Brain (2002), **125,** 1320–1325

Autosomal dominant juvenile amyotrophic lateral sclerosis and distal hereditary motor neuronopathy with pyramidal tract signs: synonyms for the same disorder?

P. De Jonghe,[1,2] M. Auer-Grumbach,[3] J. Irobi,[1] K. Wagner,[4] B. Plecko,[5,3] M. Kennerson,[7] D. Zhu,[7] E. De Vriendt,[1] V. Van Gerwen,[1] G. Nicholson,[7] H.-P. Hartung[6] and V. Timmerman[1]

[1]*Molecular Genetics Department, Flanders Interuniversity Institute for Biotechnology (VIB), Born-Bunge Foundation (BBS), University of Antwerp (UIA),* [2]*Division of Neurology, University Hospital Antwerpen (UZA), Antwerpen, Belgium,* [3]*Department of Neurology,* [4]*Institute of Medical Biology and Human Genetics and* [5]*Department of Paediatrics, Karl-Franzens University Graz, Austria,* [6]*Department of Neurology, Heinrich-Heine University, Düsseldorf, Germany and* [7]*Molecular Medicine and Neurobiology Laboratories, ANZAC Medical Research Institute, University of Sydney, Concord Hospital NSW, Australia*

Correspondence to: Dr P. De Jonghe MD, Peripheral Neuropathy Group, Molecular Genetics Laboratory, University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium
E-mail: peter.dejonghe@ua.ac.be

Summary

Autosomal dominant juvenile amyotrophic lateral sclerosis (ALS) is a rare disorder and so far only one family has been reported. Genetic linkage studies mapped the disease locus to chromosome 9q34 (ALS4). The diagnosis of ALS in this family is based on the clinical signs with almost exclusively lower motor neurone pathology in combination with less prominent pyramidal tract signs. Atypical features include normal life expectancy, the absence of bulbar involvement and the symmetrical distal distribution of atrophy and weakness. We performed a molecular genetic study in three families that we had diagnosed as having distal hereditary motor neuronopathy, i.e. distal spinal muscular atrophy or spinal Charcot–Marie–Tooth syndrome, and found linkage to the ALS4 locus. The clinical phenotype in these three families, of different geographic origin (Austria, Belgium and England), is strikingly similar to the autosomal dominant juvenile ALS family except for a younger onset age in two of the distal hereditary motor neuronopathy families. These data suggest that ALS4 and distal hereditary motor neuronopathy with pyramidal tract signs may be one and the same disorder.

Keywords: distal HMN; ALS4; genetic linkage

Abbreviations: ALS = amyotrophic lateral sclerosis; CMT = Charcot–Marie–Tooth syndrome; distal HMN = distal hereditary motor neuronopathy; PCR = polymerase chain reaction; SNAP = sensory nerve action potential; STR = short tandem repeat

Introduction

In 1999, Rabin and colleagues reported detailed clinical, electrophysiological and neuropathological findings in a large Maryland kindred in which 49 family members were affected with a chronic motor neurone disease (Rabin *et al*., 1999). Patients ranged in age from 12 to 85 years. They showed distal weakness and atrophy associated with pyramidal signs and normal sensation. Chance and colleagues performed a genetic linkage study in this pedigree and mapped the disease locus to chromosome 9q34 (Chance *et al*., 1998). The disorder segregating in this family had been diagnosed previously as Charcot–Marie–Tooth (CMT) disease (Myrianthopoulos *et al*., 1964), but after recent

