Am. J. Hum. Genet. 65:757–763, 1999

A New Locus for Autosomal Dominant "Pure" Hereditary Spastic Paraplegia Mapping to Chromosome 12q13, and Evidence for Further Genetic Heterogeneity

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Summary

Autosomal dominant pure hereditary spastic paraplegia (ADPHSP) is clinically characterized by slowly progressive lower-limb spasticity. The condition is genetically heterogeneous, and loci have been mapped at chromosomes 2p, 8q, 14q, and 15q. We have performed a genomewide linkage screen on a large family with ADPHSP, in which linkage to all four previously known loci was excluded. Analysis of markers on chromosome 12q gave a peak pairwise LOD score of 3.61 at D12S1691, allowing us to assign a new locus for ADPHSP (a locus that we have designated "SPG10") to this region. Haplotype construction and analysis of recombination events narrowed the SPG10 locus to a 9.2-cM region between markers D12S368 and D12S83. In addition, our data strongly suggest that there are at least six ADPHSP loci, since we describe a further family in which linkage to all five known ADPHSP loci has been excluded.

Introduction

The hereditary spastic paraplegias (HSPs) are neurodegenerative disorders whose principal feature is progressive lower-limb spasticity. They are classified as "pure" when spastic paraplegia exists in isolation and as complicated when other major clinical features are present. Autosomal dominant, autosomal recessive, and X-linked–recessive inheritance patterns have been described for both pure and complicated forms (Harding 1984; Kobayashi et al. 1995; Fink and Heiman-Patterson 1996; Reid 1997).

Although patients with autosomal dominant pure hereditary spastic paraplegia (ADPHSP) generally have the same core clinical features—that is, spastic gait abnormality, lower-limb hypertonicity, pyramidal weakness, hyperreflexia, and extensor-plantar responses—there is considerable variation in age at onset and severity of spasticity, both within and between families (Harding 1981; Polo et al. 1993; Dürr et al. 1994; De Jonghe et al. 1996; Nielsen et al. 1998; Reid et al., in press-*b*). In addition to locomotor problems, bladder dysfunction and overt or subclinical sensory abnormalities are common, and subclinical cognitive impairment may be present (Harding 1981; Schady and Sheard 1990; Tedeschi et al. 1991; Polo et al. 1993; Dürr et al. 1994; Webb and Hutchinson 1998).

There is considerable genetic heterogeneity in ADPHSP, with loci mapped on chromosomes 2p (SPG4 [MIM 182601]) (Hazan et al. 1994; Hentati et al. 1994*b*), 8q (SPG8 [MIM 603563–]) (Hedera et al. 1999; Reid et al., in press-*a*), 14q (SPG3 [MIM 182600]) (Hazan et al. 1993), and 15q (SPG6 [MIM 600363]) (Fink et al. 1995). The existence of at least one further ADPHSP locus is strongly suggested by the exclusion of linkage at all four of these loci in some families (Reid et al., in press-*a*).

In previous studies, we identified a large "unlinked" family, for which linkage at all known ADPHSP loci was excluded (Reid et al., in press-*a*, in press-*b*). We have now mapped, using a genomewide screen, the responsible gene in this family, to a 9.2-cM region at chromosome 12q13. Linkage at this locus was excluded in a second "unlinked" family, strongly suggesting the presence of at least one further ADPHSP locus.

Subjects and Methods

Clinical Ascertainment

The families included in the present study (families 4 [fig. 1] and 28) were ascertained as part of a United Kingdom–wide clinical and genetic study of ADPHSP,

Received April 28, 1999; accepted for publication June 23, 1999; electronically published July 29, 1999.

