Published in final edited form as:

Neuropediatrics. 2008 February ; 39(1): 33–38. doi:10.1055/s-2008-1077085.

Two Novel Mutations in the *GDAP1* and *PRX* Genes in Early Onset Charcot-Marie-Tooth Syndrome

M. Auer-Grumbach^{1,5,10}, C. Fischer^{1,10}, L. Papić^{1,10}, E. John^{1,10}, B. Plecko², R. E. Bittner³, G. Bernert⁴, T. R. Pieber⁵, G. Miltenberger⁶, R. Schwarz⁷, C. Windpassinger¹, F. Grill⁸, V. Timmerman⁹, M. R. Speicher¹, and A. R. Janecke⁶

¹Institute of Human Genetics, Medical University of Graz, Austria

²Department of Paediatrics, Medical University of Graz, Austria

³Neuromuscular Research Department, Centre of Anatomy and Cell Biology, Medical University, Vienna, Austria

⁴Department of Paediatrics, University of Vienna, Vienna, Austria

⁵Department of Internal Medicine, Medical University of Graz, Austria

⁶Division of Clinical Genetics, Medical University, Innsbruck, Austria

⁷Landes Frauen- und Kinderklinik, Linz, Austria

⁸Orthopaedic Hospital of Vienna, Speising, Austria

⁹VIB – Department of Molecular Genetics, Peripheral Neuropathy Group, University of Antwerp, Antwerp, Belgium

¹⁰Centre for Medical Research, Medical University of Graz, Graz, Austria

Abstract

Autosomal recessive Charcot-Marie-Tooth syndrome (AR-CMT) is often characterised by an infantile disease onset and a severe phenotype. Mutations in the ganglioside-induced differentiation-associated protein 1 (*GDAP1*) gene are thought to be a common cause of AR-CMT. Mutations in the periaxin (*PRX*) gene are rare. They are associated with severe demyelination of the peripheral nerves and sometimes lead to prominent sensory disturbances. To evaluate the frequency of *GDAP1* and *PRX* mutations in early onset CMT, we examined seven AR-CMT families and 12 sporadic CMT patients, all presenting with progressive distal muscle weakness and wasting. In one family also prominent sensory abnormalities and sensory ataxia were apparent from early childhood. In three families we detected four *GDAP1* mutations (L58LfsX4, R191X, L239F and P153L), one of which is novel and is predicted to cause a loss of protein function. In one additional family with prominent sensory abnormalities a novel homozygous *PRX* mutation was found (A700PfsX17). No mutations were identified in 12 sporadic cases. This study suggests that mutations in the *GDAP1* gene are a common cause of early-onset AR-CMT. In patients with early-onset demyelinating AR-CMT and severe sensory loss *PRX* is one of the genes to be tested.

Keywords

AR-CMT; *GDAP1*; *PRX*; early onset peripheral neuropathy

Introduction

Hereditary motor and sensory neuropathies (HMSN), also known as Charcot-Marie-Tooth syndrome (CMT), are a clinically and genetically heterogeneous group of peripheral neuropathies which can be inherited as an autosomal dominant, autosomal recessive or X-linked trait. The autosomal recessive forms (AR-CMT) account for less than 5% of the families with CMT in Western countries, but in countries with a high prevalence of consanguinity this mode of inheritance is estimated to account for 30–50% of all CMT phenotypes [5, 14]. Moreover, it has also been noted that in Western countries patients affected by AR-CMT may often appear as isolated cases because of the small size of the sibships [10]. As with dominant CMT subtypes, AR-CMT is classified as demyelinating (CMT1), axonal (CMT2), or intermediate (CMT intermediate) based on neurophysiological and nerve biopsy findings [14]. Usually the phenotype of AR-CMT is similar to the dominant forms but it is often severe and has an earlier age at onset [10]. Genetically, AR-CMT is very heterogeneous with 15 genes identified so far. (<http://www.molgen.ua.ac.be/CMTMutations/>). The gene encoding ganglioside-induced differentiation-associated protein 1 (*GDAP1*) is expressed in the whole brain and spinal cord and may be involved in a signal transduction pathway in neuronal development. It has been suggested to account for a significant number of early onset demyelinating AR-CMT1 cases (also known as CMT4A) [3, 10]. However, in many patients with axonal or intermediate AR-CMT mutations have also been described in *GDAP1* [9, 12, 15]. In addition to distal muscle weakness and wasting, patients with *GDAP1* mutations sometimes may show vocal cord paralysis or pyramidal tract features [6, 16, 17]. Moreover, it has been suggested that *GDAP1* mutations may be expressed in heterozygous patients and segregate dominantly in some families [8]. In CMT families with severe demyelinating neuropathy, 21 mutations in the periaxin (*PRX*) gene leading to CMT4F have been reported so far [11] (<http://www.molgen.ua.ac.be/CMTMutations/>). Some of these patients presented with a distinct phenotype consisting of prominent sensory disturbances in the upper and lower limbs [18]. *PRX* encodes 2 PDZ-domain proteins, L- and S-periaxin, that are required for maintenance of peripheral nerve myelin.

