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Novel Locus for Autosomal Dominant Hereditary Spastic Paraplegia, on Chromosome 8q

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Summary

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of disorders characterized by insidiously progressive spastic weakness in the legs. Genetic loci for autosomal dominant HSP exist on chromosomes 2p, 14q, and 15q. These loci are excluded in 45% of autosomal dominant HSP kindreds, indicating the presence of additional loci for autosomal dominant HSP. We analyzed a Caucasian kindred with autosomal dominant HSP and identified tight linkage between the disorder and microsatellite markers on chromosome 8q (maximum two-point LOD score 5.51 at recombination fraction 0). Our results clearly establish the existence of a locus for autosomal dominant HSP on chromosome 8q23-24. Currently this locus spans 6.2 cM between D8S1804 and D8S1774 and includes several potential candidate genes. Identifying this novel HSP locus on chromosome 8q23-24 will facilitate discovery of this HSP gene, improve genetic counseling for families with linkage to this locus, and extend our ability to correlate clinical features with different HSP loci.

Introduction

The hereditary spastic paraplegias (HSP) (MIM 182600, MIM 182601, MIM 270800, 312920, and MIM 600363) are a group of clinically and genetically diverse disorders characterized by progressive, usually severe, lower-extremity spasticity (Rhein 1914; Philipp 1949; Schwarz and Liu 1956; Roe 1963; Cartlidge and Bone 1973; Behan and Maia 1974; Skre 1974; Sutherland 1975; Holmes and Shaywitz 1977; Boustany et al. 1987; Keppen et al. 1987; McKusick 1988; Baraitser 1990; Scheltens et al. 1990; Harding 1993; Polo et al. 1993). (See reviews by the Hereditary Spastic Paraplegia Working Group [Fink et al. 1996] and Fink [1997]). HSP is classified according to both the mode of inheritance (autosomal dominant, autosomal recessive, and X linked) and whether progressive spasticity occurs in isolation ("uncomplicated HSP") or with other neurological abnormalities ("complicated HSP"), including optic neuropathy, retinopathy, extrapyramidal disturbance, dementia, ataxia, icthyosis, mental retardation, and deafness. The major neuropathological feature of autosomal dominant, uncomplicated HSP is axonal degeneration that is maximal in the terminal portions of the longest descending and ascending tracts (crossed and uncrossed corticospinal tracts to the legs and fasciculus gracilis, respectively) (Schwarz and Liu 1956; Behan and Maia 1974; Harding 1993) Spinocerebellar fibers are involved to a lesser extent.

Each genetic type of HSP (autosomal dominant, recessive, and X-linked) is genetically heterogeneous (see review by Fink et al. [1996]). Loci for autosomal dominant HSP are present on chromosomes 2p, 14q, and 15q (Hazan et al. 1993, 1994; Figlewicz et al. 1994; Hentati et al. 1994; Fink et al. 1995*a*, 1995*b*; Gispert et al. 1995; Lennon et al. 1995). Among the 33 HSP kindreds reported by the Hereditary Spastic Paraplegia Working Group (Fink et al. 1996), linkage to chromosome 2p was the most common, being observed in 15 (45%) of 33 kindreds. Two kindreds (6%) were linked to chromosome 14q. Linkage to chromosome 15q (Fink et al. 1995*b*) was observed in 1 (3%) of 33 kindreds. Known HSP loci on chromosomes 2p, 14q, and 15q were excluded in 15 of 33 autosomal dominant HSP kindreds. The exclusion of known loci in 45% of autosomal dominant HSP kindreds indicates the presence of additional loci for autosomal dominant HSP. We evaluated a white kindred with uncomplicated, autosomal dominant HSP and excluded linkage to known HSP loci. We performed a genomewide search for a novel HSP

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locus in this family and observed tight linkage of the disorder to a group of microsatellite markers loci on chromosome 8q.

