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Report

A New Locus for Autosomal Recessive Spastic Paraplegia Associated with Mental Retardation and Distal Motor Neuropathy, SPG14, Maps to Chromosome 3q27-q28

G. Vazza,[1] M. Zortea,[1] F. Boaretto,[1] G. F. Micaglio,[2] V. Sartori,[2] and M. L. Mostacciuolo[1]

[1]Department of Biology, University of Padua, Padua, Italy, and [2]Department of Neurology, Hospital of Montebelluna, Treviso, Italy

Hereditary spastic paraplegias (HSPs), a group of neurodegenerative disorders that cause progressive spasticity of the lower limbs, are characterized by clinical and genetic heterogeneity. To date, three loci for autosomal recessive HSP have been mapped on chromosomes 8p, 16q, and 15q. After exclusion of linkage at these loci, we performed a genomewide search in a consanguineous Italian family with autosomal recessive HSP complicated by mild mental retardation and distal motor neuropathy. Using homozygosity mapping, we obtained positive LOD scores for markers on chromosome region 3q27-q28, with a maximum multipoint LOD score of 3.9 for marker D3S1601. Haplotype analysis allowed us to identify a homozygous region (4.5 cM), flanked by markers D3S1580 and D3S3669, that cosegregates with the disease. These data strongly support the presence, on chromosome 3q27-28, of a new locus for complicated recessive spastic paraplegia, which we have named "SPG14."

Hereditary spastic paraplegias (HSPs) are a heterogeneous group of neurodegenerative disorders characterized by progressive spasticity of the lower limbs. The common neuropathologic finding is axonal degeneration, especially that which involves the terminal ends, in the longest fibers of the corticospinal tracts (Behan and Maia 1974). From a clinical point of view, HSPs are classically classified either as pure forms, when the spastic paraplegia is the exclusive manifestation (with occasional involvement of the dorsal columns or bladder symptoms), or as complicated forms, when spastic weakness of the lower limbs occurs in association with further neurological or nonneurological features, including mental retardation, optic atrophy, retinopathy, extrapyramidal disturbance, dementia, ataxia, and dysarthria (Harding 1981; Fink 1997). The number of HSPs that can be considered to be pure is rapidly shrinking as we learn more about the expanding variety of phenotypes (Figlewicz and Bird 1999). HSP is characterized by genetic heterogeneity: in addition to the more frequent autosomal dominant inheritance (ADHSP) that occurs in the majority (70%–80%) of families, autosomal recessive (ARHSP) and X-linked recessive inheritance have been reported for both pure and complicated forms (Harding 1981; Polo et al. 1993; Coutinho et al. 1999; Reid 1999).

As a result of genetic linkage studies, seven loci (known as "SPGs") for autosomal dominant pure forms have thus far been mapped on chromosomes 14q (SPG3 [MIM 182600]) (Hazan et al. 1993), 2p (SPG4 [MIM 182601]) (Hazan et al. 1994), 15q (SPG6 [MIM 600363]) (Fink et al. 1995), 8q (SPG8 [MIM 603563]) (Hedera et al. 1999; Reid et al. 1999*b*), and 12q (SPG10 [MIM 604187]) (Reid et al. 1999*a*), and two new loci have recently been mapped on chromosomes 19q (SPG12 [MIM 604805]) (Reid et al. 2000) and 2q (SPG13) (Fontaine et al. 2000). Finally, a complicated form with cataracts, gastroesophageal reflux, and amyotrophy has been mapped on chromosome 10q (SPG9 [MIM 601162]) (Seri et al. 1999). ARHSP occurs rarely, and three forms have been identified on chromosomes 8p (SPG5 [MIM 270800]) (Hentati et al. 1994), 16q (SPG7 [MIM 602783]) (De Michele et al. 1998), and 15q (SPG11 [MIM 604360]) (Martinez Murillo et al. 1999).

