Study on the gene and phenotypic characterisation of autosomal recessive demyelinating motor and sensory neuropathy (Charcot-Marie-Tooth disease) with a gene locus on chromosome 5q23-q33

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Abstract

***Objectives*—To report the occurrence of the autosomal recessive form of demyelinating Charcot-Marie-Tooth disease (CMT) with a locus on chromosome 5q23–33 in six non-related European families, to refine gene mapping, and to define the disease phenotype.**

***Methods*—In an Algerian patient with autosomal recessive demyelinating CMT mapped to chromosome 5q23-q33 the same unique nerve pathology was established as previously described in families with a special form of autosomal recessive demyelinating CMT. Subsequently, the DNA of patients with this phenotype was tested from five Dutch families and one Turkish family for the 5q23-q33 locus.**

***Results*—These patients and the Algerian families showed a similar and highly typical combination of clinical and morphological features, suggesting a common genetic defect. A complete cosegregation for markers D5S413, D5S434, D5S636, and D5S410 was found in the families. Haplotype construction located the gene to a 7 cM region between D5S643 and D5S670. In the present Dutch families linkage disequilibrium could be shown for various risk alleles and haplotypes indicating that most of these families may have inherited the underlying genetic defect form a common distant ancestor.**

***Conclusions*—This study refines the gene localisation of autosomal recessive demyelinating CMT, mapping to chromosome 5q23–33 and defines the phenotype characterised by a precocious and rapidly progressive scoliosis in combination with a relatively mild neuropathy and a unique pathology. Morphological alterations in Schwann cells of the myelinated and unmyelinated type suggest the involvement of a protein present in both Schwann cell types or an extracellular matrix protein rather than a myelin protein. The combination of pathological features possibly discerns autosomal recessive demyelinating CMT with a gene locus on chromosome 5q23–33 from other demyelinating forms of CMT disease.**

(*J Neurol Neurosurg Psychiatry* 1999;**66**:569–574)

Keywords: Charcot-Marie-Tooth disease; hereditary demyelinating neuropathy; autosomal recessive inheritance; chromosome 5

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Received 20 February 1998
and in final form
2 October 1998
Accepted 16 October 1998

Charcot-Marie-Tooth disease (CMT) or hereditary motor and sensory neuropathy (HMSN) is a heterogeneous group of disorders. By combined clinical, electrophysiological, and nerve biopsy studies two major types have been discerned, a demyelinating type (CMT1 or HMSN type I) and a neuronal-axonal type (CMT2 or HMSN type II).[1] Both forms are usually inherited as autosomal dominant traits, but autosomal recessive and X-linked forms have also been documented.[2 3] The demyelinating types show a broad range of clinical severity; the severe type with onset in infancy often being designated as Dejerine-Sottas disease or HMSN type III.[4 5] Morphological investigations of several autosomal recessive pedigrees showed distinct forms of pathology, suggesting genetic heterogeneity.[6–8]

Recently, different genetic loci were assigned in autosomal recessive CMT1. The first locus was found in four Tunisian families by Ben Othmane *et al* on chromosome 8q13–21.1.[9] The patients showed a rapidly progressing neuropathy of early onset with moderately decreased nerve conduction velocities. A second locus was assigned to chromosome 11q23 in a large consanguineous family with a severe demyelinating neuropathy and focally folded myelin in nerve biopsies. Death occurred in the fourth to fifth decade.[10 11] A third locus was mapped to chromosome 8q24 in an endogamous group of Bulgarian gypsies with a severe, progressive neuropathy and deafness.[12] LeGuern *et al* identified a forth locus on chromosome 5q23–33 in two Algerian families.[13] Kessali *et al* described the phenotypic details of these families; sural nerve biopsy was performed in one patient.[14] We had the opportunity to examine this biopsy and found the same morphological hallmarks that characterised the autosomal recessive demyelinating CMT previously described by us,[8] suggesting a common genetic defect. Therefore we tested our families with this peculiar form of autosomal recessive demyelinating neuropathy for the 5q23-q33 locus.