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0002-9297/1999/6503-0022$02.00

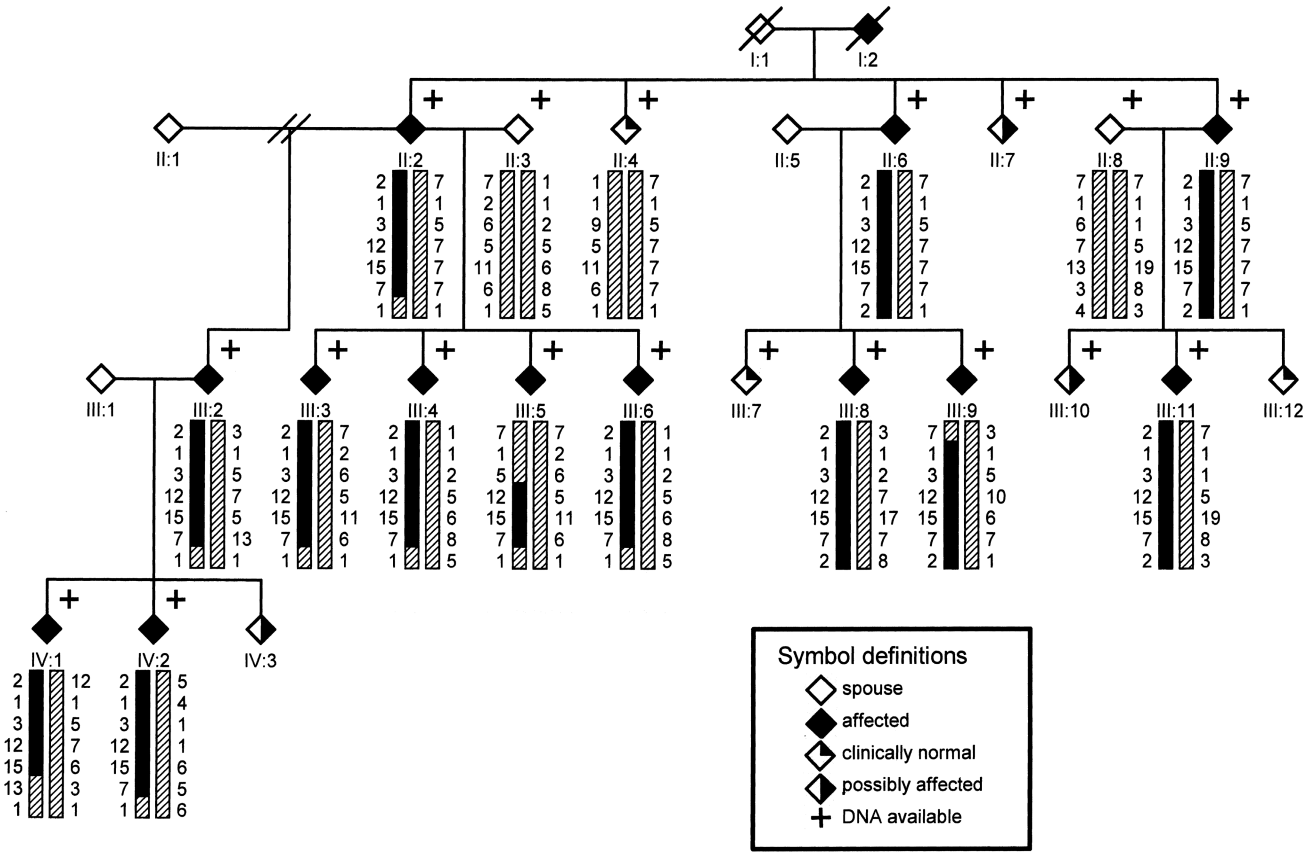

Figure 1 Family tree of ADPHSP family 4, showing haplotypes for markers around SPG10 region. The marker order, from top to bottom, is D12S345, D12S85, D12S368, D12S1586, D12S1691, D12S83, and D12S326. For clarity, noncontributory haplotypes are represented by a uniform hatched-shaded pattern. Recombination events in affected individuals narrow the SPG10 critical region to a 9.2-cM region between D12S368 and D12S83 (Dib et al. 1996). For confidentiality, the sex of the subjects has not been provided.