Only for SPG7 and SPG4 have the genes responsible for the disease been characterized. Mutations in a gene

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Address for correspondence and reprints: Dr. M. L. Mostacciuolo, Department of Biology, University of Padua, Via G. Colombo 3, 35121 Padua, Italy. E-mail: mstmls@civ.bio.unipd.it

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that encodes for paraplegin, a protein with mitochondrial localization and a chaperon-like function, have been found in both pure and complicated forms of SPG7-linked ARHSP (Casari et al. 1998). Recently, the gene responsible for SPG4-linked ADHSP has been identified; it encodes for a member of the AAA protein family known as "spastin" (Hazan et al. 1999). Two X-linked recessive forms have been described; the loci are mapped on regions Xq28 (SPG1 [MIM 312900]) (Kenwrick et al. 1986) and Xq22 (SPG2 [MIM 312920]) (Keppen et al. 1987) and are caused by mutations in the *L1CAM* gene and the *PLP* gene, respectively.

In this study, we report linkage analysis results for a family from northeastern Italy. We have gathered information on a few generations, but our findings have revealed complicated HSP in only three members of a generation including 12 siblings (fig. 1). Considering that the parents were closely related by blood (first cousins), that only 3/12 parents were affected, and that all their offspring were normal, we deduced that this was a form of ARHSP. All living affected (one male and two females) and nonaffected (three males and five females) family members were neurologically examined (by G.F.M. and V.S.). The age at onset was, on average, 30 years, and the three affected individuals were clinically examined at the age of 62, 54, and 52 years, respectively. The clinical picture was similar for all individuals who showed abnormal gait as a presenting symptom. In all cases, clinical features were characterized by spastic gait, hyperreflexia, and mild lower-limb hypertonicity. Bilateral pes cavus was present in all cases, and plantar responses were extensor. The results of electromyelographic studies showed a distal motor neuropathy; in particular, motor nerve conduction velocity (MCV) was significant in the superficial peroneal nerve, with a homogeneous delay occurring among the three affected individuals, for whom the MCV was 37–38 m/s. Results of a sural-nerve biopsy performed in the index patient were normal. All affected members showed neuropsychological impairment; this was characterized, in particular, by mild mental retardation, visual agnosia, and short- and long-term memory deficiency, in addition to signs of perseveration and confabulation. None of the affected individuals displayed abnormalities on electroencephalography. Results of computed tomography and magnetic-resonance imaging of the brain were normal in the index patient (individual II:8). All patients were able to walk unaided.

For molecular analysis, the blood samples of 11 family members (4 males and 7 females) from the fourth generation were collected; for each of them, informed consent was obtained and current privacy legislation was followed. The family's genomic DNA was extracted from whole blood samples (10 ml) by use of a salting-out procedure (Miller et al. 1988; modified).