In this study we sought to define the frequency and range of phenotypic manifestations of *GDAP1* and *PRX* mutations in a series of seven familial and twelve isolated CMT patients all with the disease onset in the first decade of life.

Patients and Methods

Patients

For the present study we selected seven affected persons with a family history suggesting AR inheritance and 12 isolated cases all carrying a diagnosis of either demyelinating (=CMT1, 6 cases), axonal (=CMT2, 8 cases) or intermediate (=CMT int, 5 cases) Charcot-Marie-Tooth (CMT) syndrome. The patients were of different ethnic origin [10 Austrian (53%) and 9 Mediterranean (47%)]. Disease onset was documented before the age of 5 years in all patients except one in whom CMT symptoms were first noticed at 8 years. Four of the familial cases were the offspring of consanguineous marriages. Patients and their family members including healthy parents were examined by experienced neurologists and neuropsychiatrists (M. A-G, B.P., G.B, R.S.) to document their features on the clinical and neurophysiological levels. All patients were screened for mutations in *GDAP1*. Seven

patients (six with CMT1 and 1 with CMT2) were screened for *PRX* mutations. All study participants received appropriate genetic counselling and signed informed consent for the use of blood and DNA samples. The study was approved by the Institutional Review Board of the Medical University of Graz, Austria.

Electrophysiological studies

Electrodiagnostic procedures were performed in all affected patients. Nerve conduction studies (NCS) were carried out using standard techniques of surface stimulation and recording. Usually motor nerve conduction velocities (MNCV) of the median and peroneal nerves were measured. Sensory nerve conduction velocity (SNCV) studies were performed antidromically for the median and/or the sural nerve in most individuals. Concentric needle electromyography was done in selected cases only.

Mutation screening

Genomic DNA was extracted from peripheral blood samples of patients and unaffected family members using standard methods. Seventeen patients with CMT1, CMT2 and intermediate CMT had been previously tested negative for the CMT1A duplication and/or for mutations in the peripheral myelin protein 22, myelin protein zero and gap junction protein $\beta 1$ (*PMP22*, *MPZ* and *GJB1*) genes. Selected patients have also been excluded for mutations in the mitofusin 2, early growth response 2, or myotubularin-related protein 2 (*MFN2*, *EGR2* and *MTMR2*) genes. For mutation analysis of the *GDAP1* and the *PRX* genes, the coding regions of *GDAP1* and *PRX* were screened. Samples were run and analysed on the ABI PRISM 3130 xl Genetic Analyzer (Applied Biosystems).

Sural nerve biopsy

Sural nerve biopsy was performed in a proband from family 2 at ankle level for diagnostic purposes. The specimen was fixed and embedded in epoxy-resin and processed for semithin sections (stained for PPD, *p*-phenylenediamine) and for electron microscopy, respectively.

Results

Clinical and neurophysiological features, and the ethnicity of the index patients included in this study are listed in • Tables 1, 2. Patients of three unrelated families (Families 1, 4, 6) were found to carry four different mutations in the *GDAP1* gene. The affected persons of family 2 were homozygous for a novel mutation in the *PRX* gene. A panel of 76 (*GDAP1*) and 90 (*PRX*) healthy European control samples were also screened for these mutations. The families are described in detail here.