which has been described elsewhere (Reid et al., in press-*b*). Both families have previously been formally excluded from linkage to the loci on chromosomes 2p, 8q, 14q, and 15q, with multipoint linkage analysis giving LOD scores <-2, throughout the candidate regions for each of these loci (Reid et al., in press-*a,* in press-*b*). After informed consent was obtained, all available affected and apparently unaffected family members were neurologically assessed by a single physician (E.R.), using a standard protocol. Diagnostic criteria for ADPHSP were based on those of Harding and have been described elsewhere (Harding 1981, 1984; Reid et al., in press-*b*). In brief, subjects were classified as being affected if they had lower-limb hyperreflexia in addition to at least one of the following: progressive spastic gait abnormality, bilateral extensor-plantar reflex, and/or bilateral sustained ($\geq$5 beats) ankle or knee clonus. Subjects were classified as being possibly affected if lower-limb hyperreflexia was present without other abnormal signs, and they were classified as being normal if the results of neurological examination were entirely normal. Ethical approval for the study was granted by the Addenbrooke's Hospital ethical committee. In total, 45 family members from the two families were clinically assessed. In addition, DNA samples were available from a further affected subject from family 28, who was a deceased obligate gene carrier, and from four spouses.

DNA Analysis

A genomewide screen, excluding the X chromosome (since male-to-male transmission was present), was performed on DNA samples from family 4, by means of ABI Linkage Mapping Set version 2 (LMS2) (Perkin-Elmer). This set consists of fluorescently labeled PCR primer pairs for 400 highly polymorphic dinucleotide-repeat microsatellite markers chosen from the Généthon human linkage map (Weissenbach et al. 1992; Gyapay et al. 1994; Dib et al. 1996). The markers have an average spacing of 10 cM and incorporate reverse-primer–tailing chemistry (Brownstein et al. 1996). DNA samples were isolated from blood of all consenting individuals. PCR reactions were performed for each marker individually, in a 5-μl reaction volume containing

~50 ng of DNA, 2.5 mM $MgCl_2$, 10 mM Tris-HCl pH 8.3, 50 mM KCl, 250 μM each dNTP, 0.625 pmol of each primer, and 0.25 units of Ampli*Taq* Gold (Perkin-Elmer). Reactions were performed on a Perkin-Elmer 9600 thermal cycler or by means of an ABI 877 integrated thermal-cycler robot. A standard thermocycling profile was used for all markers; it consisted of an initial denaturation at 95°C for 12 min, which was followed by 10 cycles each of denaturation at 95°C for 15 s, annealing at 55°C for 15 s, and synthesis at 72°C for 30 s. This was followed by 20 cycles each of denaturation at 89°C for 15 s, annealing at 55°C for 15 s, and synthesis at 72°C for 30 s and by a final extension step at 72°C for 10 min. PCR products for selected sets of markers were pooled, ethanol precipitated, and size fractionated on a 5% denaturing polyacrylamide gel (Amresco) by electrophoresis on an ABI 377XL sequencer. PCR products were sized by the Genescan version 2.1 program and were scored by the Genotyper version 2.0 program. In addition to the LMS2 marker set, two markers—D12S1586 and D12S1691—were used in genotyping. Primer sequences for these additional markers are available from the Généthon microsatellite linkage map (Dib et al. 1996). PCR reaction and thermocycling conditions were identical to those used for the LMS2 marker set.

Linkage Analysis

Pairwise linkage analysis was performed by the MLINK program of the FASTLINK version 4.0P package (Lathrop et al. 1985), accessed via the Genetic Linkage User Environment interface (UK Human Genome Mapping Project Resource Centre). Multipoint linkage analysis was performed with the program Linkmap, with previously published between-marker genetic distances, which were calculated by the CILINK program (Dib et al. 1996). For linkage calculations, allele frequencies were assumed to be equal, the gene frequency for ADPHSP was assumed to be 10^{-4}, and male and female recombination rates were assumed to be equal.

Statistical Methods

Age-at-onset data were compared by the unpaired *t*-test.