Table 1 Clinical features of 11 patients from six families with autosomal recessive demyelinating CMT

Patients	*1a*	*1b*	*2a*	*2b*	*3*	*4a*	*4b*	*5*	*6a*	*6b*	*6c*
Sex	F	F	M	M	F	F	M	F	F	F	M
Age of walking (months)	14	14	16	18	14	14	17	30	Normal	Normal	normal
Age at first examination (y)	9	5	15	8	12	15	17	16	37	36	53
Distal muscular atrophy	+	−	−	−	+	+	+	+	+	+	+
Distal sensory impairment	+	−	+	−	+	+	+	+	+	+	+
Areflexia	+	+	+	+	+	+	+	+	+	+	+
Foot deformities	PC	PP	PC	PP	PC	PC	PP	PP	PC	PC	PP
Scoliosis (age at onset (y))	+ (6)	+ (6)	+ (9)	+ (8)	−	−	+ (3)	+	+ (6)	+ (6)	+ (7)
Spine surgery (age (y))			+ (17)	+ (15)			+ (17)	+ (16)	+ (37)	+ (40)	
Wheelchair (age (y))								+ (25)	+ (45)		
Disability at first examination (age (y))*	2 (9)	1 (5)	1 (15)	1 (8)	1 (12)	1 (15)	1 (17)	2 (16)	3 (37)	1 (36)	2 (53)
Disability at last examination (age (y))*	2 (17)	1 (16)	1 (21)	1 (15)	2 (17)	3 (29)	2 (25)	4 (31)	4 (47)	2 (57)	2 (55)
Nerve biopsy	+	+	−	+	+	+	−	+	−	+	−

PC=pes cavus; PP=pes planus.
*Disability scale at first and last examination: 1=mild weakness of ankle movements; 2=weakness of lower legs, mild involvement of hands, walking without help; 3=pronounced weakness of lower legs and hands, mild involvement of upper legs, walking with help; 4=severe proximal weakness, wheelchair bound.

Patients and methods

PATIENTS

From the medical records of the Neuromuscular Center Nijmegen we selected five families with an autosomal recessive demyelinating CMT based on the following criteria: (1) chronic progressive motor and sensory neuropathy without CNS involvement; (2) median motor nerve conduction velocities (MNCVs) <35 m/s; (3) healthy non-consanguineous parents and more than one affected child or healthy consanguineous parents and affected child(ren); (4) nerve biopsies, performed in at least one patient of each family, showed the following characteristics: (*a*) chronic demyelinating neuropathy with loss of myelinated fibres; (*b*) relatively few and small onion bulbs by comparison with CMTIA; (*c*) onion bulbs consisting of concentric Schwann cell lamellae often intermingled with single and duplicated basal membranes or onion bulbs consisting only of basal membranes; (*d*) Schwann cells of unmyelinated axons showing multiple cytoplasmic processes, sometimes entirely surrounding myelinated or demyelinated axons or contributing to the outer lamellae of onion bulbs; (*e*) few tomacula.[8] An identical pathology was found in a sporadic patient born from healthy, non-consanguineous parents and this family was added to our study. Sural nerve processing and light and electron microscopical examination, including teased fibre studies, were performed according to previously described techniques.[8] The families 1–4 and 6 were of Dutch ancestry, and originated from different parts of the country without a known direct relation between the families. Parents were not consanguineous in these families. The parents of family 5 came from Turkey and were consanguineous.

We had the opportunity to examine the sural nerve biopsy of patient ALG II-3[14] by light and electron microscopy and to compare it with the nerve pathology in our patients. We found the same morphological hallmarks. Based on the striking similarities, not only in morphological but also in clinical aspects between our patients and the two Algerian families,[14] we hypothesised that the same gene on chromosome 5q23-q33 is involved.[13] Informed consent was obtained from the five autosomal recessive families and the family with a sporadic patient. Blood samples were taken from the patients, and their living parents and siblings, and high molecular weight genomic DNA was extracted and analysed for markers from the relevant region. From one family only two affected members were available for DNA analysis.