Family 1

Disease onset in this Austrian CMT2 family was between the first and second year of life and consisted of foot drop and frequent falls. Gait disturbances progressed over time and steppage gait was prominent at the age of 6 years. There was mild distal sensory loss in the lower limbs and tendon reflexes were generally absent. Bilateral weakness and atrophy in the hands started some years later and was then slowly progressive. MNCV and SNCV were compatible with a primarily axonal motor and sensory neuropathy. The non-consanguineous parents were normal on neurological and electrophysiological examination. The index patient and the affected sib were compound heterozygous for *GDAP1* mutations c.571C > T (p.R191X) and c.715C > T (p.L239F) while the parents were heterozygous for the c.571C > T (p.R191X) and the c.715C > T (p.L239F), respectively.

Family 2

In this Turkish CMT1 family the healthy parents were first cousins. Their affected children presented with delayed walking and prominent sensory abnormalities affecting both surface and deep sensibility. Although distal muscle weakness in the lower limbs was mild, profound sensory ataxia was apparent. Tendon reflexes were generally absent. MNCV and SNCV were not measurable. Later on, marked kyphosis was noted in one child, who was also afflicted with congenital loss of toe and finger nails. Sural nerve biopsy was carried out in this child and indicated the presence of a severe ongoing demyelination (● Fig. 1).

Due to the prominent sensory abnormalities in the affected children we decided to first screen the *PRX* gene in this family. We detected a novel homozygous frame shift mutation c.2098delG; p.A700PfsX17 in the affected children. Parents were both heterozygous for this mutation.

Family 4

In this Turkish family with intermediate CMT the healthy parents are first cousins. In the affected children motor milestones were significantly delayed and independent walking was not possible before the age of two years. On examination at 8 years the index patient presented with progressed weakness and wasting of distal hand and foot muscles and complete paralysis of small hand muscles and foot extensors. Tendon reflexes were generally absent and there was mild distal sensory loss. MNCV and SNCV were within the intermediate range. A novel homozygous *GDAP1* mutation (c.174_176del3insTGTG [p.L58LfsX4]) was detected in all similarly affected sibs. The parents were shown to be heterozygous for this mutation.

Family 6

The index patient of this Turkish family was born to healthy consanguineous parents and was diagnosed with CMT2 before the age of two years. Further information as well as detailed results of NCS were not available. Affected children were homozygous for the c.458C > T; p.P153L mutation in exon 3 of *GDAP1*. Parents and further family members were not available for genetic testing.

Discussion

For the present study we selected 19 patients with early-onset CMT. Affected siblings and/or parental consanguinity suggested autosomal recessive inheritance in seven families. Parents of familial and sporadic patients were unaffected upon examination or by history.

Screening of *GDAP1* detected four mutations in three recessive CMT families, one of which was novel. *GDAP1* mutations c.174_176del3insTGTG (p.L58LfsX4) and c.571C > T (p.R191X) are known to introduce premature translation-termination codons which either trigger nonsense-mediated mRNA decay resulting in no GDAP1 protein at all or result in truncated proteins lacking one (p.R191X) or both (p.L58LfsX4) predicted glutathione S-transferase domains and are most likely non-functional. The *GDAP1* mutation c.458C>T (p.P153L) has been reported very recently in another CMT2 family. In addition, hoarseness was a feature in the affected patients but this was not the case in our patients [13].

An *in-silico* analysis using SIFT (Sorting Intolerant From Tolerant (<http://blocks.fhcrc.org/sift/SIFT.html>)) predicted the p.P153L mutation not to affect protein function. SIFT predicts whether an amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids. In contrast, the PolyPhen tool for prediction of possible impact of an amino acid substitution on the structure and function of a human

protein (<http://coot.embl.de/PolyPhen/>) classified p.P153L as probably damaging supporting the hypothesis that it is a disease-causing mutation. There was no indication that the p.P153L mutation interfered with mRNA splicing by changing binding sites for exonic splicing enhancers or silencers as analysed using the program ESEfinder (http://rulai.cshl.edu/cgi-bin/tools/ESE3/ese_finder.cgi?process=home).