Results

Clinical Features

Clinical information on families 4 and 28 has been presented elsewhere (Reid et al., in press-*a,* in press-*b*). All except a single affected subject in family 4 had a symptomatic spastic-gait abnormality, in addition to lower-limb hyperreflexia, meeting the Hereditary Spastic Paraplegia Working Group diagnostic criteria for being "definitely affected," as well as our own diagnostic criteria (Fink and Heiman-Patterson 1996). The asymptomatic patient from family 4 (II:9) was an obligate gene carrier who had bilateral lower-limb hyperreflexia, bilateral extensor-plantar responses, and unilateral sustained ankle clonus. One previously asymptomatic affected patient from family 4 had become symptomatic since our earlier descriptions of this family (Reid et al., in press-*a,* in press-*b*). The mean $\pm$ SD age at onset of symptoms in family 4 was 10.8 $\pm$ 9.6 years (range 8–40 years), and that in family 28 was 6.9 $\pm$ 6.2 years (range 5–22 years). Asymptomatic patients were not included in age-at-onset calculations.

Identification of a Novel ADPHSP Locus

We performed a genome screen on family 4, a large family with ADPHSP and in which linkage at all four previously identified ADPHSP loci has been excluded (Reid et al., in press-*a,* in press-*b*). In view of the age-dependent penetrance of ADPHSP, pairwise LOD scores for genome-screen markers were calculated by the conservative, affected-only approach. No pairwise LOD score >3.0 was obtained with the genome-screen markers. We therefore constructed haplotypes around markers for which the pairwise LOD score was >0.5. This allowed us to identify a region, flanked by markers D12S368 and D12S83 (both of which showed recombinations with the disease gene, albeit in different subjects), where complete segregation of the disease with intervening markers might be possible. Markers D12S1586 and D12S1691 (Dib et al. 1996), located between D12S368 and D12S83, were genotyped. Both of these markers segregated entirely with the disease; pairwise LOD scores for these markers, based on affected-only analysis, are shown in table 1. The peak two-point LOD score is 3.31 at marker D12S1691. Pairwise LOD scores were recalculated with the inclusion of genotyping data from an elderly (age 55 years, 15 years older than maximum age at onset of disease within family 4) clinically normal subject, who was coded as unaffected. Disease penetrance was assumed to be 99%, as has been suggested elsewhere (Hazan et al. 1994) (table 1). The peak LOD score rose to 3.61 at D12S1691, strongly supporting the assignment of a new ADPHSP locus (which we have designated "SPG10") to this region. Haplotypes were constructed for markers D12S345, D12S85, D12S368, D12S1586, D12S1691, D12S83, and D12S326. Recombination events in affected individuals place the disease locus within a 9.2-cM interval, flanked by D12S368 and D12S83 (figs. 1 and 2).

Exclusion Mapping

We went on to examine a further family, family 28, for linkage to the SPG10 locus. Linkage at the ADPHSP loci on chromosomes 2p, 8q, 14q, and 15q had previ-

Table 1

LOD Scores for Families 4 and 28, with Markers from SPG10 Region

Family and Marker	LOD Score at θ = 0	.05	.1	.2	.3	.4	.5
	Affected-Only Analysis						
4:							
D12S368	−∞	.89	.96	.77	.45	.13	0
D12S1586	2.41	2.16	1.91	1.38	.81	.27	0
D12S1691	3.31	3.02	2.72	2.06	1.33	.56	0
D12S83	−∞	−.25	−.04	.05	.07	.02	0
28:							
D12S368	−∞	−.57	−.09	.24	.28	.19	0
D12S1586	−∞	−.58	−.09	.24	.29	.19	0
D12S1691	−∞	−.30	.16	.45	.44	.28	0
D12S83	−∞	−.86	−.35	.04	.14	.12	0
	Analysis with Unaffected Subject Included[a]						
4:							
D12S368	−∞	1.16	1.21	0.97	0.58	0.17	0
D12S1586	2.71	2.44	2.17	1.57	0.94	0.31	0
D12S1691	3.61	3.30	2.97	2.26	1.46	0.60	0
D12S83	−∞	−0.17	0.03	0.13	0.10	0.03	0

[a] Unaffected individual was 15 years older than oldest age at onset in the family.

ously been excluded in this family, by multipoint linkage analysis giving LOD scores <-2 throughout the relevant candidate regions (Reid et al., in press-*a,* in press-*b*). DNA samples from this family were genotyped with four markers from the SPG10 critical region. Two-point LOD scores for these markers, based on affected-only analysis, are given in table 1. Multipoint analysis was performed, by affected-only analysis, with markers D12S368, D12S1691, and D12S83. This generated LOD scores <-2 throughout the SPG10 critical region, formally excluding linkage at this locus.