HAPLOTYPING

Polymorphic repeat markers were selected from the 5q23-q33 region encompassing the locus for the recessive HMSN type I disease reported by LeGuern *et al*.[13] Genotyping was performed by polymerase chain reaction (PCR) amplification of genomic DNA as described previously.[15] Haplotypes were constructed according to the principles of Thomson.[16] The order of markers was kept similar as given in the consensus CEPH/

Table 2 Electrophysiological data of 11 patients from six families with autosomal recessive demyelinating HMSN

Patients	*1a*	*1b*	*2a*	*2b*	*3*	*4a*	*4b*	*5*	*6a*	*6b*	*6c*
Age (y)	9	5	15	8	12	15	17	16	37	36	53
Motor conduction:											
Median nerve											
MNCV (m/s)	34		31	21	24	33	26	16	10	29	17
Distal latency (ms)	5.7		5.9	4.6	8.4	9.0	12.1		10.5	11.9	32.7
Amplitude (mV)			2.3	7.9	0.9	8.5					0.7
Peroneal nerve:											
MNCV (m/s)	23	27	17	34	24	12	25	0	0	21	0
Distal latency (ms)	12.8		21.9	6.7	25.6	12.6	11.8				
Amplitude (mV)	10.7		0.7	1.3	0.7						
Sensory conduction:											
Median nerve											
Distal latency (ms)	4.3		4.6	3.3	4.1	0	4.4	3.0		0	0
Amplitude (μV)	5		5.0	14.2	3.2		5	2			
Sural nerve											
Distal latency (ms)			4.4	3.3	0	0	3.3	0			0
Amplitude (μV)			1.3	10.9			3				

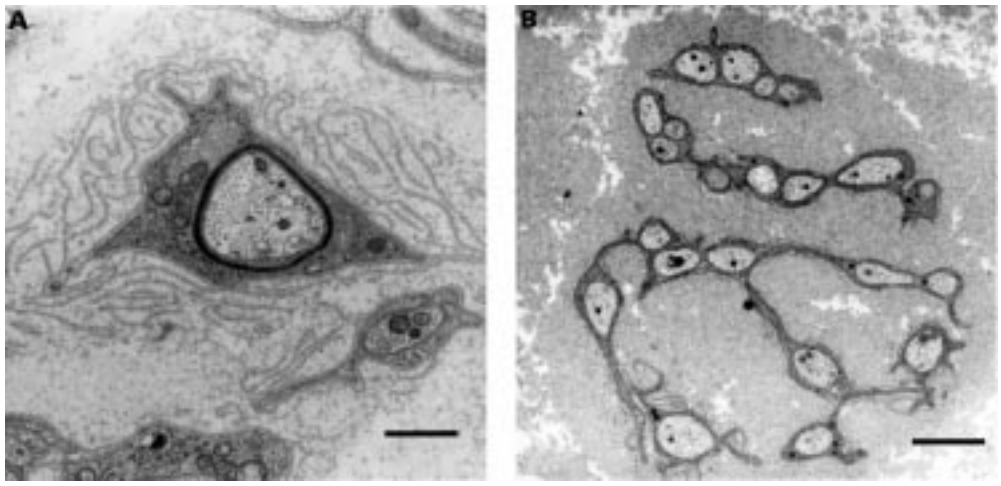

Figure 1 Electron micrographs: (A) patient 1b. Myelinated and unmyelinated fibres show cytoplasmic extensions of the Schwann cell and are surrounded by multiple basal membranes. Bar=2 μm. (B) Patient 3. Schwann cells with unmyelinated fibres, forming many cytoplasmic processes; few extra basal membranes. Bar=2 μm.

Genethon chromosome 5 linkage map of GDB, which is slightly different from the order used by LeGuern *et al*.[13] Most importantly, several recombination events seen in the present and other families place D5S402 proximal to the other markers. Therefore, the order of the markers and the distance between them are D5S402-(D5S436, D5S638, D5S643)-2cM-(D5S413, D5S434)-3 cM-D5S636–4 cM -D5S410–5 cM-D5S412 (markers occupying the same location without information about their relative order are placed between parentheses). The size in base pairs of the observed alleles for each of these markers was determined by comparison with a known sequence: D5S402 (A=169, B=166, C=163); D5S436 (A=262, B=259, C=257, D=255, E=253, F=251, G=249, H=247); D5S638 (A=143, B=140, C=138, D=136); D5S643 (A=145, B=143, C=141, D=139, E=137, F=135); D5S413 (A=279, B=278, C=277, D=276, E=275, F=280, G=281); D5S434 (A=260, B=258, C=256, D=254, E=252); D5S636 (A=152, B=149, C=147, D=144, E=142, G=133, H=154); D5S410 (A=162, B=160, C=158, D=156, E=169, F=164, G=171); D5S412 (A=183, B=181, C=179, D=177, E=175, F=173, G=171, H=169).