The mutation c.715C > T (p.L239F) has been originally described in a German-Italian patient and has now been reported recently in Czech patients also with evidence of a founder effect as substantiated by haplotype analyses [1, 2]. The geographic relationship between the Austrian family reported here and Germany and Czechia where this founder mutation was initially identified [1, 2], might underline the importance of this founder mutation. However, haplotype analysis has not yet been carried out in our family to confirm a relationship between our family and the reported families. Moreover, the c.571C > T (p.R191X) was detected in a Czech patient and now also in the Austrian CMT patients.

The novel homozygous *PRX* mutation c.2098delG (p.A700PfsX17) identified in family 2 causes truncation of 761 amino acids including the C-terminal acidic domain of the long isoform of periaxin (L-periaxin) and pathogenicity of this mutation is thus very likely.

All affected patients carried mutations on both alleles of the *GDAP1* and the *PRX* mutations and all mutations were absent among a panel of 76 (*GDAP1*) and 90 (*PRX*) healthy European control samples.

Phenotype-genotype correlation studies showed that in all patients with *GDAP1* mutations onset of symptoms was before the age of two years. First signs consisted of delayed walking and prominent distal muscle weakness in the lower limbs. Weakness and wasting of the small hand muscles followed some years later. Sensory abnormalities were mild. None of the patients had additional features such as vocal cord paralysis until the age of 10 years. Despite the unique neurological presentation, patients in two families were classified as CMT2 and in one family as CMT intermediate according to results of NCS, and this classification remained consistent within families.

The phenotype of affected sibs of family 2 with a *PRX* mutation was obviously different from that seen in the three families with *GDAP1* mutations. Delayed walking and gait disturbances were related to prominent sensory ataxia and were shown to be caused by loss of L-periaxin. The nerve biopsy which was performed in one child confirmed severe demyelination of the peripheral nerves. So far, there are only few reports on patients with *PRX* mutations but prominent sensory abnormalities have already been highlighted in this genetically defined CMT subtype [18].

In contrast to other reports we could not detect *GDAP1* and *PRX* mutations in 12 early onset CMT patients without family history. Also, there was no evidence that mutations in these two genes are likely to produce CMT phenotypes complicated by cerebellar involvement, cataracts, pyramidal tract features, and other rare abnormalities (● Table 1). These patients might be afflicted with a rare and complicated form of cerebellar ataxia or another rare syndrome associated with peripheral neuropathy. Whether loss of toe nails in one of the sibs homozygous for the *PRX* mutation was related to CMT or, e.g., the result of another recessive mutation in the consanguineous family remains unclear. Our family has not yet been tested for mutations in the gene encoding R-spondin 4 (RSPO4), which are known to cause inherited onychia [4, 7].

In summary, our study confirms that *GDAP1* mutations are a common cause of severe early-onset CMT with autosomal recessive inheritance. We therefore suggest that *GDAP1* should be one of the first genes to be tested in clear AR-CMT patients with early onset CMT. The

presence of prominent sensory disturbances in patients with early onset demyelinating AR-CMT might point to mutations in *PRX* and might thus be a suitable feature to distinguish CMT4F from other AR-CMT subtypes. Also, CMT patients with extremely low or unmeasurable NCVs should be included in a screening for CMT4F.

Acknowledgments

The authors gratefully acknowledge the cooperation and participation of the family members in this research project. This research project was supported by the Fonds zur Förderung der wissenschaftlichen Forschung (FWF P19455, P17494 and P18470, Austria). Further support was obtained by the University of Antwerp, the Fund for Scientific Research (FWO-Flanders), the Interuniversity Attraction Poles P6/43 program of the Belgian Federal Science Policy Office (BELSPO) and the Medical Foundation Queen Elisabeth (GSKE), Belgium.