Locus-Phenotype Correlations

It has been suggested that age at onset of ADPHSP correlates with genetic locus (e.g., see Reid et al., in press-*b*). In terms of mean ± SD age at onset of symptoms, there was no significant difference between family 4 (10.8 ± 9.6 years) and family 28 (6.9 ± 6.2 years; linkage excluded at all known ADPHSP loci); however, the mean ± SD age at onset of symptoms in family 4 is younger than that (i.e., 29.6 ± 11.0 years) which has been reported elsewhere (Reid et al., in press-*a*) for a family with linkage to SPG8 (P = .0001). We assessed whether there was any significant age-at-onset difference between families 4 and 28 and seven U.K. families (families 2, 5, 7, 22, 24, 25, and 27 in the study by Reid et al. [in press-*b*]; mean age at onset 24.1 ± 12.3 years) in which linkage to the chromosome 2 ADPHSP locus is likely. Families 4 and 28 both had a significantly younger mean age at onset than was reported for the pooled families with linkage to chromosome 2 (P = .001 for family 4; P = .0002 for family 28).

Discussion

Our results confirm the presence of extensive genetic heterogeneity in ADPHSP. Previously, four loci for ADPHSP had been identified, on chromosomes 2p, 8q, 14q, and 15q, and had been narrowed to regions of 3 cM, 3.4 cM, 5 cM, and 7 cM, respectively (in a family with *complicated* HSP, the phenotype mapped to a 0-cM interval at the SPG4 locus, but it is possible that the responsible gene in this family may be different from that involved in autosomal dominant *pure* HSP [Heinzlef et al. 1998]) (Hazan et al. 1993, 1994; Hentati et al. 1994*b;* Fink et al. 1995; Bürger et al. 1996; Scott et al. 1997; Paternotte et al. 1998; Hedera et al. 1999; Reid et al., in press-*a*). We have now identified a fifth locus for ADPHSP, in a 9.2-cM region between D12S368 and D12S83, at chromosome 12q13 (Genome Database). In addition, our results strongly suggest that there are at least six ADPHSP loci, since we have identified a family in which linkage to all five known ADPHSP loci has been excluded.

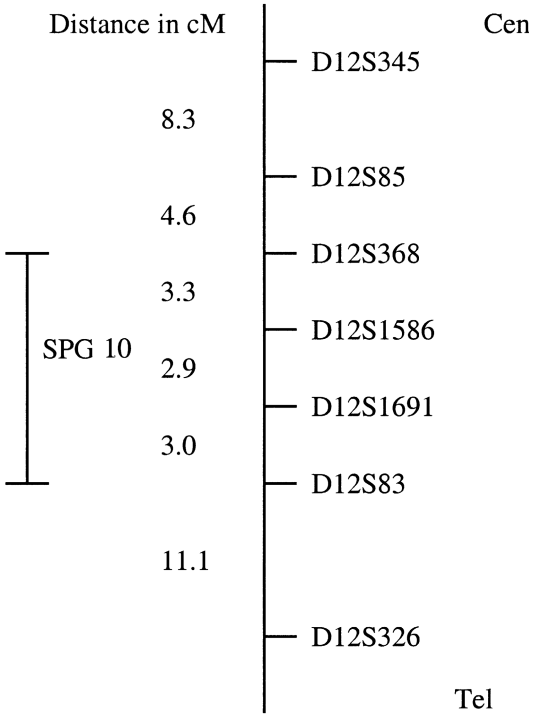

Figure 2 Schematic genetic map showing selected chromosome 12 markers. The SPG10 critical region lies between D12S368 and D12S83. Previously published genetic distances between markers, calculated by the CILINK program, are shown on the left (Dib et al. 1996).

