | - | - | - | - | - | - | - | - | - | - |
| Deafness | - | - | - | - | - | - | - | - | - | - |
| Hyperkeratosis | - | - | - | - | - | - | - | - | - | - |
| Sydactyly | - | - | - | - | - | - | - | - | - | - |
| Cold induced hand cramps | - | - | - | - | - | - | - | - | - | - |
| Bulbar | - | - | - | - | - | - | - | - | - | - |
| Upper motor neuron | - | - | - | - | - | - | - | - | - | - |
| Migraine | - | - | - | - | - | - | - | - | - | - |
| Cognitive impairment | - | - | - | - | - | - | - | - | - | - |
| MS as additional diagnosis | - | - | - | - | - | [4]| + | - | na | - |

CS, current study; Lit, literature; CMT, Charcot-Marie-Tooth neuropathy; *homozygous patient(s); M, male; F, female; na, not available; DI, dominant intermediate; AAE, age at examination; CSF, cerebrospinal fluid; CTS, carpal tunnel syndrome; FSGS, focal segmental glomerular sclerosis; RLS, restless legs syndrome; MRI, magnetic resonance imaging; NCV, nerve conduction velocity; UL, upper limb; MS, multiple sclerosis. For abbreviations of genes see text.
References:
1. Street VA, Meekins G, Lipe HP, Seltzer WK, Carter GT, Kraft GH et al. (2002) Charcot-Marie-Tooth neuropathy: clinical phenotypes of four novel mutations in the MPZ and Cx 32 genes. Neuromuscul Disord 12 (7-8):643-650.
2. Eggers SD, Keswani SC, Melli G, Cornblath DR (2004) Clinical and genetic description of a family with Charcot-Marie-Tooth disease type 1B from a transmembrane MPZ mutation. Muscle Nerve 29 (6):867-869.
3. Gabriels-Festen AA, Hoogendijk JE, Meijerink PH, Gabreels FJ, Bolhuis PA, van Beersum S et al. (1996) Two divergent types of nerve pathology in patients with different P0 mutations in Charcot-Marie-Tooth disease. Neurology 47 (3):761-765.
4. Fabrizi GM, Pellegrini M, Angiari C, Cavallaro T, Morini A, Taioli F et al. (2006) Gene dosage sensitivity of a novel mutation in the intracellular domain of P0 associated with Charcot-Marie-Tooth disease type 1B. Neuromuscul Disord 16 (3):183-187.
5. Gerding WM, Koetting J, Epplen JT, Neusch C (2009) Hereditary motor and sensory neuropathy caused by a novel mutation in LITAF. Neuromuscul Disord 19 (10):701-703.
6. Bort S, Nelis E, Timmerman V, Sevilla T, Cruz-Martinez A, Martinez F et al. (1997) Mutational analysis of the MPZ, PMP22 and Cx32 genes in patients of Spanish ancestry with Charcot-Marie-Tooth disease and hereditary neuropathy with liability to pressure palsies. Hum Genet 99 (6):746-754.
7. Mersiyanova IV, Perepelov AV, Polyakov AV, Sitnikov VF, Dadali EL, Oparin RB et al. (2000) A new variant of Charcot-Marie-Tooth disease type 2 is probably the result of a mutation in the neurofilament-light gene. Am J Hum Genet 67 (1):37-46.
8. Mademan I, Deconinck T, Dinopoulos A, Voit T, Schara U, Devriendt K et al. (2013) De novo INF2 mutations expand the genetic spectrum of hereditary neuropathy with glomerulopathy. Neurology 81 (22):1953-1958.
9. Zuchner S, Mersiyanova IV, Muglia M, Bissar-Tadmouri N, Rochelle J, Dadali EL et al. (2004) Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. Nat Genet 36 (5):449-451.
10. Chung KW, Kim SB, Park KD, Choi KG, Lee JH, Eun HW et al. (2006) Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. Brain 129 (Pt 8):2103-2118.
11. Verhoeven K, Claeyss KG, Zuchner S, Schroder JM, Weis J, Ceuterick C et al. (2006) MFN2 mutation distribution and genotype/phenotype correlation in Charcot-Marie-Tooth type 2. Brain 129 (Pt 8):2093-2102.
12. Watanabe M, Yamamoto N, Ohkoshi N, Nagata H, Kohno Y, Hayashi A et al. (2002) Corticosteroid- responsive asymmetric neuropathy with a myelin protein zero gene mutation. Neurology 59 (5):767-769.
13. Sanmaneechai O, Feely S, Scherer SS, Herrmann DN, Burns J, Muntoni F et al. (2015) Genotype-phenotype characteristics and baseline natural history of heritable neuropathies caused by mutations in the MPZ gene. Brain.
14. Houlden H, Reilly MM, Smith S (2009) Pupil abnormalities in 131 cases of genetically defined inherited peripheral neuropathy. Eye (Lond) 23 (4):966-974.
Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten in dem Institut für Neuropathologie des Universitätsklinikums Aachen hinterlegt sind.
Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Friederike Werheid**, an Eides statt, dass ich **den wesentlichen Anteil an der Publikation:**