To exclude the known ARHSP loci, we used published

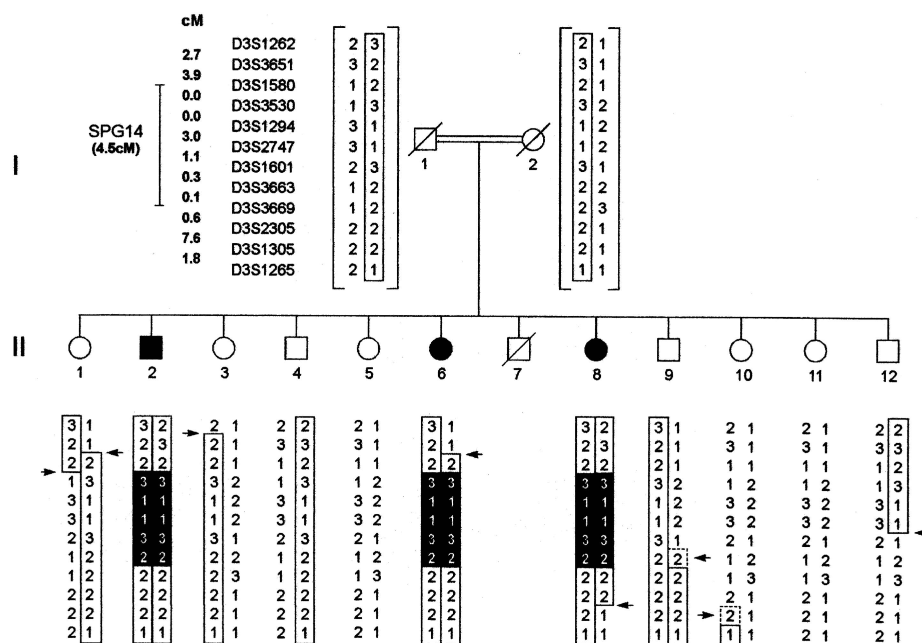

Figure 1 Pedigree of the family with ARHSP. Blackened and unblackened symbols represent affected and unaffected individuals, respectively. Genetic map is according to information from the Genetic Location Database. Haplotype analysis for the 3q27-q28 region showed a homozygous region cosegregating with the disease. Boxes represent the disease-bearing chromosome; blackened portions of the boxes, the regions of homozygosity carried only by affected individuals; arrows, recombination events. Bracketed haplotypes are deduced.

markers D8S260 and D8S285, for SPG5; D16S520, D16S303, and D16S3023, for SPG7; and D15S1007 and D15S1012, for SPG11 (The Genome Database). To map the disease gene, we performed a genomewide search using the ABI PRISM Linkage Mapping Set, version 2 (LMS2 [PE Biosystems]). The PCR reactions were performed according to the conditions described in the LMS2 user's manual. PCR products for each set of markers were loaded in a 7% denaturing polyacrylamide gel (BioRad), were separated by electrophoresis on an ABI373 automatic sequencer, and were analyzed using GENESCAN 672 1.1 and GENOTYPER 1.0 software (ABI).

Potential LOD scores were calculated by the SLINK program (Weeks et al. 1990). Two-point linkage analysis was performed by the MLINK program from the LINKAGE package, version 5.2 (Lathrop et al. 1984), under the assumption of equal allele frequencies and equal male and female recombination rates. Multipoint linkage analysis was performed using GENEHUNTER, version 1.3, software (Kruglyak et al. 1996), which allowed us to avoid the computing constraints derived from the presence of the consanguinity loop in this family. The genetic intermarker distances used in the analysis were the sex-averaged distances based on published maps (Genetic Location Database). The disease was assumed to have an autosomal recessive inheritance, with complete penetrance and an allele frequency of 10^{-4}.

By means of linkage analysis to known ARHSP loci mapping on chromosomes 8p, 16q, and 15q, we obtained negative LOD scores, with values <-2 for all markers analyzed, at recombination fraction (θ) 0 (data not shown). These results suggest the involvement of a different gene for ARHSP in this family.

After exclusion of the known loci, we performed a genomewide search using a total of 382/400 fluorescent labeled markers from the LMS2 (Weissenbach et al. 1992; Gyapay et al. 1994; Dib et al. 1996), since the X chromosome was excluded. A LOD score of >1 was obtained for four markers: D1S2726, on chromosome 1 ($Z = 1.43$, at $\theta = 0.00$); D3S1580 and D3S1601, on chromosome 3 ($Z = 1.23$, at $\theta = 0.05$, and $Z = 2.71$, at $\theta = 0.00$, respectively); and D9S1677, on chromosome 9 ($Z = 1.19$, at $\theta = 0.00$). With a positive LOD score confirmed, in all affected individuals, by the homozygous status of alleles for the marker D3S1601, and given the proximity to marker D3S1580 (~4 cM), the following microsatellite markers were analyzed on the 3q27-q28 region: D3S3530, D3S1294, D3S1288, and D3S2747 (mapping between LMS2 markers D3S1580 and D3S1601), and D3S3651, D3S3320, D3S2363, D3S3663, D3S3557, D3S2418, D3S3669, D3S2305, D3S1523, D3S2748, D3S240, D3S1305, and D3S1265 (flanking this interval). Annealing temperatures in the PCR reactions were optimized for each of these markers; PCR products were separated in a 9% denaturing polyacrylamide gel and were analyzed by silver staining (Santos et al. 1993). The markers D3S1288, D3S3320, D3S2363, D3S1523, D3S2748, and D3S240 were uninformative, and, for this reason, they have been excluded from linkage and haplotype analyses. As shown in table 1, the maximum two-point LOD score (Z_{max}) for the markers D3S1294 and D3S2747 was 2.71, at $\theta = 0$. This value was very close to the Z_{max} obtained by analysis of 100 simulated pedigrees by use of SLINK software (simulated $Z_{max} = 2.8$). Multipoint linkage analysis performed using the informative markers (D3S1262, D3S3651, D3S1580, D3S3530, D3S1294, D3S2747, D3S1601, D3S3663, D3S3669, D3S2305, and D3S1305) gave $Z_{max} = 3.9$ at marker D3S1601, with a peak greater than the threshold of 3 between markers D3S1580 and D3S3669.