Subjects, Material, and Methods

Subjects

We examined 21 members of a nonconsanguineous North American kindred of German descent (fig. 1). One additional subject (subject V-13; see fig. 1) was interviewed but was not examined; medical records from his referring neurologist were reviewed. Pedigree information was obtained from many relatives. Informed consent was obtained from each subject, as specified by the University of Michigan institutional review board. Subjects were diagnosed according to published criteria (Fink et al. 1996), at the time of blood collection and prior to genotyping. Deceased subjects were diagnosed as "affected" or "unaffected" on the basis of the descriptions of at least two relatives. Age at onset of symptoms was obtained by interviewing the living affected subjects.

We performed genetic-linkage analysis, using 15 living affected subjects, 4 living unaffected subjects, and 3 spouses of descendants. Marrying-in spouses were asymptomatic, had normal neurological examinations, and had no evidence of similar neurological disorders in their families. We did not include in our analysis either subjects for whom the diagnosis was uncertain or subjects considered "at risk" of developing HSP (i.e., asymptomatic subjects with normal neurological examinations who were <50 years of age).

Genotyping and Linkage Analysis

DNA was extracted from peripheral blood leukocytes as described elsewhere (Bell et al. 1981). Microsatellite DNA polymorphisms were amplified by PCR, according to standard procedures. Amplifications were performed in 25-μl vols in 96-well trays, by Coy and M.J. Research thermocyclers, for 35 cycles. One primer was labeled with [γ^{32}P]-ATP, by means of T4 polynucleotide kinase. Amplified DNA was electrophoresed on 7% polyacrylamide/6M urea-formamide gels, and alleles were scored on the basis of autoradiographs.

Two-point linkage analyses were performed by the MLINK subroutine of the LINKAGE program (Lathrop et al. 1985), with an autosomal dominant model of disease inheritance and with a disease-allele frequency of .001. We assigned a genetic penetrance of .90 for LOD-score calculations.

Marker-allele frequencies were not calculated from data for this family, since only three unrelated spouses

