Autosomal dominant (AD) pure spastic paraplegia (HSP) linked to locus SPG4 affects almost exclusively males in a large pedigree

A Starling, P Rocco, M R Passos-Bueno, J Hazan, S K Marie, M Zatz

H
ereditary spastic paraplegia (HSP) includes a hetero-
geneous group of degenerative disorders of the central
motor system characterised by progressive spasticity of
the lower limbs. The inheritance may be autosomal dominant
(AD), autosomal recessive (AR), or X linked.

Clinically, two forms of HSP can be distinguished: a pure
form, with leg spasticity and weakness, and a complicated
form, with other manifestations such as optic neuropathy,
retinopathy, movement disorders, dementia, epilepsy, ataxia,
ichthyosis, mental retardation, and deafness. Both compli-
cated and pure forms are genetically heterogeneous. Although
X linked forms have been reported,1,2 pure HSP usually
displays AD inheritance. The major neuropathological finding
in the latter form is axonal degeneration involving the termi-
nal ends of the longest fibres of the corticospinal tracts and
dorsal columns.1,4

AD-HSP is the most common form of the disease, account-
ing for approximately 70-80% of the families. Seven AD loci
have been mapped to date: SPG3 on chromosome 14q11.2-
q24.3,1,2 SPG4 on chromosome 2p,7 SPG6 on chromosome
15q11.1,1,1 SPG8 on chromosome 8q23-q24,16,17 SPG10 on chro-
mosome 12q13,14 and more recently two novel loci were
mapped on chromosome 2q24-q3415 and chromosome
19q13.15 SPG4 is the most common form, accounting for about
40% of all AD-HSP families.1,10 The protein encoded by SPG4,
spastin,10 and more recently by SPG3, a GTPase (SPG3A),19 has
just been identified but the gene product of the other AD-HSP
forms is still unknown.

Here we report a large three generation family referred to us
with a diagnosis of pure spastic paraplegia. Pedigree analysis
showed the existence of 24 clinically affected males but only
one clinically affected female. However, X linked inheritance
was ruled out since there were several instances of male to
male transmission. Linkage analysis showed that the disease
gene is linked to the SPG4 locus (lod score=8.29, θ=0). Screening
of mutations in the spastin gene showed no mutation
in the coding region, suggesting the possibility of a novel
mutation or the existence of another gene in close proximity.

SUBJECTS AND METHODS
This family was referred to us at the Centro de Estudos do
Genoma Humano (Human Genome Research Center), at the
Departamento de Biologia, Universidade de Sao Paulo, with a
diagnosis of “pure” spastic paraplegia. The proband, a 50 year
old male (III.6), reported that he had 23 male relatives
affected by the same condition, which suggested X linked
recessive inheritance. However, pedigree analysis (fig 1) indi-
cated that his father and grandfather were also affected and
that there were several other instances of male to male trans-
mision, thus confirming an AD pattern of inheritance. The
family members were submitted to a careful clinical and
neurological evaluation and all of them were re-examined
after a period varying from two to five years (table 1). Six other
affected members (III.12, III.14, III.19, III.22, III.23, III.24) were
examined by another neurologist. Based on clinical and
neurological examination, patients were classified into four
groups: (1) definitely not affected, (2) asymptomatic but with
one abnormality on neurological examination, (3) possibly
affected with two or more abnormalities on neurological
examination, and (4) definitely affected with abnormal gait
and neurological examination. Subjects who were dead were
diagnosed as “affected” or “unaffected” based on relatives’
information.

After informed consent, DNA was extracted from blood, as
described elsewhere.24 Linkage analysis was performed based
on 25 clinically affected subjects, four asymptomatic mothers
of affected sons, 42 unaffected subjects, and five normal
spouses. We considered to be “affected” those with clinical
or abnormal neurological signs as well as asymptomatic
“transmitting” mothers who were classified by pedigree
analysis (that is, the daughters of “affected” subjects who had
symptomatic sons).

Two point lod scores between HSP and SPG4 markers were
calculated by the MLINK and LINKAGE package (version 5.0)
under the assumption of an autosomal dominant gene with a
frequency of 10-4, equal female and male recombination rates,
and penetrance of 90%. Allele frequencies were assumed to be
equal for all markers.