© *Guarantors of Brain 2002*

Table 1 *Clinical features*

Pedigree	Age at onset	Age at examination	Weakness		Reflexes			Babinski	Sensory	Pes cavus
	(years)	(years)	LL	UL	LL	UL	sign	abnormalities		
CMT-61										
II.8	?	73	+++	+++	Normal	Normal	–	–	–	
II.9	?	70	+++	+++	Brisk	Brisk	–	–	–	
III.4	<5	44	+++	+++	Normal	Brisk	–	–	–	
IV.1	<5	25	++	+	Normal	Brisk	–	–	–	
IV.2	?	24	++	–	Brisk	Brisk	–	–	–	
CMT-106										
II.2	6	60	+++	+++	Weak	Weak	–	–	–	
II.4	12	45	+++	++	Brisk	Brisk	+	–	–	
III.2	<5	34	++	+	Brisk	Brisk	+	–	+	
III.4	6	27	++	++	Brisk	Brisk	+	–	+	
III.6	15	18	++	–	Brisk	Brisk	+	–	+	
IV.2	6	11	++	+	Brisk	Brisk	–	–	+	
IV.3	6	6	–	–	Brisk	Brisk	–	–	–	
F-54										
II.1	5	43	+++	+	Normal	Normal	+	–	+	
II.3	49	49	–	++	Normal	Normal	+	–	+	
II.4	40	54	+	+	Brisk	Normal	–	+	+	
II.6	20	44	+	–	Brisk	Brisk	–	–	+	
III.2	4	20	++	–	Normal	Normal	+	–	+	
III.5	10	11	+	–	Brisk	Weak	+	–	–	

LL = lower limbs; UL = upper limbs. Weakness (on the MRC scale: – = 5/5; + = 4/5; ++ = 2–3/5; +++ = complete paralysis): LL = strength in tibialis anterior; UL = strength in intrinsic hand muscles. Babinski sign, sensory abnormalities and pes cavus: + = present, – = absent.

re-evaluation the diagnosis was changed to autosomal dominant juvenile amyotrophic lateral sclerosis (ALS). The disease locus on chromosome 9q34 was designated ALS4 (Chance *et al*., 1998). We performed a genetic linkage study in three unrelated families that we diagnosed as distal hereditary motor neuronopathy (distal HMN) and found suggestive linkage to the ALS4 locus.

Patients and methods

Family data

We performed a genealogical study in a Belgian family, an Austrian family and an English family (living in Australia) (Families CMT-61, CMT-106 and F-54, respectively) with distal HMN. The study was approved by the institutional review boards at the Universities of Antwerp (Belgium), Graz (Austria) and Sydney (Australia) and informed consent was obtained from all family members according to the Declaration of Helsinki. Motor and sensory nerve conduction velocity measurements and concentric needle EMG studies were performed according to standard procedures.

Molecular genetic studies

Genotype analysis was performed with 10 short tandem repeat (STR) markers covering the 9q34 region: D9S64, D9S1847, D9S2127, D9S2126, D9S1830, D9S1199, D9S1198, D9S164, D9S122 and D9S66 (Dib *et al*., 1996; Kwiatkowski *et al*., 1992). The order of the STRs and their genetic distances are according to the sex-average genetic maps of Généthon (http://www.cephb.fr/ceph-genethon-map.html), the Cooperative Human Linkage Center (http://lpg.nci.nih.gov/CHLC/) and GeneMap '99 (http://www.ncbi.nlm.nih.gov/genemap/). Genomic DNA (50 ng) was amplified by the polymerase chain reaction (PCR) in a reaction volume of 25 µl, containing 10 pmol of each primer and 0.1 U *Taq* DNA polymerase (Gibco BRL, Merelbeke, Belgium). PCR amplification was performed in a thermal cycler (PTC200; MJ Research, Waltham, MA, USA). Forward primers were labelled with fluorophores (Applied Biosystems, Foster City, CA, USA). Fragment analysis was performed on 4% polyacrylamide gels, using an ABI automated DNA sequencer 377, provided with the ABI GENESCAN software version 2.2 and GENOTYPER version 2.0 (Applied Biosystems). The English family was genotyped using [^{33}P]dATP incorporation of amplified products, as described previously (Nicholson *et al*., 1996). Two-point LOD (log of the odds) scores were computed using the MLINK program of the FASTLINK package (Cottingham *et al*., 1993). The calculations assumed autosomal dominant inheritance, a disease frequency of 1 in 10 000, complete disease penetrance and equal male and female recombination rates. Allele frequencies of the STR markers were obtained from the Genome Data Base (GDB; http://www.gdb.org).