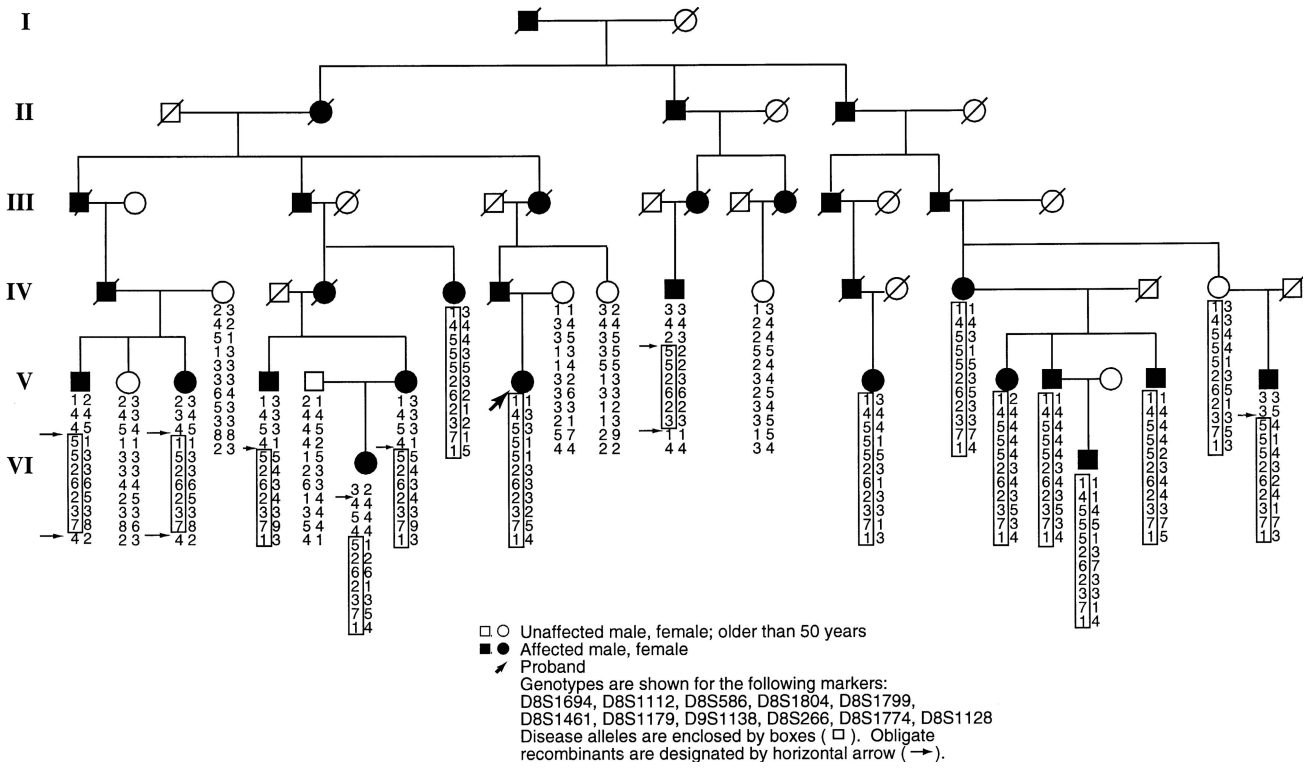

Figure 1 Kindred with HSP linked to chromosome 8q23-24 (*SPG8*)

were available. Instead, LOD scores were calculated with marker-allele frequencies assumed to be equal. The LINKMAP program of LINKAGE, used for multipoint linkage analysis, utilized published locations (Marshfield Medical Research Foundation) of markers D8S1084, D8S1799, D8S1179, D8S266, D8S1461, and D8S1774.

Results

Clinical Analysis

HSP was diagnosed in 15 living subjects who developed insidiously progressive gait disturbance at age 22–60 years (mean age 37.3 years; SD 12.2 years). Neurological examination of affected subjects demonstrated spastic diplegic gait disturbance (ranging from mild to profound), frank corticospinal-tract deficits in the lower extremities (including spasticity, grade 4 hyperreflexia, and extensor plantar responses), weakness of hip flexion and ankle dorsiflexion, diminished vibratory sensation in the feet, and, often, pes cavus. Mild terminal dysmetria on finger-to-nose testing was noted in several subjects. There was no muscle wasting, with the exception of mild muscle atrophy, which, when present, was noted in the shins of subjects in wheelchairs. Bladder disturbance (urgency and incontinence) was present in 7 of 15 affected subjects.

We observed one instance of probable incomplete genetic penetrance. Subject V-13 (fig. 1) is unequivocally affected with insidiously progressive, severe spastic paraplegia, which began at age 23 years. His mother (subject IV-15; see fig. 1), who is asymptomatic and whose neurological examination at age 60 years demonstrated only subtle decreased stride length, is either nonpenetrant or presymptomatic.

Exclusion Analysis

We tested linkage to microsatellite polymorphisms located at known autosomal dominant HSP loci on chromosomes 2p, 14q, and 15q. We observed negative LOD scores for markers flanking and within these loci (table 1). These data indicated that the disorder in this kindred was not linked to these known HSP loci.