Haplotype reconstruction showed a homozygous region on chromosome 3 cosegregating with the disease in affected individuals. Considering the recombination events with loss of homozygosity in the affected individuals, an interval of ~16 cM defined, at the centromeric and telomeric boundary, by markers D3S3651 and D3S1305 (recombination events in individuals II:6 and II:8, respectively), was individuated (fig. 1). If we also consider the nonaffected individuals, because of the homozygous status for the marker D3S1580 and because of the recombination event between markers D3S1580 and D3S3530 in individual II:1, the upper limit can be defined by the marker D3S1580. The definition of the lower limit was based on the haplotype of individual II:9; recombination between markers D3S3663 and D3S3669 brought a homozygous region in this nonaffected individual. These two events restricted the candidate region to an interval of 4.5 cM cosegregating in homozygosis in all affected subjects and flanked by markers D3S1580 and D3S3669. In individual II:9, the same lower recombination could occur between markers

Table 1

Two-Point LOD Scores for Selected Markers in the 3q27-q28 Region

	LOD Score at θ =								
Marker	.00	.01	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D3S1262	$-\infty$	−1.20	−.01	.34	.42	.26	.06	.42	.2
D3S3651	$-\infty$	−1.20	−.02	.30	.37	.20	.04	.37	.2
D3S1580	$-\infty$	.75	1.23	1.25	.99	.59	.20	1.25	.1
D3S3530	2.70	2.64	2.40	2.10	1.49	.89	.34	2.70	0
D3S1294	2.71	2.65	2.41	2.11	1.50	.90	.34	2.71	0
D3S2747	2.71	2.65	2.41	2.11	1.50	.90	.34	2.71	0
D3S1601	2.70	2.65	2.42	2.14	1.55	.95	.37	2.70	0
D3S3663	1.28	1.26	1.16	1.02	.75	.46	.18	1.28	0
D3S3669	$-\infty$	.96	1.44	1.47	1.19	.77	.32	1.47	.1
D3S2305	.99	.97	.89	.79	.57	.35	.14	.99	0
D3S1305	$-\infty$	−1.03	−.39	−.17	−.01	.03	.02	.03	.3
D3S1265	.99	.97	.89	.79	.57	.35	.14	.99	0

D3S1601 and D3S3663, but this could not be clearly determined as a result of a homozygous allele status in one of the parents. To accept this possibility, and, if so, to further restrict the region by ∼0.4 cM, we analyzed two close markers (D3S3557 and D3S2418), which unfortunately gave the same result as did D3S3663 (data not shown). These results demonstrate the existence of a new locus for the complicated ARHSP, which we have denoted as "SPG14," on chromosome 3q27-q28.

In recent years, a series of studies have revealed the extreme clinical and genetic heterogeneity associated with HSP. This has led to the discovery of important information on the clinical aspects of the disorder, in the search for a possible genotype-phenotype correlation. With regard to the autosomal dominant pure HSPs, several studies of wide samples of families support a significant locus-phenotype correlation as far as the age at onset is concerned (Reid 1999; Reid et al. 1999*c*). As for the recessive forms, to date, only three loci have been mapped (on chromosomes 8q [SPG5], 16q [SPG7], and 15q [SPG11], respectively). The SPG5 locus was identified in four nonconsanguineous Tunisian families with a homogeneous clinical picture characterized by pure HSP with a early age at onset (Hentati et al. 1994); the SPG11 locus was identified in several small families with either pure or complicated forms (Martinez Murillo et al. 1999). For the SPG7 locus, the gene (for paraplegin) has been identified, and different mutations have been associated with the different forms of HSP (Casari et al. 1998). The ARHSPs occur less frequently than the autosomal dominant forms, and the data reported in the literature are still scarce; nevertheless, some indications are emerging. In a sample of 46 families with this hereditary disorder, Coutinho (1999) has deduced that (*a*) the pure form occurs with a frequency that is 58% greater than that of the complicated or complex forms; (*b*) on the basis of clinical studies, five phenotypes have been defined (families with pure early onset and those with pure late onset, complex families with mental retardation, complex families with mental retardation and peripheral neuropathy, and complex families with cerebellar ataxia); and (*c*) the association between these forms and the loci mapped to date suggests the involvement of further loci, because only a minority of the families examined show linkage with SPG5 and SPG7.