Results

Clinical and electrophysiological features

The clinical features of the subjects are summarized in Table 1. In Families CMT-61 and CMT-106, the disease often

started before the age of 6 years, whereas in Family F-54 the age at onset seemed to be later. Weakness and atrophy always primarily affected the distal parts of the lower limbs and the distal muscles of the upper limbs became involved only later. Older patients did not develop bulbar signs despite pronounced atrophy and weakness of limb muscles. Most patients had brisk tendon reflexes and eight out of 18 had a Babinski sign. Sensory abnormalities were absent, except in Patient II.4 of Family F-54. Four and five patients had pes cavus in Families CMT-106 and F-54, respectively. The retrospective study demonstrated that all patients in Family F-54 had foot problems going back to school age that had not been attributed to the disease. Some patients in Family F-54 had been diagnosed previously as having spastic paraplegia with amyotrophy (Silver's disease). Electrophysiological studies showed normal to moderately slowed motor nerve conduction velocities for the median (range 35–60 m/s, $n = 7$), ulnar (range 39–56 m/s, $n = 7$) and peroneal nerves (range 32–45 m/s, $n = 3$). The amplitudes of the compound motor action potentials were decreased (range for the median nerve 100–5000 μV). Sensory nerve action potential (SNAP) amplitudes for the median and sural nerves were normal, whereas the sensory nerve conduction velocities were at the lower limit of normal or slightly slowed. Concentric needle EMG showed high amplitudes (up to 12 mV) of the motor unit action potentials. Furthermore, spontaneous activity, consisting of positive sharp waves, fibrillations and complex repetitive discharges, were found. Magnetic transcranial motor cortex stimulation was performed in five patients of Family CMT-106 and revealed prolonged central motor conduction latencies to the upper and lower limbs. MRI of the brain showed diffuse white-matter lesions in Patient III.4 in Family CMT-61 but these abnormalities were absent in her affected son, IV.1. A sural nerve biopsy specimen from three patients of Family CMT-106 showed only minor atypical abnormalities (data not shown).

Genetic linkage

We excluded the known loci and genes for CMT and related disorders in Families CMT-61, CMT-106 and F-54 (data not shown). In this study, STR analysis was performed with markers located within the ALS4 locus on chromosome 9q34. Positive linkage results were obtained in all families with markers D9S64, D9S1847, D9S2127, D9S2126, D9S1830, D9S1199, D9S1198 and D9S164 (Table 2). Cumulative significant LOD scores ($Z > 3$) were reached with seven STR markers. Recombination events leading to negative LOD scores were obtained with D9S122 and D9S66. Genotyping data demonstrated that the families did not share a common disease haplotype (Fig. 1). In four patients of Family CMT-61, the disease haplotype was 5-2-24-8-3-2-4-4-4-4, representing the 10 STRs tested from the ALS4 region. In Patient IV.2, a recombination event occurred with distal markers D9S122 and D9S66. In Family CMT-106, the disease haplotype in all affected individuals was 3-8-37-7-1-1-7 for D9S64, D9S1847, D9S2127, D9S2126, D9S1830, D9S1199 and D9S1198. In Family F-54, the disease haplotype in all patients was 2-3-7-9-4-2-5-5-5-9 for the 10 STR markers tested. One person (III.4) in Family F-54, currently aged 18 years, was an asymptomatic carrier of the disease haplotype. In two healthy relatives (III.1 and III.3) a recombination event occurred with the proximal marker D9S64. The marker D9S1199 shared a disease allele (allele 2, size = 98 base pairs) in Families CMT-61 and F-54. However, this allele was also found in married-in individuals and its frequency was 11% (GBD). These results indicate that the distal HMN locus with pyramidal tract signs is located within the 5 centimorgan (cM) ALS4 region, i.e. between the flanking markers D9S64 and D9S164.

Discussion

The large Maryland family that has been studied thoroughly over the past 35 years is currently the only family linked to the ALS4 locus on chromosome 9q34 (Chance *et al*., 1998). This family had been reported as a CMT family, although from the beginning it was noted that some individuals had additional pyramidal tract signs (Myrianthopoulos *et al*., 1964). After a recent clinical, electrophysiological and pathological re-evaluation, the diagnosis was changed to autosomal dominant juvenile ALS (Rabin *et al*., 1999). The clinical phenotype is characterized by progressive muscle atrophy and weakness in the absence of overt sensory abnormalities, pointing to the lower motor neurones and their axons as the prime site of pathology. In addition, pyramidal tract signs, such as brisk tendon reflexes and the Babinski sign, were present in several patients, indicating that the central motor tracts were also involved. The neuropathological examinations largely confirmed the primarily lower motor neurone pathology and the involvement of the central motor pathways. However, they also demonstrated that peripheral sensory nerves and central sensory tracts are involved to a lesser degree. Striking differences between classical ALS and the phenotype in the Maryland ALS4 family are the long survival, the symmetrical distal distribution of the weakness and atrophy, and the sparing of bulbar and respiratory muscles in the latter.