Genomewide Search for a Novel HSP Locus

We then undertook genomewide genetic-linkage analysis to identify the novel HSP locus in this family. We analyzed 284 microsatellite polymorphisms, spaced 5–20 cM throughout the genome, for linkage with the disorder in this HSP kindred. We observed positive LOD scores for individual markers located on chromosomes 2, 10, and 18: D2S1391, 3.11 ($\theta = 0$); D10S1709, 2.77 ($\theta = 0$); D18S380, 2.04 ($\theta = 0$). However, we observed significantly negative LOD scores for markers as close as 1–2 cM from each of these loci. For example, D2S364 and D2S1787 gave LOD scores of −10.20 and −17.17, respectively, at $\theta = 0$ and of −2.20 and −3.69, respectively, at $\theta = .10$; D10S1739 and D10S159 gave LOD scores of −3.63 and −10.82, respectively, at $\theta = 0$ and of −1.34 and −2.68, respectively, at $\theta = .05$; D18S870 and D18S812 gave LOD scores of −4.03 and −3.55, respectively, at $\theta = 0$ and of −0.74 and −0.38, respectively, at $\theta = .05$. These data indicated that positive LOD scores for these single microsatellite markers were simply random associations observed in a relatively small kindred.

Table 1

Exclusion of Linkage to Known Autosomal Dominant HSP Loci

HSP Locus and Marker (Penetrance)	Two-Point LOD Score at θ =					
	.001	.05	.1	.2	.3	.4
2p:						
D2S352 (.90)	−5.45	−1.72	−.99	−.41	−.18	−.07
D2S367 (.90)	−1.22	.26	.34	.27	.16	.07
14q:						
D14S269 (.90)	−1.94	−.33	−.12	.01	.03	.01
D14S306 (.90)	−6.70	−2.24	−1.39	−.64	−.31	−.12
D14S288 (.90)	−4.17	−.97	−.51	−.17	−.06	−.02
15q:						
D15S122 (.90)	−2.12	−.53	−.32	−.15	−.07	−.02
D15S128 (.908)	−1.64	−.06	.10	.12	.06	.02
D15S156 (.90)	.44	.39	.33	.21	.11	.04
D15S165 (.90)	−2.57	−.87	−.56	−.26	−.11	.04

Linkage to Chromosome 8q

We observed linkage of the disorder to a group of marker loci mapped to chromosome 8q (table 2). Under the assumption that genetic penetrance was .90, the maximum two-point LOD score was 5.51 ($\theta = 0$) for D8S1179 (CHLC.GATA 7G06.P6384). Three additional markers—namely, D8S1138 (CHLC.GATA 50B06.P15277), D8S1799 (AFM283xb5), and D8S1461 (CHLC.ATA 42A09.P34343)—also yielded two-point LOD scores >3.0 (table 2). Marker D8S266 (AFM151ye3) yielded a two-point LOD score of 2.94 at $\theta = 0$. A significantly positive two-point LOD score was obtained for D8S1138 (LOD score 3.6 at $\theta = 0$), although this marker could not be located precisely on the same genetic map of this region (Marshfield Medical Research Foundation) on which the other markers were located. However, two-point LOD-score analysis demonstrated that this marker (D8S1138) had no recombinations with markers D8S266 and D8S1461, both of which were located in the nonrecombinant disease haplotype.

As noted above, we observed one individual (subject IV-15; see fig. 1) who is either presymptomatic or nonpenetrant. Therefore, we repeated two-point linkage analysis, assigning genetic penetrances .80 and .70 (table

Table 2

Results of Two-Point Linkage Analysis for Microsatellite Polymorphisms on Chromosome 8q23-24