References

1. Ammar N, Nelis E, Merlini L, et al. Identification of novel *GDAP1* mutations causing autosomal recessive Charcot-Marie-Tooth disease. *Neuromusc Disorders*. 2003; 13:720–728. [PubMed: 14561495]
2. Baránková L, Vyhnálková E, Züchner S, Mazanec R, Sakmaryová I, Vondráček P, et al. *GDAP1* mutations in Czech families with early-onset CMT. *Neuromusc Disorders*. 2007; 17:482–489. [PubMed: 17433678]
3. Baxter RV, Othmane KB, Rochelle JM, Stajich JE, Hulette C, Dew-Knight S, et al. Ganglioside-induced differentiation-associated protein-1 is mutant in Charcot-Marie-Tooth disease type 4A/8q21. *Nat Genet*. 2002; 30:21–22. [PubMed: 11743579]
4. Bergmann C, Senderek J, Anhuf D, Thiel CT, Ekici AB, Poblete-Gutierrez P, et al. Mutations in the gene encoding the Wnt-signaling component R-spondin 4 (*RSPO4*) cause autosomal recessive anonychia. *Am J Hum Genet*. 2006; 79:1105–1109. [PubMed: 17186469]
5. Bernard R, Sandre-Giovannoli A De, Delague V, Levy N. Molecular genetics of autosomal recessive axonal Charcot-Marie-Tooth neuropathies. *NeuroMolecular Medicine*. 2006; 8:87–106. [PubMed: 16775369]
6. Biancheri R, Zara F, Striano P, Pedemonte M, Cassandrini D, Stringara S, et al. *GDAP1* mutation in autosomal recessive Charcot-Marie-Tooth with pyramidal features. *J Neurol*. 2006; 253:1234–1235. [PubMed: 16607474]
7. Blyndon DC, Ishii Y, O'Toole EA, Unsworth HC, Teh M-T, Ruschendorf F, et al. The gene encoding R-spondin 4 (*RSPO4*), a secreted protein implicated in Wnt signaling, is mutated in inherited anonychia. *Nature Genet*. 2006; 38:1245–1247. [PubMed: 17041604]
8. Claramunt R, Pedrola L, Sevilla T, de Munain A Lopez, Berciano J, Cuesta A, et al. Genetics of Charcot-Marie-Tooth disease type 4A: mutations, inheritance, phenotypic variability, and founder effect. *J Med Genet*. 2005; 42:358–365. (Letter). [PubMed: 15805163]
9. Cuesta A, Pedrola L, Sevilla T, García-Planells J, Chumillas MJ, Mayordomo F, et al. The gene encoding ganglioside-induced differentiation-associated protein 1 is mutated in axonal Charcot-Marie-Tooth type 4A disease. *Nat Genet*. 2002; 30:22–25. [PubMed: 11743580]
10. Dubourg O, Azzedine H, Verny C, Durosier G, Birouk N, Gouider R, et al. Autosomal recessive forms of demyelinating Charcot-Marie-Tooth neuropathies. *NeuroMolecular Medicine*. 2006; 8:75–85. [PubMed: 16775368]
11. Guillbot A, Williams A, Ravisé N, Verny C, Brice A, Sherman DL, et al. A mutation in periaxin is responsible for CMT4F, an autosomal recessive form of Charcot-Marie-Tooth disease. *Hum Mol Genet*. 2001; 10:415–421. [PubMed: 11157804]
12. Kabzinska D, Kochanski A, Drac H, Ryniewicz B, Rowińska-Marcińska K, Hausmanowa-Petrusewicz I. Autosomal recessive axonal form of Charcot-Marie-Tooth disease caused by compound heterozygous 3'-splice site and Ser130Cys mutation in the *GDAP1* gene. *Neuropediatrics*. 2005; 36:206–209. [PubMed: 15944907]
13. Kabzinska D, Saifi GM, Drac H, Rowinska-Marcinska K, Hausmanowa-Petrusewicz I, Kochanski A, Lupski JR. Charcot-Marie-Tooth disease type 4C4 caused by a novel Pro153Leu substitution in the *GDAP1* gene. *Acta Myologica*. 2007; 16:108–111. [PubMed: 18421898]