We have diagnosed Families CMT-61, CMT-106 and F-54 as having distal HMN on the basis of the distal distribution of the weakness and atrophy and the absence of clinical sensory abnormalities. The slight slowing of the sensory nerve conduction velocities in the presence of normal SNAP amplitudes in some patients has been observed in other distal HMN families (personal observations). Also, the disease progression follows the stereotyped course seen in CMT patients, i.e. the disease invariably starts in the distal parts of the legs and only later spreads to the hands. The presence of brisk reflexes, Babinski signs and prolonged central motor conduction times points to the additional involvement of the CNS. The similarity between the clinical phenotype in the

Table 2 *Two-point linkage results (LOD score Z at recombination fraction θ) obtained for chromosome 9q34 STR markers in Families CMT-61, CMT-106 and F-54*

Marker	*Z* at θ								Family
	0	0.001	0.01	0.05	0.1	0.2	0.3	0.4	
D9S64	1.39	1.39	1.36	1.25	1.10	0.80	0.49	0.21	CMT-61
	0.78	0.77	0.76	0.70	0.62	0.46	0.30	0.15	CMT-106
	–∞	–3.60	–1.62	–0.35	0.09	0.33	0.29	0.14	F-54
Total	**–∞**	**–1.43**	**0.50**	**1.60**	**1.81**	**1.59**	**1.08**	**0.50**	
D9S1847	0.47	0.47	0.45	0.40	0.32	0.19	0.08	0.02	CMT-61
	2.63	2.62	2.58	2.41	2.18	1.69	1.17	0.61	CMT-106
	2.41	2.40	2.37	2.21	2.00	1.54	1.03	0.49	F-54
Total	**5.50**	**5.49**	**5.41**	**5.01**	**4.50**	**3.42**	**2.28**	**1.11**	
D9S2127	1.16	1.16	1.14	1.04	0.90	0.64	0.39	0.18	CMT-61
	2.63	2.63	2.59	2.41	2.18	1.70	1.18	0.61	CMT-106
	0.90	0.90	0.89	0.81	0.72	0.52	0.30	0.09	F-54
Total	**4.70**	**4.69**	**4.61**	**4.26**	**3.81**	**2.86**	**1.87**	**0.88**	
D9S2126	1.45	1.44	1.42	1.30	1.14	0.81	0.49	0.20	CMT-61
	1.74	1.74	1.71	1.57	1.39	1.02	0.62	0.23	CMT-106
	2.41	2.40	2.37	2.21	2.00	1.54	1.03	0.49	F-54
Total	**5.60**	**5.59**	**5.50**	**5.07**	**4.53**	**3.37**	**2.13**	**0.92**	
D9S1830	1.46	1.46	1.43	1.31	1.16	0.83	0.51	0.21	CMT-61
	1.79	1.78	1.75	1.60	1.41	1.02	0.62	0.25	CMT-106
	0.90	0.90	0.89	0.81	0.72	0.52	0.30	0.09	F-54
Total	**4.15**	**4.14**	**4.06**	**3.72**	**3.28**	**2.37**	**1.42**	**0.56**	
D9S1199	1.46	1.46	1.43	1.31	1.16	0.83	0.51	0.21	CMT-61
	2.26	2.25	2.22	2.05	1.83	1.37	0.89	0.39	CMT-106
	2.41	2.40	2.37	2.21	2.00	1.54	1.03	0.49	F-54
Total	**6.13**	**6.11**	**6.02**	**5.56**	**4.98**	**3.74**	**2.42**	**1.10**	
D9S1198	0.18	0.18	0.17	0.15	0.12	0.07	0.03	0.01	CMT-61
	1.47	1.47	1.45	1.34	1.21	0.93	0.63	0.33	CMT-106
	1.81	1.80	1.78	1.65	1.49	1.13	0.74	0.33	F-54
Total	**3.46**	**3.45**	**3.39**	**3.14**	**2.81**	**2.13**	**1.40**	**0.67**	
D9S164	1.44	1.44	1.41	1.29	1.14	0.83	0.51	0.22	CMT-61
	–2.18	–0.69	0.26	0.82	0.93	0.83	0.57	0.26	CMT-106
	1.81	1.80	1.78	1.65	1.49	1.13	0.74	0.33	F-54
Total	**1.07**	**2.55**	**3.45**	**3.76**	**3.56**	**2.78**	**1.82**	**0.81**	
D9S122	–∞	–1.59	–0.61	–0.01	0.16	0.20	0.12	0.03	CMT-61
	0.51	0.50	0.49	0.45	0.39	0.27	0.17	0.08	CMT-106
	1.51	1.50	1.48	1.39	1.28	1.02	0.73	0.40	F-54
Total	**–∞**	**0.42**	**1.37**	**1.83**	**1.83**	**1.49**	**1.02**	**0.50**	
D9S66	–∞	–1.54	–0.57	0.03	0.20	0.23	0.14	0.04	CMT-61
	–3.10	–1.78	–0.81	–0.16	0.07	0.21	0.22	0.14	CMT-106
	0.90	0.90	0.89	0.81	0.72	0.52	0.30	0.09	F-54
Total	**–∞**	**–2.42**	**–0.49**	**0.68**	**0.99**	**0.96**	**0.65**	**0.27**	