	Two-Point LOD Score at θ =					
Marker and Penetrance	.001	.05	.10	.20	.30	.40
D8S1804 (AFM312yg5):						
.9	−1.79	1.28	1.50	1.30	.85	.38
.8	−1.64	1.36	1.56	1.33	.87	.38
.7	−1.54	1.43	1.61	1.35	.87	.38
D8S1138 (CHLC.GATA 50B06.P15277):						
.9	3.60	3.19	2.27	1.92	1.11	.45
.8	3.69	3.26	2.82	1.94	1.12	.45
.7	3.75	3.30	2.85	1.96	1.13	.45
D8S1179 (CHCL.GATA 7G06.P6384):						
0.9	5.51	4.92	4.33	3.14	1.95	.85
.8	5.39	4.83	4.25	3.07	1.91	.84
.7	5.29	4.73	4.17	3.01	1.87	.82
D8S1799 (AFM283xb5):						
.9	3.28	2.91	2.53	1.77	1.07	.47
.8	3.48	3.08	2.68	1.88	1.13	.49
.7	3.28	2.89	2.50	1.74	1.04	.45
D8S266 (AFM151ye3):						
.9	2.94	2.64	2.33	1.67	1.02	.46
.8	3.11	2.78	2.43	1.73	1.06	.47
.7	3.24	2.88	2.52	1.78	1.08	.46
D8S1461 (CHLC.ATA 42A09.P34343):						
.9	3.09	2.65	2.20	1.37	.67	.19
.8	3.28	2.81	2.34	1.46	.73	.22
.7	2.88	2.45	2.03	1.26	.62	.18
D8S1774 (AFMb321wc1):						
.9	2.30	3.47	3.25	2.47	1.58	.71
.8	2.24	3.40	3.18	2.42	1.54	.69
.7	2.19	3.34	3.12	2.37	1.50	.67

2). Even at a lowered penetrance of .70, three markers with LOD scores >3.0 ($\theta = 0$) remained statistically significant (table 2). The LOD score for D8S266 (AFM151ye3) increased from 2.94 ($\theta = 0$) to 3.24 ($\theta = 0$) when penetrance was reduced from .90 to .70. The most informative marker, D8S1179 (CHLC.GATA 7G06.P6384), did not change substantially when LOD scores were calculated at a penetrance of either .90 (LOD score 5.51 at $\theta = 0$) or .70 (LOD score 5.29 at $\theta = 0$). The genotypes for all markers with no recombination and the two adjacent flanking markers showing obligate recombinants at D8S1804 and D8S1774 are shown with the pedigree in figure 1.

Multipoint linkage analysis was performed for the disease locus and two adjacent markers at a time, sequentially, for all markers from D8S1799 to D8S266 (D8S1799, D8S1461, D8S1179, and D8S266). Published distances between these markers were obtained from Marshfield Medical Research Foundation (fig. 2). A genetic penetrance of .90 was used for these calculations. Multipoint linkage analysis produced a maximum LOD score of 7.26, at D8S1179.

Discussion

Our data establish the existence of a locus for autosomal dominant, uncomplicated HSP, in the telomeric region of chromosome 8q. Previous physical mapping (NIH/CEPH Collaborative Mapping Group 1992) of the microsatellite markers allows us to assign the HSP locus to chromosome 8q23-24. At present, our data localize this region to a 6.2-cM interval between D8S1804 and D8S1774 (fig. 2).

The Genome Database designations for HSP ("spastic gait" [SPG]) loci are "*SPG1*" (X linked), "*SPG2*" (X linked), "*SPG3*" (chromosome 14q, autosomal dominant), "*SPG4*" (chromosome 2p, autosomal dominant), "*SPG5*" (chromosome 8q, autosomal recessive), and "*SPG6*" (chromosome 15q, autosomal dominant) (see review by Fink et al. [1996]). It would be appropriate to designate the recently identified chromosome 16 locus for autosomal recessive HSP as "*SPG7*" (De Michele et al. 1998). We propose that the chromosome 8q23-24 locus for autosomal dominant, uncomplicated HSP be designated "*SPG8*."