14. Martin, JJ.; Brice, A.; Van Broeckhoven. The Netherlands Neuromuscul Disorders; 1999, 4th Workshop of the European CMT-Consortium-62nd ENMC International Workshop. Rare forms of Charcot-Marie-Tooth disease and related disorders; Soestduinen. 16–18 October 1998; 1999. p. 279-287.
15. Senderek J, Bergmann C, Ramaekers VT, Nelis E, Bernert G, Makowski A, et al. Mutations in the ganglioside-induced differentiation-associated protein-1 (GDAP1) gene in intermediate type autosomal recessive Charcot-Marie-Tooth neuropathy. *Brain*. 2003; 126:642–649. [PubMed: 12566285]
16. Sevilla T, Cuesta A, Chumillas MJ, Mayordomo F, Pedrola L, Palau F, et al. Clinical, electrophysiological and morphological findings of Charcot-Marie-Tooth neuropathy with vocal cord palsy and mutations in the GDAP1 gene. *Brain*. 2003; 126:2023–2033. [PubMed: 12821518]
17. Stojkovic T, Latour P, Viet G, Seze J De, Hurtevent JF, Vandenberghe A, et al. Vocal cord and diaphragm paralysis, as clinical features of a French family with autosomal recessive Charcot-Marie-Tooth disease, associated with a new mutation in the GDAP1 gene. *Neuromuscul Disord*. 2004; 14:261–264. [PubMed: 15019704]
18. Takashima H, Boerkoel CF, Jonghe P De, Ceuterick C, Martin JJ, Voit T, et al. Periaxin mutations cause a broad spectrum of demyelinating neuropathies. *Ann Neurol*. 2002; 51:709–715. [PubMed: 12112076]

Fig. 1.

Nerve biopsy of a patient with the periaxin mutation c.2098delG. Left: Semithin sections stained for PPD shows pronounced loss of myelinated axons (bar: 2 μ m). Right: An electron micrograph showing multiple onion bulb formations of Schwann cell processes and empty basal laminas (arrows) and denervated, empty Schwann cells (asterisks).

Clinical and genetic data of the respective index patients. All patients have progressive distal muscle weakness and wasting of the upper and lower limbs

Table 1

Patient/ Family N°	Origin of the family	Consanguinity of parents	Familial/ sporadic	Age at onset (y)	Initial symptoms	Additional features	CMTNS	Clinical diagnosis	GDAP1 mutation	PRX muta- tion
1	Austria	no	familial	2	gait disturbance	no	19	CMT2	c.571 C > T, R191X c.715 C > T, L239F	neg
2	Turkey	first cousins	familial	1–2	delayed walking	congenital loss of nails in one affected child, kyphosis, sensory ataxia	20	CMT1	neg	c.2098 delG, A700PfsX17
3	Austria	no	familial	3–4	unsteady gait	proximal weakness, predominant motor neuropathy, slightly elevated CK levels	18	CMT int	neg	nd
4	Turkey	first cousins	familial	1–2	delayed walking	no	20	CMT int	c.174_176 del3ins1GTG L58LfsX4	nd
5	Turkey	first cousins	familial	1–2	gait abnormality	no	20	CMT1	neg	neg
6	Turkey	first cousins	familial	1	delayed walking	no	?	CMT2	c.458 C > T, P153L	nd
7	Bosnia	no	familial	1	gait abnormality	no	11	CMT2	neg	nd
8	Austria	no	sporadic	1–5	bilateral foot drop	proximal muscle weakness, partially wheelchair bound at 25y	26	CMT2	neg	nd
9	Bosnia	no	sporadic	2	hand tremor, delayed walking, gait abnormality	hand tremor, hypacusis (otitis), sensory loss in hands and feet	24	CMT1	neg	neg
10	Croatia	no	sporadic	1	toe walking, frequent falls	no	17	CMT2	neg	nd
11	Austria	no	sporadic	8	gait abnormalities	hand tremor	17	CMT1	neg	neg
12	Austria	no	sporadic	birth	delayed walking, con- genital club feet	brisk tendon refl exes in LL	10	CMT2	neg	nd
13	Austria	no	sporadic	1	delayed walking	hip dysplasia	?	CMT1	neg	neg
14	Germany/ Asia	no	sporadic	3–4	frequent falls	skoliosis, growth retardation, hypogo- nadism, cataracts	19	CMTint	neg	nd
15	Austria	no	sporadic	4	frequent falls	proximal muscle weakness, slightly elevated CK levels	26	CMTint	neg	nd
16	Austria	no	sporadic	5	toe walking	no	7	CMT1	neg	neg
17	Croatia	no	sporadic	2	frequent falls	dysarthria, mental retardation, hand tremor, cerebellar signs	19	CMT2	neg	nd
18	Austria	no	sporadic	birth	club feet at birth	no	8	CMT2	neg	nd
19	Austria	no	sporadic	4	frequent falls	skoliosis, hand tremor	?	CMT int	neg	nd

