

## Hereditary spastic paraplegia linked to chromosome 14q11-q21: reduction of the SPG3 locus interval from 5.3 to 2.7 cM

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EDITOR—Recently, Reid *et al*<sup>1</sup> reported reduction of the chromosome 12q locus for autosomal dominant hereditary spastic paraplegia. We now report reduction of the chromosome 14q locus for autosomal dominant hereditary spastic paraplegia (SPG3, OMIM 182600). Hereditary spastic paraplegia (HSP) (also known as Strümpell-Lorrain syndrome<sup>2</sup>) is a heterogeneous group of disorders characterised by progressive lower extremity weakness and spasticity. Gait disturbance may begin at any age and progresses insidiously. Postmortem studies show axonal degeneration that is maximal in the distal ends of the corticospinal tracts and fasciculus gracilis fibres<sup>3,4</sup> (website <http://www.geneclinics.org>).

Loci for autosomal dominant HSP have been identified on chromosomes 2p22 (SPG4), 2q24-34 (SPG13), 8q23-q24 (SPG8), 12q13 (SPG10), 10q23.3-q24.2 (SPG9), 14q11-q21 (SPG3), 15q11.1 (SPG6), and 19q13 (SPG12).<sup>5-16</sup> Forty-five percent of kindreds with autosomal dominant, uncomplicated HSP are linked to the SPG4 locus on chromosome 2p22. Mutations in a novel gene (designated "spastin") were recently discovered as the basis for chromosome 2p22 (SPG4) linked HSP.<sup>6</sup> Spastin's functions are unknown, although homology to 26S proteasome subunit and Sap1 proteins suggests that spastin participates in formation of nuclear protein complexes.

Approximately 15% of autosomal dominant, uncomplicated HSP is linked to the SPG3 locus on chromosome 14q11-21.<sup>3</sup> This locus was identified initially by Hazan *et al*<sup>4</sup> and subsequently reduced to the interval between D14S259 and D14S281 by Gispert *et al*.<sup>17</sup> This region was originally considered to span 7 cM,<sup>17</sup> although more recent assessment places these

flanking markers approximately 5.3 cM apart ([http://research.marshfieldclinic.org/genetics/Physical\\_Maps/PhysicalMapPage.htm](http://research.marshfieldclinic.org/genetics/Physical_Maps/PhysicalMapPage.htm)).

We evaluated a large kindred with autosomal dominant, uncomplicated HSP. HSP was diagnosed according to published criteria.<sup>3</sup> Age of symptom onset ranged from 1 to 6 years (average 3.1). We performed two point linkage analysis using polymorphic microsatellite markers flanking and within loci for autosomal dominant HSP. We used disease allele frequency = 0.001 and genetic penetrance = 0.90 for lod score calculations. DNA samples were extracted from peripheral blood leucocytes and microsatellite markers were amplified and analysed as previously described.<sup>10</sup> We observed significantly negative two point lod scores for markers at HSP loci SPG4 (lod score for D2S352 = -6.45 at  $\theta = 0$  and -2.02 at  $\theta = 0.10$ ), SPG8 (lod score for D8S1799 = -3.44 at  $\theta = 0$  and -1.90 at  $\theta = 0.05$ ; lod score for D8S1138 = -4.79 at  $\theta = 0$  and -1.99 at  $\theta = 0.05$ ), and SPG6 (lod score for D15S542 = -4.21 at  $\theta = 0$ ; lod score for D15SS128 = -5.23 at  $\theta = 0$  and -1.91 at  $\theta = 0.05$ ). In contrast, we observed two point lod scores  $>+2.0$  (table 1) for markers flanking and within the SPG3 locus on chromosome 14q11-21. The maximum two point lod score was +4.63 ( $\theta = 0$ ) for D14S746 (CHLC.GATA85A11). Three additional markers, D14S1068 (AFM114xg7), D14S269 (AFM267zd5), and D14S748 (CHLC.GATA90G11), also yielded two point lod scores greater than 2.0 (table 1). These observations indicated that the disorder in this family was linked to the SPG3 locus.