The 17 exons of the spastin gene (and all their flanking
intrinsic boundaries) were screened for mutations by use of
SSCP (single strand conformation polymorphism) analysis. A
bi-directional sequencing of all PCR products including part of
the promoter region of the spastin gene was carried out in an
ABI 377 automated DNA sequencer. The Dye Deoxy Termina-
tor Cycle Sequencing Ready Reaction Kit (Perkin Elmer) was
used and the reaction was performed according to the ABI
standard protocol, after purification of 100 ng of the PCR
RESULTS

Linkage analysis with markers of chromosomes 14q and 15q first excluded loci SPG3 and SPG6, respectively (data not shown). A total of eight microsatellite markers from the SPG4 region (D2S2383, D2S2255, D2S2283, D2S352, D2S2203, D2S2351, D2S2347, D2S367) were then tested. Positive lod scores were found with markers D2S352 and D2S2203 from the SPG4 locus (table 2). The haplotypes observed with these eight markers are shown in fig 1. The order of the markers is consistent with the physical map of the region. Recombination events were observed for III.44, IV.3, IV.6, and IV.8.

In an attempt to identify the disease causing mutation, the 17 exons of the spastin gene were screened by sequencing but no mutation could be identified.

A total of 74 family members were clinically examined, 65 personally by one of us (table 1). None of them had any additional neurological abnormality, thus confirming the diagnosis of “pure” spastic paraplegia. All spouses were asymptomatic and had a normal neurological examination. With the exception of one affected man (IV.9) who was more severely affected at the age of 33, all others showed a mild course with onset ranging from 20 to 40 years old. None of them was confined to a wheelchair.

In this family there was a total of 47 men and 45 women, which did not differ from the expected 1:1 ratio. Among 34 men who underwent clinical examination and had their DNA analysed, the proportion of those who had inherited the “at risk” haplotype did not differ from expected (18 of 34, p >0.05). However, among 40 women who were clinically examined and who had their DNA analysed, this proportion was significantly less than expected (13 of 40, \( \chi^2 = 4.9 \), p <0.05). Also a gender difference in clinical manifestation was observed. Among the 13 women who carried the “at risk” haplotype, 10 showed some abnormality on neurological examination but only one showed symptoms typical of pure HSP whereas 100% of the men with the disease haplotype and who were older than 35 were clinically affected.

DISCUSSION

The present family is probably the largest one with autosomal dominant spastic paraplegia reported to date. The SPG4 gene has 17 exons, spans a physical distance of \( \sim 90 \) kb, and encodes the spastin protein. At least 59 different mutations in the spastin gene, scattered throughout the coding region, have been identified. No apparent correlation between the type of mutation (missense versus truncating) and severity of the phenotype was observed. In addition, both pure and complicated forms of AD-HSP may be caused by SPG4 mutations.

Haploinsufficiency as the physiopathological mechanism has been proposed with the abnormal phenotype being caused by a 50% reduction in spastin level. According to these authors, relatively small differences in the level of wild type spastin expression might have important clinical consequences accounting for the highly variable course. Interestingly, however, a homozygous missense mutation associated with a mild phenotype has also been reported.

In the present family, although the lod score of 8.29 with marker D2S352 indicates linkage to the SPG4 locus, screening of the entire coding region of the spastin gene in affected members did not show any mutation. This might be explained either by a novel mutation in the non-coding region, such as a mutation in the promoter region, or the appearance of a new splice site in an intron, or by the presence of another gene closely linked to the spastin gene. Indeed, Higgins et al have just found an atypical intronic deletion in the SPG4 gene that causes this form of AD-HSP. On the other hand, the existence of closely linked genes causing similar disorders has been
found for other diseases, such as autosomal recessive limb-girdle muscular dystrophy (α sarcoglycanopathy and telethoninopathy at 17q27) and more recently for X linked spastic paraplegia.12 The intrafamilial variability in the severity of the clinical course observed in the present family was also found in other published SPG4 families.17 23 25 28 Clinical anticipation has also been reported for some families,29 but no evidence for long CAG/CTG repeats in families linked to the SPG4 locus was found in another study.22 30 In our family, although the most severely affected subject belonged to the last generation, it was not possible to determine if there was clinical anticipation since most affected subjects did not recall when they noticed the first symptoms.