Legend: CK = creatine-kinase levels; nd = not done; neg = negative; CMT = Charcot-Marie-Tooth syndrome, int = intermediate; CMTNS = CMT neuropathy score

Table 2

Electrophysiological data of respective index patients

Patient/ Family N°	Median nerve			Peroneal nerve			Sural nerve		Other nerves	
	MNCV (m/sec)	CMAP (mV)	SNCV (m/sec)	SNAP (μ V)	MNCV (m/sec)	CMAP (mV)	SNCV (m/sec)	SNAP (μ V)	MNCV in m/sec	CMAP in mV
1	44	3.5	47	5.7	NR	NR	21	5.8	—	—
2	ND	ND	ND	ND	NR	NR	NR	NR	—	—
3	43	5.3	49	7.0	NR	NR	26	5	—	—
4	40	2.6	33	3.4	ND	ND	ND	ND	—	—
5	NR	NR	NR	NR	NR	NR	ND	ND	N. femoralis: very prolonged DML	U
6	ND	ND	ND	ND	NR	NR	NR	NR	—	—
7	ND	ND	ND	ND	41	1.8	61	9	—	—
8	47	0.2	NR	NR	NR	NR	NR	NR	—	—
9	12	1.0	NR	NR	NR	NR	ND	ND	—	—
10	50	3.6	47	14	36	0.9	48	6.3	—	—
11	ND	ND	ND	ND	25	U	ND	ND	—	—
12	60	12.5	ND	ND	NR	NR	NR	NR	—	—
13	ND	ND	ND	ND	ND	ND	ND	ND	N. tibialis: 24	3.4
14	32	1.9	39	17	NR	NR	ND	ND	—	—
15	37	1.6	NR	NR	NR	NR	NR	NR	—	—
16	19	9.2	20	7	21	1.8	ND	ND	—	—
17	58	12.5	NR	NR	NR	NR	NR	NR	N. tibialis: 37	U
18	55	6.0	63	41.1	40.7	0.6	53	7.4	—	—
19	42	13	33	8.6	27	3.6	NR	NR	—	—

ND = not done; NR = no response; U = unknown; MNCV = motor nerve conduction velocity; SNCV = sensory nerve conduction velocity; CMAP = compound motor action potential; SNAP = sensory nerve action potential; mV = millivolt; m/sec = meter per second; μ V = microvolt; DML = distal motor latency

Normal values: Median MNCV = 47–56 m/sec (mean: 51 m/sec); median CMAP (peak-peak) = 4–8 mV (mean: 6.5 mV); median SNCV = 46–64 m/sec (mean: 54.5 m/sec); median SNAP = 10–31 μ V (mean: 18 μ V); peroneal MNCV = 45–56 m/sec (mean: 48 m/sec); peroneal CMAP (peak-peak) = 3.5–7.0 mV (mean: 5 mV); sural SNCV = 46–60 m/sec (mean: 53 m/sec); sural SNAP = 10–24 μ V (mean: 16 μ V); tibial MNCV = 45–51 m/sec (mean: 48 m/sec); tibial CMAP (peak-peak) = 8–14 mV (mean: 10.5 mV); femoral distal motor latency: 3.5–5.8 msec (mean: 4.8 msec)