Maryland kindred (Rabin *et al*., 1999) and in our three families is striking. The only difference is a younger age at onset in both families, CMT-61 and CMT-106.

Genetic linkage analysis showed positive LOD scores in all three families (CMT-61, CMT-106 and F-54) with markers covering the ALS4 locus at chromosome 9q34. In all three families, a disease-associated haplotype was present in all affected individuals. On the basis of the recombination events, we mapped the distal HMN/ALS4 linkage region between D9S64 and D9S164. This region represents a 3.5 Mb region according to the Golden Path at UCSC (University of California, Santa Cruz) (http://genome.ucsc.edu/goldenPath/

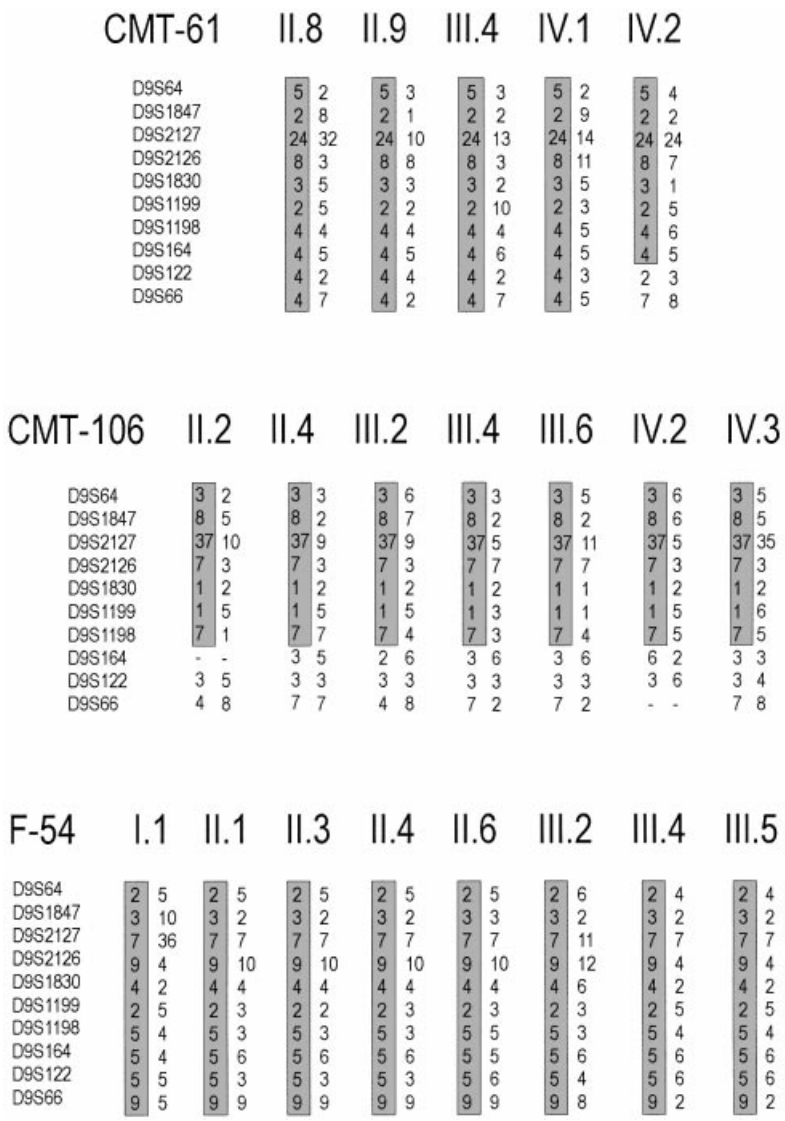

Fig. 1 Haplotypes in three distal HMN/ALS4 families. The haplotypes of 10 STR markers from the ALS4 region on chromosome 9q34 are shown for five, seven and eight patients in Families CMT-61, CMT-106 and F-54, respectively. The common disease haplotype is boxed. The markers are ordered from centromere (top) to telomere (bottom). Person III.4 in Family F-54 is an asymptomatic carrier of the disease haplotype.

septTracks.html) and overlaps with the previously reported fine mapping data of the ALS4 region (Blair *et al*., 2000), assigning the ALS4 locus to a critical interval of <3 cM or ~500 kb, flanked by D9S149 and D9S1198. Mutation analysis excluded *RING3L/ORFX* and *RALGDS* as disease-causing genes for ALS4 (Blair *et al*., 2000).

We have no intention of starting an argument about the nomenclature and classification of these disorders. However, we feel that it might be productive to search for additional families with a similar phenotype that have been diagnosed as having distal HMN, distal spinal muscular atrophy or spinal CMT in order to fine-map the ALS4 locus and eventually to identify the gene involved in this intriguing disorder.

Acknowledgements