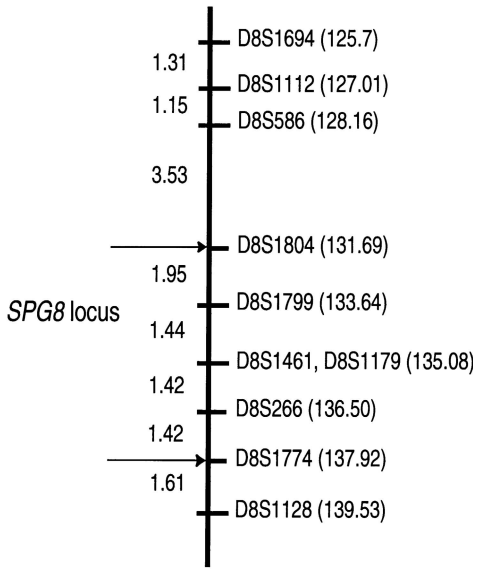

Figure 2 *SPG8* locus on chromosome 8q23-24: genetic map. Locations of genetic markers (Kosambi distances [in cM] are given in parentheses) were obtained from Marshfield Medical Research Foundation Center for Medical Genetics.

With identification of autosomal dominant HSP loci on chromosomes 2p, 8q, 14q, and 15q, it is possible to compare phenotypes in families in which the disorder is linked to each of these loci and in those families in which each of these loci is excluded. The disorder in the chromosome 8q–linked family that we studied was insidiously progressive and very severe. Ten of 15 subjects >40 of age required wheelchairs. The average age at onset of symptoms in this family (37.3 years) was later than that in the single reported chromosome 15q–linked family (22.5 years [Fink et al. 1995*a*]) but was similar to both that in the chromosome 14q–linked family reported by Hazan et al. (1993) (average age at onset of symptoms 31.6 years) and that in the four chromosome 2p–linked families reported by Nance et al. (1998) (average age at onset of symptoms 35 years).

We could discern no clinical features that distinguished between the disorder in this chromosome 8q–linked HSP family and those reported in uncomplicated autosomal dominant HSP families with linkage to chromosomes 2p, 14q, or 15q (Fink et al. 1996). This observation suggests that the different abnormal gene products responsible for these disorders participate in a common biochemical cascade that results in a similar pattern of CNS degeneration. Alternatively, phenotypic similarity of HSP that links to different loci could be explained by the presence of a family of structurally related genes that are present at each HSP locus.

Although not common, genetic anticipation has been described in HSP (Fink et al. 1996). For example, Nielsen et al. (1997, 1998) reported genetic anticipation in autosomal dominant uncomplicated HSP kindreds in which the disorder was linked to chromosome 2p. Furthermore, they also observed an expanded trinucleotide repeat that segregated with the disorder in these kindreds (Nielsen et al. 1997).

We determined age at onset of symptoms by interviewing the living affected subjects. Estimated age at onset of symptoms in deceased subjects was not included, because this information was considered inaccurate. Only three sets of living affected parents and their living affected children were available for which we could compare age at onset of symptoms in succeeding generations. Subject IV-13 (fig. 1) had symptom onset later (age 60 years) than his children (age at onset of symptoms in subjects V-9, V-10, and V-12 was 40, 38, and 40 years, respectively). In contrast, the age at onset of symptoms (28 years) in subject V-6 was similar to that (age 30 years) in her daughter (subject VI-1). Similarly, the age at onset of symptoms (38 years) in subject V-10 was similar to that (age 30 years) in his son (subject VI-2). Thus, although we have only limited data, we did not observe a consistent trend toward progressively younger age at onset of symptoms in succeeding generations in this family.

Analysis of candidate genes is an important approach toward discovery of both the *SPG8* gene and genes responsible for other types of HSP. The distribution of axonal degeneration to the terminal portions of the longest CNS axons raises the possibility that genes involved in neurotrophic regulation, maintenance of axonal cytoskeleton, or axoplasmic flow could be involved. The defect is quite selective. Pathological changes are confined to central—not peripheral—axons.