Our mapping of the SPG10 locus brings to 10 the number of genes implicated in HSP that have been mapped or cloned, including 2 recessive genes and 2 X-linked genes. Recessive HSP genes map to chromosome 8q (SPG5 [MIM 270800]) and chromosome 16q (SPG7 [MIM 602783]) (Hentati et al. 1994*a;* De Michelle et al. 1998). The SPG7 gene has been cloned, and different mutations in this gene are associated with pure or complicated (by optic, cerebellar, and cortical atrophy) HSP (Casari et al. 1998). The protein product of this gene, paraplegin, is a nuclear-encoded mitochondrial metalloprotease that also has a chaperone function, and HSP patients with paraplegin mutations have defects in oxidative phosphorylation (Casari et al. 1998). Mutations in a myelin gene, the proteolipid protein (PLP) gene (SPG2 [MIM 312900]), at Xq22, are associated with X-linked pure and complicated HSP (Saugier-Veber et al. 1994; Cambi et al. 1996), whereas a form of X-linked HSP, in which spasticity is accompanied by mental retardation and adducted thumbs, is caused by mutations in the neural cell–adhesion molecule L1 (L1-CAM) gene (SPG1 [MIM 312920], at Xq28 (Jouet et al. 1994). Finally, a gene (SPG9 [MIM 601162]) causing autosomal dominant HSP complicated by cataracts, gastroesophageal reflux, and amyotrophy has been mapped to chromosome 10q (Seri et al. 1999).

Correlations between ADPHSP genetic locus and age at onset of symptoms are likely to exist. Three separate studies involving a total of 24 families with linkage to chromosome 2 have found no significant age-at-onset difference between families (Dürr et al. 1996; Nielsen et al. 1998; Reid et al., in press-*b*), and, in the two families with linkage to chromosome 8 and in the single family with linkage to chromosome 15 that have been identified, the mean age at onset was similar to that in families with linkage to chromosome 2 (Fink et al. 1995; Hedera et al. 1999; Reid et al., in press-*a*). On the other hand, families with linkage to chromosome 14 have a consistently early mean age at onset, usually <10 years (Hazan et al. 1993; Hentati et al. 1994*b;* Gispert et al. 1995; Haung et al. 1997; Paternotte et al. 1998), and our data indicate that chromosome 12-linked ADPHSP may also have an early age at onset. These apparent correlations need to be confirmed by further data on families with linkage to known loci, but they suggest that there are locus-specific differences in the molecular pathology of ADPHSP. As in the case of families with HSP mapped to other loci, there was a wide range in disease severity within family 4, with some patients requiring a wheelchair, whereas one patient was asymptomatic at age 40 years. This intriguing variability suggests that genetic background or perhaps environmental influences may modify the disease process.

In summary, the data presented in this study identify a fifth locus for ADPHSP and strongly suggest that there are at least six ADPHSP loci. Clarification of the full extent of genetic heterogeneity in ADPHSP will facilitate the eventual cloning of ADPHSP genes and also will allow more-accurate genetic counseling of affected families.

Acknowledgments

We are grateful to the families involved in this study for their participation. We thank Dr. Doug Easton for very helpful discussions regarding the genome-screen linkage results, and we thank Frank Visser for help with the GLUE interface and with linkage calculations. The genome screen was performed in the Medical Research Council's UK Human Genome Mapping Project Resource Centre Linkage Hotel. E.R. is a Wellcome Research Training Fellow, and D.C.R. is a Glaxo-Wellcome Senior Research Fellow. E.R. is supported by a Sackler Award.

Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Genome Database, http://www.gdb.org (for cytogenetic locations of SPG10 markers)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for HSP loci SPG1 [MIM 312920], SPG2 [MIM 312900], SPG3 [MIM 182600], SPG4 [MIM 182601], SPG5 [MIM 270800], SPG6 [MIM 600363], SPG7 [MIM 602783], SPG8 [MIM 603563], and SPG9 [MIM 601162])

UK Human Genome Mapping Project Resource Centre, http://www.hgmp.mrc.ac.uk (for GLUE interface and other linkage utilities)

References

Brownstein MJ, Carpten JD, Smith JR (1996) Modulation of non-templated nucleotide addition by *Taq* DNA polymerase: primer modifications that facilitate genotyping. Biotechniques 20:1004–1010, 1008–1010