Subject III.1 (fig 1) shows a recombination between markers D14S1031 and D14S978. Since this subject is affected with HSP, the HSP gene mutation must be centromeric to D14S978. This defines the SPG3 critical region to a 2.7 cM region between D14S259 and D14S978 (fig 2). The reduction of the SPG3 locus from 5.3 cM to 2.7 cM restricts this locus to chromosome 14q21-q22 and will permit investigators to direct their search for candidate genes to this restricted region. Identification of the SPG3 gene will provide insight into the biochemical basis of HSP on which development of rational treatment depends.

Table 1 Two point lod scores for markers at the SPG3 locus

Marker	Penetrance	$\theta$						
		0	0.05	0.10	0.20	0.30	0.40	
D14S269 AFM267zd5	0.9	2.95	2.59	2.22	1.50	0.81	0.22	
D14S748 CHLC.GATA90G11	0.9	2.30	2.08	1.85	1.39	0.86	0.33	
D14S1068 AFM114xg7	0.9	4.19	3.81	3.41	2.56	1.68	0.75	
D14S746 CHLC.GATA85A11	0.9	4.63	4.22	3.79	2.88	1.90	0.86	
D14S1031 AFMb359zd1	0.9	0.78	0.71	0.63	0.46	0.31	0.15	
D14S978 AFMa122ya5	0.9	0.08	1.63	1.71	1.41	1.01	0.46	