The family in the present study is characterized by autosomal recessive transmission and a homogeneous phenotype in the three affected members. Other clinical findings, such as mild mental retardation and evidence of mild distal motor neuropathy, place this HSP among the complicated forms. The age at onset of the disorder is ∼30 years: this peculiar finding, associated with slow progression of the disease, differentiates this new complicated form from those that have previously been described, for which the onset is always before adulthood (Polo et al. 1991; Coutinho et al. 1999). On the other hand, the phenotype in this family is similar to that described for two families who show linkage at the SPG11 locus and who are characterized by spastic paraplegia, mild mental retardation, agenesis of the corpus callosum, and a late age at onset (Martinez Murillo et al. 1999). However, the results of analysis of the markers in the 15q13-q15 region led us to exclude linkage at the SPG11 locus and allowed us to consider the ARHSP in this family to be a new form of HSP. Indeed, our data, which are strongly supported by the results of multipoint linkage analysis ($Z_{max} = 3.9$, for the marker D3S1601) and by analysis of recombination events, made it possible to finely map a new ARHSP locus in a 4.5-cM region on chromosome 3q27-q28.

Analysis of the identified genes and partial transcripts is essential in the search for the genes involved and for understanding of the molecular pathology in the HSPs. In this region, 24 Unigene EST clusters and 4 genes—*LPP* (LIM domain containing preferred translocation partner in lipoma), *TP63* (tumor protein 63), *SEMP1* (senescence-associated epithelial membrane protein 1), and *FGF12* (fibroblast growth factor 12)—have been mapped to date (see the Unified Database). The *FGF12* gene is a member of the fibroblast growth factor (FGF) family, referred to as "fibroblast growth factor homologous factors" (FHFs). Each FHF is expressed in the developing and adult nervous system, suggesting, for this branch of the FGF family, a role in nervous system development and function (Smallwood et al. 1996). For these reasons, the *FGF12* represents a positional candidate gene for SPG14.

In summary, we have identified a new locus for a complicated form of ARHSP with distal motor neuropathy and mild mental retardation. These data, in addition to confirming the proposed genetic heterogeneity for the recessive forms, will be useful for improving the genetic counseling of families and for obtaining a better definition of a clinical and molecular classification of ARHSPs.

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Electronic-Database Information

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

Genetic Location Database, The, http://cedar.genetics.soton

.ac.uk/public_html/ldb.html (for location of SPG14 markers)

Genome Database, The, http://www.gdb.org/ (for sequences of unlabeled primers)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SPG1 [MIM 312900], SPG2 [MIM312920], SPG3 [MIM 182600], SPG4 [MIM 182601], SPG5 [MIM270800], SPG6 [MIM 600363], SPG7 [MIM 602783], SPG8 [MIM 603563], SPG9 [MIM 601162], SPG10 [MIM 604187], SPG11 [MIM 604360], and SPG12 [MIM 604805])

Unified Database, Bioinformatics Unit and Genome Center, Weizmann Institute of Science, http://bioinformatics.weizmann.ac.il/udb (for mapping data on candidate genes)

References

Behan WMH, Maia M (1974) Strümpell's familial spastic paraplegia: genetics and neuropathology. J Neurol Neurosurg Psychiatry 37:8–20

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 mitochodrial metalloprotease. Cell 93:973–983

Coutinho P, Barros J, Zemmouri R, Guimaraes J, Alves C, Chorao R, Lourenco E, et al (1999) Clinical heterogeneity of autosomal recessive spastic paraplegias: analysis of 106 patients in 46 families. Arch Neurol 56:943–949

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

Figlewicz DA, Bird TD (1999) "Pure" hereditary spastic paraplegia: the story becomes complicated. Neurology 53:5–7