**Werheid F., Azzedine H., Zwerenz E., Bozkurt A., Moeller M.J., Lin L., Mull M., Häusler M., Schulz J.B., Weis J. and Claeys K.G.**:

“Underestimated associated features in CMT neuropathies: clinical indicators for the causative gene?”; Brain and Behavior.; veröffentlicht online 04. März 2016

geleistet habe.

Die Anteile an der Arbeit waren wie folgt:

**Friederike Werheid:**
- Patientenselektion und Datenbankrecherche, Erhebung des Großteils der dargestellten klinischen und elektrophysiologischen Daten. Begutachtung und Auswertung der klinischen und elektrophysiologischen Befunde sowie zusätzlicher Untersuchungsergebnisse der Patienten wie Lungenfunktionsuntersuchungen.
- Auswertung der genetischen, neuropathologischen und neuroradiologischen Befunde.
- Literaturrecherche.
- Erstellung von Datenübersichtstabellen und –schemata und Vergleich mit der Fachliteratur.
- Erstellung des Manuskriptes.

**Hamid Azzedine:**
- Unterstützung bei der Interpretation genetischer Untersuchungsergebnisse.
- Korrektur des Manuskriptes.

**Eva Zwerenz:**
- Bereitstellung eines Teils der klinischen Daten.
- Korrektur des Manuskriptes.

**Ahmet Bozkurt:**
- Durchführung von Nervenbiopsien und damit Gewinnung und Bereitstellung histologischen Materials.
- Korrektur des Manuskriptes.

**Marcus J. Moeller:**
- Bereitstellung eines Teils der klinischen Daten.
- Korrektur des Manuskriptes.

**Lilian Lin:**
- Durchführung eines Teils der genetischen Untersuchungen.
- Korrektur des Manuskriptes.
Michael Mull:
- Bereitstellung von neuroradiologischen Befunden.
- Korrektur des Manuskriptes.

Martin Häusler:
- Bereitstellung eines Teils der klinischen Daten.
- Korrektur des Manuskriptes.

Jörg B. Schulz:
- Anregungen zum Studiendesign.
- Korrektur des Manuskriptes.

Joachim Weis:
- Bereitstellung von Patientenbiopsien zu Fällen mit Charcot-Marie-Tooth Neuropathie und diagnostische histopathologische Aufarbeitung der eingeschlossenen Patienten.
- Korrektur des Manuskriptes.

Kristl G. Claeys:
- Studiendesign und –Überwachung, fachliche Beratung und Supervision, Unterstützung bei der Patientenselektion und Auswertung der Gesamtdaten.
- Berücksichtigung der Literatur.
- Korrektur des Manuskriptes.

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautorin.

Friederike Werheide
Unterschrift der Doktorandin

Als Doktorin und korrespondierende Autorin bestätige ich die Angaben von Friederike Werheide

Prof. Dr. Kristl G. Claeys
Unterschrift der Doktorandin
Ich schließe mich der Erklärung von Prof. Dr. Kristl G. Claeys als Koautor an

Dr. Hamid Azzeddine

Ich schließe mich der Erklärung von Prof. Dr. Kristl G. Claeys als Koautor an

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Ich schließe mich der Erklärung von Prof. Dr. Kristl G. Claeys als Koautor an

Prof. Dr. Joachim Weis

____________________________________________________________________________

Namens und Unterschriften aller deutschsprachigen Koautoren