Recently, mutations in a novel mitochondrial metalloprotease gene (*paraplegin*) on chromosome 16 were identified in subjects with autosomal recessive HSP (Casari et al. 1998). Evidence of mitochondrial disturbance was provided by abnormal-appearing mitochondria ("ragged red fibers") in the muscle biopsy from two patients. Although Casari et al. (1998) found evidence of three structurally related *paraplegin*-like genes on chromosomes 4, 10, and 16, there was no evidence of a homologous gene on chromosome 8. Nonetheless, both the discovery of the *paraplegin* gene and evidence of mitochondrial disturbance in one form of autosomal recessive HSP provide important insight into biochemical pathways that, if disturbed, could result in HSP's selective axonal degeneration.

Analysis of X-linked HSP also suggests a potential class of candidate genes for autosomal dominant HSP. Cambi et al. (1995) found a missense mutation in the proteolipoprotein (PLP) gene coding sequence in affected

males of one family but not in a second family. Mutations in the two PLP exons also were identified in affected subjects from another, unrelated kindred with uncomplicated X-linked HSP (Dube et al. 1997). Thus, in these families, uncomplicated X-linked HSP is allelic to both complicated X-linked HSP (Zatz et al. 1976; Kobayashi et al. 1994) and Pelizaeus-Merzbacher disease, since they all result from PLP-gene mutations. Uncomplicated HSP is characterized by progressive axonal degeneration, rather than by the primary dysmyelination characteristic of Pelizeaus-Merzbacher disease. Nonetheless, the presence of PLP-gene mutations in X-linked, uncomplicated HSP indicates that consideration of potential candidate genes should include those involved in myelin synthesis.

We searched the Genome Database for genes mapped to the *SPG8* locus (D8S1804–D8S1774) on chromosome 8q23-24. Interesting and potential candidate genes among this list include KCNQ3 (the potassium-channel gene implicated in benign familial neonatal convulsions); syntrophin beta 1 (SNT2B1), a widely expressed dystrophin-associated protein; protein kinase (PTK2); phospholipase, A2 like (PLA2L); phosphodiesterase I/nucleotide pyrophosphatase 2 (PDNP2); and plectin 1 (PLEC1), an intermediate filament–binding protein. Fine mapping the *SPG8* locus and construction of a physical map across this locus will permit assessment of these genes, as well as identification and analysis of other potential *SPG8* candidate genes. Identification of genetic mutations responsible for autosomal dominant HSP will provide insight into the pathophysiology of this condition and, it is hoped, into other inherited and degenerative brain and spinal-cord disorders characterized by axonal degeneration.

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Electronic-Database Information

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

Genome Database, http://gdbwww.gdb.org (for HSP genes/loci)

Marshfield Medical Research Foundation, http://www.marshmed.org/genetics (for marker locations)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.mlm.nih.gov/Omim (for HSPs [MIM 182600, MIM 182601, MIM 270800, MIM 312920, and MIM 600363])

References

Baraitser M (1990) Spastic paraplegia/HSP. In: Motulsky AG, Bobrow M, Harper PS, Scriver C (eds) The genetics of neurological disorders. Oxford University Press, New York, pp 275–290

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

Bell GJ, Karam JH, Rutter WJ (1981) Polymorphic DNA region adjacent to the 5′ end of the human insulin gene. Proc Natl Acad Sci USA 78:5759–5763

Boustany R-MN, Fleischnick E, Alper CA, Marazita ML, Spense MA, Martin JB, Kolodny EH (1987) The autosomal dominant form of "pure" familial spastic paraplegia. Neurology 37:910–915

Cambi F, Tartaglino L, Lublin FD, McCarren D (1995) X-linked pure familial spastic paraparesis: characterization of a large kindred with magnetic resonance imaging studies. Arch Neurol 52:665–669

Cartlidge NE, Bone G (1973) Sphincter involvement in hereditary spastic paraplegia. Neurology 23:1160–1163

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

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

Dube M-P, Boutros M, Figlewicz DA, Rouleau GA (1997) A new pure hereditary spastic paraplegia kindred maps to the proteolipid protein gene locus. Am J Hum Genet Suppl 61: A169