Bürger J, Metzke H, Paternotte C, Schilling F, Hazan J, Reis A (1996) Autosomal dominant spastic paraplegia with anticipation maps to a 4-cM interval on chromosome 2p21-2p24 in a large German family. Hum Genet 98:371–375

Cambi F, Tang X-M, Cordray MS, Fain PR, Keppen LD, Barker DF (1996) Refined genetic mapping and proteolipid protein mutation analysis in X-linked pure hereditary spastic paraplegia. Neurology 46:1112–1117

Casari G, De Fusco M, Ciarmatori S, Zeviani M, Mora M, Fernandez P, De Michele G, et al (1998) Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. Cell 93:973–983

De Jonghe P, Krols L, Michalik A, Hazan J, Smeyers G, Löfgren A, Weissenbach J, et al (1996) Pure familial spastic para-

plegia: clinical and genetic analysis of nine Belgian pedigrees. Eur J Hum Genet 4:260–266

De Michele G, De Fusco M, Cavalcanti F, Filla A, Marconi R, Volpe G, Monticelli A, et al (1998) A new locus for autosomal recessive hereditary spastic paraplegia maps to chromosome 16q24.3. Am J Hum Genet 63:135–139

Dib C, Fauré S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, et al (1996) A comprehensive genetic map of the human genome based on 5,264 microsatellites. Nature 380:152–154

Dürr A, Brice A, Serdaru M, Rancurel G, Derouesné C, Lyon-Caen O, Agid Y, et al (1994) The phenotype of "pure" autosomal dominant spastic paraplegia. Neurology 44: 1274–1277

Dürr A, Davoine C-S, Paternotte C, von Fellenberg J, Cogilnicean S, Coutinho P, Lamy C, et al (1996) Phenotype of autosomal dominant spastic paraplegia linked to chromosome 2. Brain 119:1487–1496

Fink JK, Heiman-Patterson T (1996) Hereditary spastic paraplegia: advances in genetic research. Neurology 46: 1507–1514

Fink JK, Wu C-tB, Jones SM, Sharp GB, Lange BM, Lesicki A, Reinglass T, et al (1995) Autosomal dominant familial spastic paraplegia: tight linkage to chromosome 15q. Am J Hum Genet 56:188–192

Gispert S, Santos N, Damen R, Voit T, Schulz J, Klockgether T, Orozco G, et al (1995) Autosomal dominant familial spastic paraplegia: reduction of the FSP1 candidate region on chromosome 14q to 7 cM and locus heterogeneity. Am J Hum Genet 56:183–187

Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, et al (1994) The 1993–94 Généthon human genetic linkage map. Nat Genet 7:246–339

Harding AE (1981) Hereditary "pure" spastic paraplegia: a clinical and genetic study of 22 families. J Neurol Neurosurg Psychiatry 44:871–883

——— (1984) The hereditary ataxias and related disorders. Churchill Livingstone, Edinburgh

Haung S, Zhuyu, Li H, Labu, Baizhu, Lo WH, Fischer C, et al (1997) Another pedigree with pure autosomal dominant spastic paraplegia (AD-FSP) from Tibet mapping to 14q11.2-q24.3. Hum Genet 100:620–623

Hazan J, Fontaine B, Bruyn RPM, Lamy C, van Deutekom JC, Rime CS, Dürr A, et al (1994) Linkage of a new locus for autosomal dominant familial spastic paraplegia to chromosome 2p. Hum Mol Genet 3:1569–1573

Hazan J, Lamy C, Melki J, Munnich A, de Rocondo J, Weissenbach J (1993) Autosomal dominant familial spastic paraplegia is genetically heterogeneous and one locus maps to chromosome 14p. Nat Genet 5:163–167

Hedera P, Rainier S, Alvarado D, Zhao X, Williamson J, Otterud B, Leppert M, et al (1999) Novel locus for autosomal dominant hereditary spastic paraplegia, on chromosome 8q. Am J Hum Genet 64:563–569

Heinzlef O, Paternotte C, Mahieux F, Prud'homme J-F, Dien J, Madigand M, Pouget J, et al (1998) Mapping of a complicated familial spastic paraplegia to locus SPG4 on chromosome 2p. J Med Genet 35:89–93