Table 3 Sural nerve morphometry of seven patients with autosomal recessive demyelinating CMT

	Patients						
	1b	*2b*	*1a*	*3*	*4a*	*5*	*6b*
Age (y)	5	8	9	12	15	16	36
MF density (number/mm^2)	8580	5190	5570	3450	2620	3350	3920
% of normal for age	61	39	42	33	25	32	40
TTFA (mm^2)	1.05	1.32	1.42	2.03	1.10	0.43	0.66
% of normal for age	172	183	197	233	126	49	57
Teased fibres:							
% type A	92	77	75	75	51	23	48
% type E	0	0	0	0	0	0	0
% type CDF	8	23	25	25	49	77	52

MF density=myelinated fibre density, mean of age matched controls: 14170 (2–5 y, n=6); 13180 (6–10 y, n=11); 10530 (11–20 y, n=5); 9760 (31–50 y, n=5).
TTFA=total transverse fascicular area, mean of age matched controls: 0.61 (2–5 y, n=4); 0.72 (6–10 y, n=5); 0.87 (11–30 y, n=5); 1.16 (31–50 y, n=3).
Teased fibres: A=normal fibre, although with many small and a few larger focal myelin thickenings; E=with axonal degeneration; C=with paranodal demyelination; D=with demyelinated segment(s); F=with remyelinated segment(s).

Results

Clinical and electrophysiological features of the patients are summarised in tables 1 and 2. Most patients walked before the age of 18 months. An early and severe disabling scoliosis or kyphoscoliosis was the presenting sign in most patients. At first neurological examination all patients showed weakness of ankle flexion with areflexia and (except for the two youngest patients) slight distal sensory loss. Mild distal muscular atrophy usually became apparent in the second decade. Involvement of hand muscles was present in four patients. Some patients had slight sensory ataxia. Tremor and cerebellar ataxia were not found. Cranial nerves were not involved. Patient 5 showed fine nystagmus. The protein in CSF was examined in two patients; it was normal in patient 4a and slightly increased in patient 1a. The severity and progress of the spine deformity required surgery in six of the nine patients with a scoliosis. Two patients became wheelchair dependent, at the ages of 25 years and 45 years.

The morphological details of the sural nerve biopsies of patients 2b, 4a, 5, and 6b have been described before[8] and are summarised in the patients and methods section. Similar pathological characteristics were found in the nerve biopsies of patients 1a, 1b, and 3 (figure 1, table 3). In all biopsies there was a slight variation in myelinated fibre density between fascicles of the same nerve or a focally more pronounced large fibre loss. Histograms of myelinated fibre diameters were usually unimodal showing a broad peak and a loss of large diameter fibres; only few fibres with diameters>8 μm were present. Nearly half of the teased fibres had many small and a few large focal myelin thickenings. Signs of demyelination and remyelination seemed to occur preferentially on small diameter fibres. Total transverse fascicular area was slightly increased in most patients. Although there was a tendency for increasing pathology with age, the number of cases were too small for final conclusions.