Figlewicz DA, Dube MP, Farlow MR, Ebers G, Harper P, Kolodny EH, Baumbach L, et al (1994) Autosomal dominant familial spastic paraplegia: linkage analysis and evidence for linkage to chromosome 2p. Am J Hum Genet Suppl 55:A185

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

Fink JK, Heiman-Patterson T, Bird T, Cambi F, Dubé M-P, Figlewicz DA, Haines JL, et al (1996) Hereditary spastic paraplegia: advances in genetic research. Neurology 46: 1507–1514

Fink JK, Sharp G, Lange B, Wu C-TB, Haley T, Otterud B, Peacock M, et al (1995*a*) Autosomal dominant hereditary spastic paraparesis, type I: clinical and genetic analysis of a large North American family. Neurology 45:325–331

Fink JK, Wu C-TB, Jones SM, Sharp GB, Lange BM, Lesicki A, Reinglass T, et al (1995*b*) 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

Harding AE (1993) Hereditary spastic paraplegias. Semin Neurol 13:333–336

Hazan J, Fontaine B, Bruyn RPM, Lamy C, Van Deutekom JCT, Rime CS, Durr 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

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

Holmes G, Shaywitz B (1977) Strumpell's pure familial spastic paraplegia: case study and review of the literature. J Neurol Neurosurg Psychiatry 40:1003–1008

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

Kobayashi H, Hoffman EP, Marks HG. (1994) The rumpshaker mutation in spastic paraplegia. Nat Genet 7:351–352

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

Lennon F, Gaskell PC, Woopert C, Aylsworth AS, Malin D, Warner C, Farrell CD, et al (1995) Linkage and heterogeneity in hereditary spastic paraparesis. Am J Hum Genet Suppl 57:A217

McKusick VA (1988) Spastic paraplegia, hereditary. In: McKusick VA. Mendelian inheritance in man. Johns Hopkins University Press, Baltimore, p 1189

Nance MA, Raabe WA, Midani H, Kolodny EH, David WS, Megna L, Pericak-Vance MA, et al (1998) Clinical heterogeneity of familial spastic paraplegia linked to chromosome 2p21. Hum Hered 48:169–178

Nielsen JE, Jensen S, Jennum P, Koefoed P, Neerup Jensen L, 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

Nielsen JE, Koefoed P, Abell K, Hasholt L, Eiberg H, Fenger K, Niebuhr E, et al (1997) CAG repeat expansion in autosomal dominant pure spastic paraplegia linked to chromosome 2p21-p24. Hum Mol Genet 6:1811–1816

NIH/CEPH Collaborative Mapping Group (1992) A comprehensive genetic linkage map of the human genome. Science 258:67–86

Philipp E (1949) Hereditary (familial) spastic paraplegia: report of six cases in one family. NZ Med J 48:22–25

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

Rhein J (1914) Family spastic paralysis. J Nerv Ment Dis 44: 115–144

Roe P (1963) Hereditary spastic paraplegia. J Neurol Neurosurg Psychiatry 26:516–519

Scheltens P, Bruyn RPM, Hazenberg GJ (1990) A Dutch family with autosomal dominant pure spastic paraparesis (Strumpell's disease). Acta Neurol Scand 82:169–173

Schwarz GA, Liu C-N (1956) Hereditary (familial) spastic paraplegia: further clinical and pathologic observations. AMA Arch Neurol Psychiatry 75:144–162

Skre H (1974) Hereditary spastic paraplegia in western Norway. Clin Genet 6:165–183

Sutherland JM (1975) Familial spastic paraplegia. In: Vinken PJ, Bruyn GW. Handbook of clinical neurology. Vol 22: System disorders and atrophies. part II. North-Holland, Amsterdam, pp 420–431

Zatz M, Penha-Serrano C, Otto PA (1976) X-linked recessive type of pure spastic paraplegia in a large pedigree: absence of detectable linkage with Xg. J Med Genet 13:217–222