However, the most intriguing finding in the present family, which has apparently not been reported for other published AD HSP families, was the gender difference in clinical manifestation. This difference is so striking that, with the exception of one mildly affected female, the disease is limited to males. Interestingly, Byrne et al31 have just reported an Irish family linked to the SPG4 locus with four clinically affected males, but where four among five asymptomatic members carrying the at risk haplotype were women. An excess of affected men has been reported for other autosomal

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Classification: (1) definitely not affected; (2) asymptomatic but with one abnormality on neurological examination; (3) possibly affected with two or more abnormalities on neurological examination; and (4) definitely affected.
dominant neurological disorders such as myotonic dystrophy,\(^{2,3}\) Machado-Joseph disease or SCA3 cerebellar ataxia,\(^{4,5}\) DRPLA,\(^{6}\) and more recently facioscapulohumeral muscular dystrophy (FSHMD).\(^{7}\) For SCA3, myotonic dystrophy, and DRPLA it has been suggested that the excess of affected males could be explained by meiotic drive favouring the transmission of enlarged alleles. However, in the case of FSHMD, DNA analysis showed that the proportion of men and women carrying the deleted abnormal EcoRI/Blrl allele was the same, thus suggesting other mechanisms to explain why women were less often or more mildly affected than men.

In this kindred, there was a total of 47 men and 45 women, which did not differ from the expected 1:1 ratio. Therefore, the gender difference in the proportion of affected males versus females could not be explained by chance ascertainment of a family with an excess of males.

The observation of a significantly greater proportion of men than women who inherited the “at risk” haplotype suggests meiotic drive, that is, preferential transmission of the normal allele to females or a selection against sperm carrying the X chromosome together with the abnormal HSP allele. In addition, with the exception of one case (III.4), women carrying the “at risk” allele were not clinically affected. Thus, the lack of affected females in the present family would be explained by the deleterious effect of the pathogenic gene.

It is important to point out that this gender difference cannot be explained by age dependent penetrance, since on average women were five years older than men at examination (the mean age for women was 40 (SD 4.5) years old and the mean age for men was 35 (SD 5.0) years old).

Meiotic drive was described for Drosofila long ago and more recently a segregation distorter locus coding for a truncated RanGAP (a nuclear transport protein) has been reported to explain this phenotype.\(^2\) According to these authors, defective RanGAP encoded by the Sd gene would interfere with nuclear transport in spermatids carrying a sensitive responder gene.

With the exception of the present family and the family recently reported by Byrne et al.,\(^8\) the fact that a gender difference in the phenotypic expression has not been reported for other pure AD HSP families is intriguing. However, an explanation could be if a putative distorter locus was segregating only in some families. If such a distorter locus selected against spermatids carrying the X chromosome together with the SPG4 disease locus, it would explain the smaller proportion of women carrying the “at risk” haplotype but not the significantly higher proportion of non-penetrant women.

On the other hand, a partially penetrant mutation in the spastin gene was reported by Svensson et al.\(^9\) The mutant allele produced both mutant and full length transcript. If the production of the normal or the abnormal transcript were gender dependent, it might provide an explanation for the sex difference observed in the present family.

It has been also suggested that retrotransposons could be mediators of phenotypic variation in mammals producing phenotypic variation even between genetically identical subjects.\(^10\)

Understanding the mechanisms to explain the gender difference observed in the present family as well as why some subjects are protected from the clinical manifestation of pathological mutations will be of utmost importance for future therapeutic approaches.

**ACKNOWLEDGEMENTS**

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| Table 2 Lod score values with markers from the SPG4 locus |
|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Marker              | 0.00               | 0.01               | 0.05               | 0.10               | 0.20               | 0.30               | 0.40               |
| D2S2383             | -10.89             | -10.64             | -9.61              | -8.9               | -6.43              | -3.3               | -2.79              |
| D2S2255             | 2.85               | 2.82               | 2.68               | 2.47               | 1.94               | 1.34               | 0.69               |
| D2S2283             | 6.52               | 6.41               | 6.34               | 5.89               | 4.64               | 3.17               | 1.53               |
| D2S352              | 8.29               | 8.14               | 7.54               | 6.78               | 5.22               | 3.54               | 1.72               |
| D2S2203             | 6.45               | 6.36               | 5.95               | 5.40               | 4.19               | 2.85               | 1.37               |
| D2S2351             | -8.09              | -3.18              | -1.31              | -0.38              | 0.39               | 0.57               | 0.41               |
| D2S2347             | -8.09              | -3.18              | -1.31              | -0.38              | 0.39               | 0.57               | 0.41               |
| D2S367              | -10.89             | -10.64             | -9.61              | -8.9               | -6.43              | -3.3               | -2.79              |

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Autosomal dominant (AD) pure spastic paraplegia (HSP) linked to locus SPG4 affects almost exclusively males in a large pedigree

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