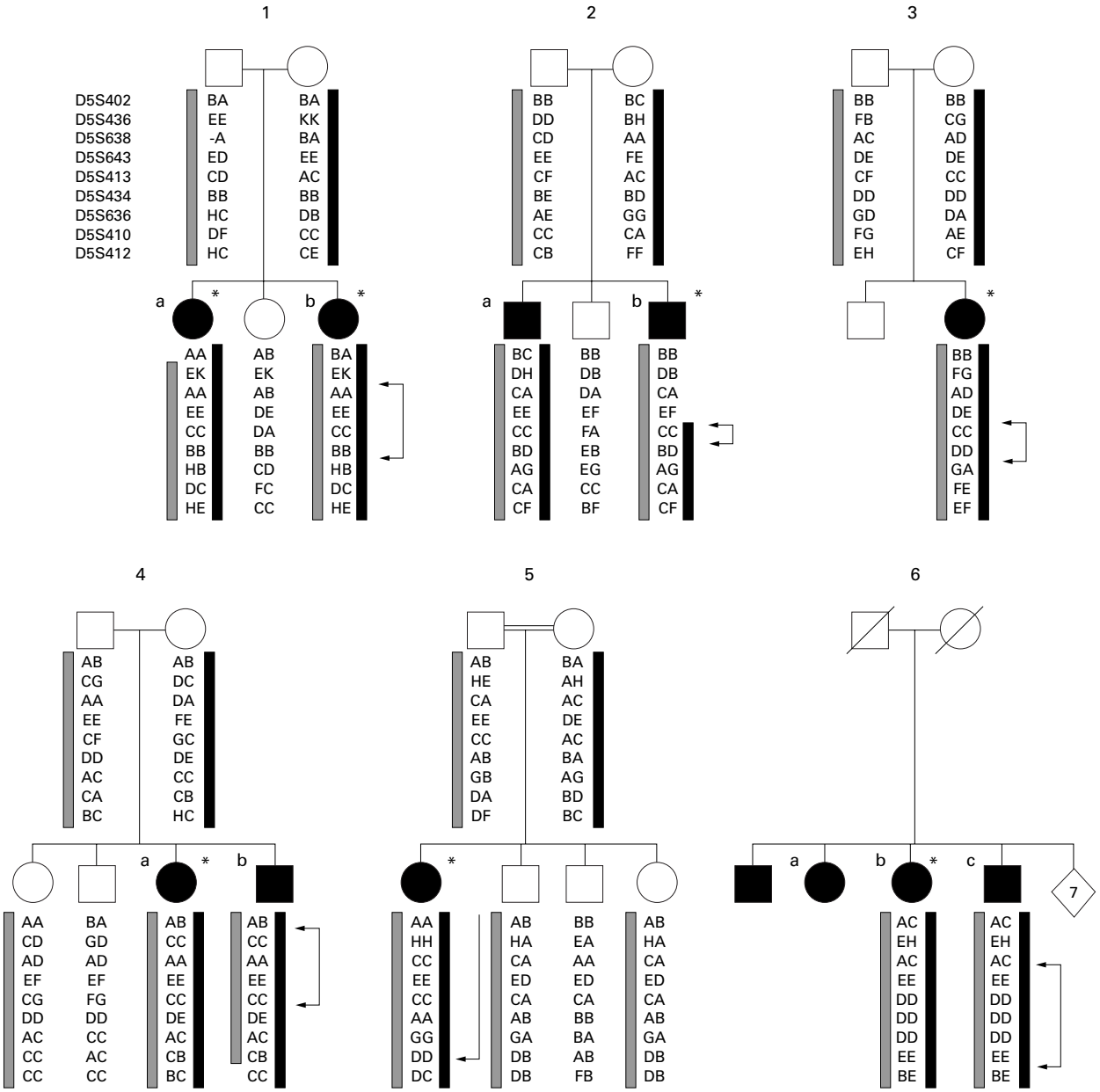

Figure 2 Pedigrees of the six investigated families. Cosegregating haplotypes are marked by bars. The double headed arrows mark the region of homozygosity by descent. Asterisks indicate the patients with a sural nerve biopsy.

DNA analysis of the patients did not show a duplication or deletion of chromosome 17p11.2. No mutations were detected in the PMP22 and the P_0 gene by SSCP analysis. The chromosome 8q13-q21.1 locus responsible for an autosomal recessive HMSN type (CMT4A)[9] was excluded in our families (data not shown). Complete cosegregation was found for markers D5S413, D5S434, D5S636, and D5S410 of chromosome 5q23-q33. For the marker D5S413 a maximum lod score of Z=3.10 at no recombination was determined. Subsequently, haplotypes were constructed to determine more accurately the cosegregating interval. Figure 2 shows that recombinations were found between the disorder and D5S402 in family 1, all markers proximal to D5S413 in family 2, and marker D5S412 in family 4. Therefore, the genetic defect would be located between D5S643 and D5S412. In keeping with this localisation is the fact that the patient from consanguineous parents (family 5, figure 2) is homozygous for all markers proximal to D5S412. Taken together with the data of LeGuern *et al*,[13] the gene would be mapped by genetic recombination to the 7-cM region between D5S643 and D5S670, which is colocalised with D5S410 in the CEPH/Genethon chromosome 5 linkage map. In the present families, there seems to be linkage disequilibrium for various of the markers in the relevant region. Omitting family 5, which is of Turkish origin, the allele C of marker D5S413 is overrepresented in the parental risk haplotypes of the Dutch families with respect to the frequency of the allele in the Dutch population ($p<0.005$; Fisher's exact test). The same is true for the haplotype A-E-C for the markers

D5S638, D5S643, and D5S413 ($p<0.005$; Fisher's exact test). It shows that the disorder in the Dutch families is probably due to a founder and may be ascribed to a common genetic defect. One exception may be family 6, in which only allele E for marker D5S643 is shared with the other families. Although the patient of family 5 shares the risk alleles E and C of markers D5S643, and D5S413 with most of the Dutch patients, we cannot be sure whether or not this is due to a common ancestral genetic defect as we do not know the allele frequencies of the Turkish population.