Hentati A, Pericak-Vance MA, Hung W-Y, Belal S, Laing N, Boustany R-M, Hentati F, et al (1994*a*) Linkage of "pure" autosomal recessive familial spastic paraplegia to chromosome 8 markers and evidence of genetic locus heterogeneity. Hum Mol Genet 3:1263–1267

Hentati A, Pericak-Vance MA, Lennon F, Wasserman B, Hentati F, Juneja T, Angrist MH, et al (1994*b*) Linkage of a locus for autosomal dominant familial spastic paraplegia to chromosome 2p markers. Hum Mol Genet 3:1867–1871

Jouet M, Rosenthal A, Armstrong G, MacFarlane J, Stevenson R, Paterson J, Metzenberg A (1994) X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. Nat Genet 7: 402–407

Kobayashi H, Garcia CA, Alfonso G, Marks HG, Hoffman EP (1996) Molecular genetics of familial spastic paraplegia: a multitude of responsible genes. J Neurol Sci 137:131–138

Lathrop GM, Lalouel JM, Julier C, Ott J (1985) Multipoint linkage analysis in humans: detection of linkage and estimation of recombination. Am J Hum Genet 37:482–498

Nielsen JE, Krabbe K, Jennum P, Koefoed P, Jensen LN, Fenger K, Eiberg H, et al (1998) Autosomal dominant pure spastic paraplegia: a clinical, paraclinical, and genetic study. J Neurol Neurosurg Psychiatry 64:61–66

Paternotte C, Rudnicki D, Fizames C, Davoine C-S, Mavel D, Dürr A, Samson D, et al (1998) Quality assessment of whole genome mapping data in the refined familial spastic paraplegia interval on chromosome 14q. Genome Res 8: 1216–1227

Polo JM, Calleja J, Combarros O, Berciano J (1993) Hereditary "pure" spastic paraplegia: a study of nine families. J Neurol Neurosurg Psychiatry 56:175–181

Reid E (1997) Syndrome of the month: pure hereditary spastic paraplegia. J Med Genet 34:499–503

Reid E, Dearlove AM, Whiteford ML, Rhodes M, Rubinsztein DC. Autosomal dominant spastic paraplegia: refined SPG8 locus and further genetic heterogeneity. Neurology (in press-*a*)

Reid E, Grayson C, Rogers MT, Rubinsztein DC. Locus-phenotype correlations in autosomal dominant pure hereditary spastic paraplegia: a clinical and molecular genetic study of 28 United Kingdom families. Brain (in press-*b*)

Saugier-Veber P, Munnich A, Bonneau D, Rozet J-M, Le Merrer M, Gil R, Boespflug-Tanguy O (1994) X-linked spastic paraplegia and Pelizaeus-Merzbacher disease are allelic disorders at the proteolipid protein locus. Nat Genet 6: 257–262

Schady W, Sheard A (1990) A quantitative study of sensory function in hereditary spastic paraplegia. Brain 113: 709–720

Scott WK, Gaskel PC, Lennon F, Wolpert CM, Menold MM, Aylsworth AS, Warner C, et al (1997) Locus heterogeneity, anticipation and reduction of the chromosome 2p minimal candidate region in autosomal dominant familial spastic paraplegia. Neurogenetics 1:95–102

Seri M, Cusano R, Forabosco P, Cinti R, Caroli F, Picco P, Bini R, et al (1999) Genetic mapping to 10q23.3-q24.2, in a large Italian pedigree, of a new syndrome showing bilateral cataracts, gastroesophageal reflux, and spastic paraparesis with amyotrophy. Am J Hum Genet 64:586–593

Tedeschi G, Allocca S, Di Costano A, Carlomango S, Merla F, Petretta V, Toriello A, et al (1991) Multisystem involvement of the central nervous system in Strümpell's disease. J Neurol Sci 103:55–60

Webb S, Hutchinson M (1998) Cognitive impairment in families with pure autosomal dominant hereditary spastic paraparesis. Brain 121:923–929

Weissenbach J, Gyapay G, Dib C, Vignal A, Morissette J, Millasseau P, Marc S, et al (1992) A second-generation linkage map of the human genome. Nature 359:794–801