Fink JK (1997) Advances in hereditary spastic paraplegia. Curr Opin Neurol 10:313–318

Fink JK, Wu CT, 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

Fontaine B, Davoine CS, Durr A, Paternotte C, Feki I, Weissenbach J, Hazan J, et al (2000) A new locus for autosomal dominant pure spastic paraplegia, on chromosome 2q24-q34. Am J Hum Genet 66:702–707

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(2 Spec No):246–339

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

Hazan J, Fonknechten N, Mavel D, Paternotte C, Samson D, Artiguenave F, Davoine CS, et al (1999) Spastin, a new AAA protein, is altered in the most frequent form of autosomal dominant spastic paraplegia. Nat Genet 23:296–303

Hazan J, Fontaine B, Bruyn RPM, Lamy C, van Deutekom JCT, Rime C-S, 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 Recondo J, Weissenbach J (1993) Autosomal dominant familial spastic paraplegia is genetically heterogeneous and one locus maps to chromosome 14q. Nat Genet 5:163–167

Hedera P, DiMauro S, Bonilla E, Wald J, Eldevik OP, Fink JK (1999) Phenotypic analysis of autosomal dominant hereditary spastic paraplegia linked to chromosome 8q. Neurology 53:44–49

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

Kenwrick S, Ionasescu V, Ionasescu G, Searby C, King A, Dubowitz M, Davies KE (1986) Linkage studies of X-linked recessive spastic paraplegia using DNA probes. Hum Genet 73:264–266

Keppen LD, Leppert MF, O'Connell P, Nakamura Y, Stauffer D, Lathrop M, Lalouel J-M, et al (1987) Etiological heterogeneity in X-linked spastic paraplegia. Am J Hum Genet 41:933–943

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Martinez Murillo F, Kobayashi H, Pegoraro E, Galluzzi G, Creel G, Mariani C, Farina E, et al (1999) Genetic localization of a new locus for recessive familial spastic paraparesis to 15q13-15. Neurology 53:50–56

Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acid Res 16:1215

Polo JM, Calleja J, Combarros O, Berciano J (1991) Hereditary ataxias and spastic paraplegias in Cantabria, Spain: an epidemiological and clinical study. Brain 114:855–866

——— (1993) Hereditary "pure" spastic paraplegia: a study of nine families. J Neurol Neurosurg Psychiatry 56:175–181

Reid E (1999) The hereditary spastic paraplegias. J Neurol 246:995–1003

Reid E, Dearlove AM, Osborn O, Rogers MT, Rubinsztein DC (2000) A locus for autosomal dominant "pure" hereditary spastic paraplegia maps to chromosome 19q13. Am J Hum Genet 66:728–732

Reid E, Dearlove AM, Rhodes M, Rubinsztein DC (1999*a*) A new locus for autosomal dominant "pure" hereditary spastic paraplegia mapping to chromosome 12q13, and evidence for further genetic heterogeneity. Am J Hum Genet 65: 757–763

Reid E, Dearlove AM, Whiteford ML, Rhodes M, Rubinsztein DC (1999*b*) Autosomal dominant spastic paraplegia: refined SPG8 locus and further genetic heterogeneity. Neurology 53: 1844–1849

Reid E, Grayson C, Rogers MT, Rubinsztein DC (1999*c*) Locus-phenotype correlation in autosomal dominant pure he-

reditary spastic paraplegia: a clinical and molecular genetic study of 28 United Kingdom families. Brain 122:1741–1755

Santos FR, Pena SDJ, Epplen JT (1993) Genetic and population study of a Y-linked tetranucleotide repeat DNA polymorphism with a simple non-isotopic technique. Hum Genet 90:655–656

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

Smallwood PM, Munoz-Sanjuan I, Tong P, Macke JP, Hendry SH, Gilbert DJ, Copeland NG, et al (1996) Fibroblast growth factor (FGF) homologous factors: new members of the FGF family implicated in nervous system development. Proc Natl Acad Sci USA 93:9850–9857

Weeks DE, Ott J, Lathrop GM (1990) SLINK: a general simulation program for linkage analysis. Am J Hum Genet Suppl 47:A204

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