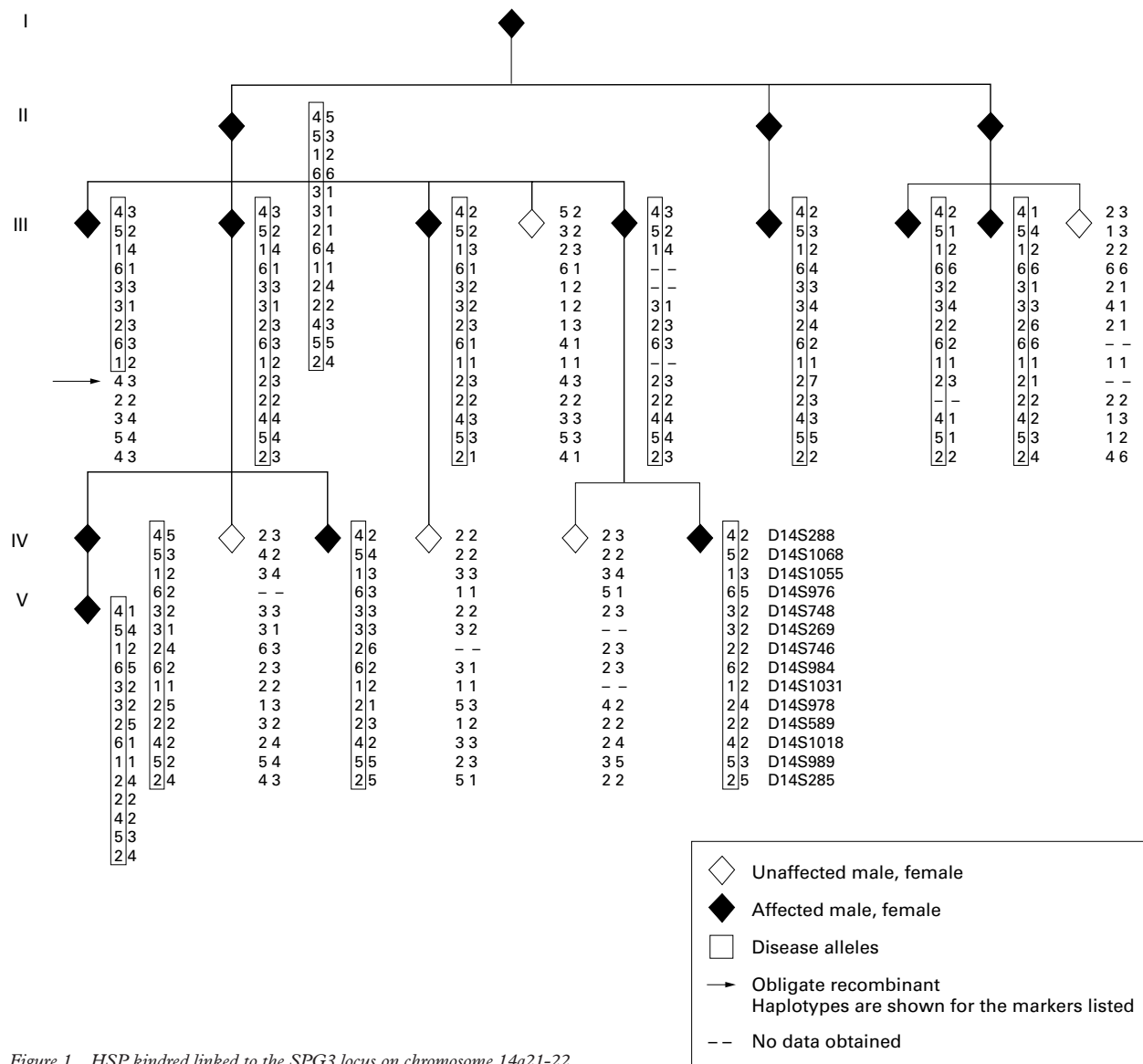


Figure 1 HSP kindred linked to the SPG3 locus on chromosome 14q21-22.

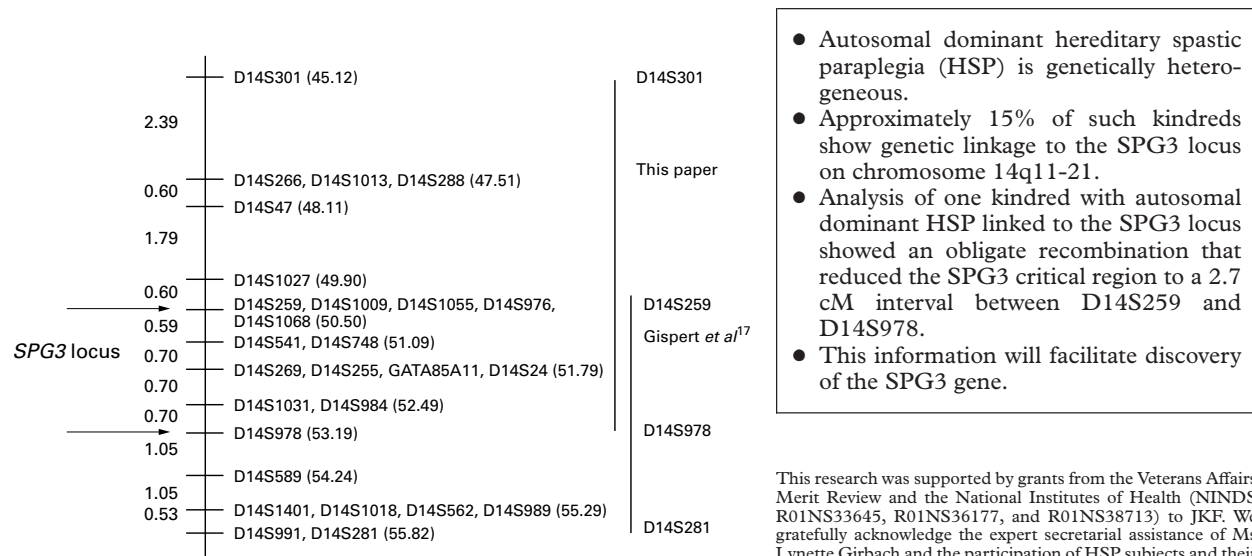


Figure 2 Autosomal dominant HSP locus (SPG3) on chromosome 14q21-22.

- Autosomal dominant hereditary spastic paraplegia (HSP) is genetically heterogeneous.
- Approximately 15% of such kindreds show genetic linkage to the SPG3 locus on chromosome 14q11-21.
- Analysis of one kindred with autosomal dominant HSP linked to the SPG3 locus showed an obligate recombination that reduced the SPG3 critical region to a 2.7 cM interval between D14S259 and D14S978.
- This information will facilitate discovery of the SPG3 gene.

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