The authors gratefully acknowledge the co-operation and participation of the family members in this study. This research project was supported by the University of Antwerp, the Fund for Scientific Research–Flanders (FWO), the Geneeskundige Stichting Koningin Elisabeth and the Austrian Science Fund (FWF-P13563BIO). J.I. is a doctoral fellow supported by the University of Antwerp and V.T. is a postdoctoral fellow of the FWO.

References

Blair IP, Bennett CL, Abel A, Rabin BA, Griffin JW, Fischbeck KH, et al. A gene for autosomal dominant juvenile amyotrophic

lateral sclerosis (ALS4) localizes to a 500-kb interval on chromosome 9q34. Neurogenetics 2000; 3: 1–6.

Chance PF, Rabin BA, Ryan SG, Ding Y, Scavina M, Crain B, et al. Linkage to the gene for an autosomal dominant form of juvenile amyotrophic lateral sclerosis to chromosome 9q34. Am J Hum Genet 1998; 62: 633–40.

Cottingham RW, Idury RM, Schäffer AA. Faster sequential genetic linkage computations. Am J Hum Genet 1993; 53: 252–63.

Dib C, Fauré S, Fizames C, Samson D, Drouot N, Vignal A, et al. A comprehensive genetic map of the human genome based on 5,264 microsatellites. Nature 1996; 380: 152–4.

Kwiatkowski DJ, Henske EP, Weimer K, Ozelius L, Gusella JF, Haines J. Construction of a GT polymorphism map of human 9q. Genomics 1992; 12: 229–40.

Myrianthopoulos NC, Lane MH, Silberberg DH, Vincent BL. Nerve conduction and other studies in families with Charcot–Marie–Tooth disease. Brain 1964; 87: 589–608.

Nicholson GA, Dawkins JL, Blair IP, Kennerson ML, Gordon MJ, Cherryson AK, et al. The gene for hereditary sensory neuropathy type I (HSN-I) maps to chromosome 9q22.1-q22.3. Nature Genet 1996; 13: 101–4.

Rabin BA, Griffin JW, Crain BJ, Scavina M, Chance PF, Cornblath DR. Autosomal dominant juvenile amyotrophic lateral sclerosis. Brain 1999; 122: 1539–50.

Received October 10, 2001.
Accepted January 24, 2002