We could exclude the chromosome 5q23-q33 locus as the responsible disease locus in two other families with autosomal recessive demyelinating HMSN but with a different pathology. The patients in one family showed a severe hypomyelination with nearly exclusively basal lamina onion bulbs[6 17] (patients 4 and 5[17]); pathology in the other family was characterised by the abundant presence of focal myelin foldings (patients 4a and 4b[18]).

Discussion

The clinical, electrophysiological, and pathological features in 10 patients from five unrelated families with autosomal recessive CMT1 and one sporadic patient were similar to the phenotype of the patients of two Algerian families in which linkage to chromosome 5q23-q33 was shown.[13] Assuming a common genetic defect, we were able to confirm this locus in our patients as the responsible gene locus for this particular form of autosomal recessive CMT1. The gene is most likely located between D5S643 and D5S670, which is located between D5S410 and D5S412. It overlaps with the region of homozygosity in family ALG-ABD but not with that in family ALG-BOU.[13] Although this might still point to locus heterogeneity for the present families, which are individually small, the homozygous region in the ALG-BOU family was limited to two colocalised markers D5S436 and D5S643 despite the close consanguinity, which makes the relevance of homozygosity in this family for gene localisation questionable. In the present Dutch families linkage disequilibrium could be shown for various risk alleles and haplotypes, indicating that most of these families may have inherited the underlying genetic defect from a common distant ancestor. Our data confirm the existence of autosomal recessive CMT1, localised on 5q23-q33 in European families.

The phenotype of this autosomal recessive CMT1 subtype is characterised by the occurrence of an early and severe scoliosis, a relatively mild motor deficit, moderate slowing of nerve conduction velocities, and a unique morphology.[8 14] Scoliosis is not an unusual phenomenon in patients with CMT, especially in type I and it is more frequent in autosomal recessive/sporadic type I than in autosomal dominant type I cases.[2] However, it is rare that scoliosis occurs as a presenting sign in clinically mild CMT1 and that its severity requires an operative correction at an early age. Despite the marked progression of the scoliosis, neuropathic signs remained stationary or were only slightly progressive over many years in most patients. The unique combination of pathological features, characterised by an increase of basal membranes around several (de)myelinated and unmyelinated axons, relatively few classic onion bulbs and, most typically, large cytoplasmic extensions of the Schwann cells of especially unmyelinated fibres, but also of myelinated fibres, distinguishes this form from other types of demyelinating CMT. We found three presumably identical cases in the medical literature, all sporadic cases from healthy parents and all having an early, severe scoliosis[19 20] (patient 1[20]). Also, some of the sporadic Swedish cases described by Hagberg *et al*[21] and Nordborg *et al*[22] bear a close resemblance to our cases. On the other hand, this combination of morphological features was not reported in any patient with autosomal dominant demyelinating CMT. Although so-called basal membrane onion bulbs are encountered in other types of autosomal dominant and autosomal recessive demyelinating neuropathies,[4 5] they lack the marked cytoplasmic extensions of Schwann cells seen in this type of autosomal recessive demyelinating CMT.

It is tempting to interpret the remarkable changes of the myelinated as well as the unmyelinated Schwann cells as an abnormal plasticity of the Schwann cell. The presence of morphological alterations in both myelinated and unmyelinated Schwann cells suggests the involvement of a protein present in both Schwann cell types or an extracellular matrix protein rather than a myelin protein. The early occurrence of a severe scoliosis might comply with a defect in an extracellular matrix protein. Although the 5q23-q33 region seems to be a gene rich segment of the human genome, none of the genes identified so far is an obvious candidate.

We thank Dr H Vingerhoets for electrophysiological investigations and Dr P Bolhuis for 17p11.2 duplication/deletion analysis and PMP22 sequencing.

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