LETTER TO THE EDITORS

Reevaluation of a large family defines a new locus for X-linked recessive pure spastic paraplegia (SPG34) on chromosome Xq25

Lúcia Inês Macedo-Souza · Fernando Kok · Silvana Santos · Luciana Licinio · Karina Lezirovitz · Rafaela M. P. Nascimento · Clarissa Bueno · Marcília Martyn · Emília K. E. A. Leão · Mayana Zatz

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Herein, we report a new locus, named SPG34, for a pure form of X-linked hereditary spastic paraplegia (HSP) in a large Brazilian family followed by our group since 1976 [1]. In 2002, a study of seven patients suggested linkage to Xq22.2 [2]. We now were able to perform a more comprehensive clinical and molecular evaluation, including five patients not previously ascertained, and reassigned the putative locus to Xq25.

After Institutional Review Board approval, we genotyped 12 affected individuals (aged 24 to 79 years), one unaffected 60-year-old man, and 11 women (aged 40 to 81), seven of which were obligate carriers (Fig. 1). Neurological examination was performed in 11 of the 12 affected men and in all obligate women carriers. Age of onset varied from 12 to 25 years but was sometimes difficult to be determined. The clinical phenotype was stereotyped, and shuffling gait was the first recognized clinical sign. The disease was invariably progressive, and after two decades of onset, patients usually need support to walk; after three to four decades, they are usually wheelchair-bound. In upper limbs, strength was never affected, even late in life, but tendon reflexes were brisk. Lower limbs spasticity was progressive and debilitating. Babinski sign, ankle clonus, and brisk reflexes were frequently present. Lower limb vibratory sensibility was commonly reduced after the sixth decade of life; spontaneous lower limb pain was also a common complaint. No urinary or bowel sphincter dysfunction were ever reported.

The SPG34 locus encompasses a 14 cM region at Xq24–q25, in which 69 genes and bona fide transcripts have been assigned. Using a candidate gene approach to try to identify the causative sequence abnormality of SPG34, we fully sequenced AIFM1, which encodes a mitochondrial flavoprotein essential for apoptotic nuclear disassembly [3], but no mutation was detected. Therefore, the molecular basis for SPG34 remains unknown and we will sequence additional candidate genes that are highly expressed in the central nervous system.

The calculated logarithm of the odds score of 4.13 at marker DXS8057 was much higher than in the previous study [2], and additional markers definitely excluded Xq22.2. No other X-linked HSP have been so far assigned to this region, which defines the fourth locus for X-linked HSP. Differently from the other two well-characterized X-linked HSP, SPG1 and SPG2 [4, 5], SPG34 is not associated to mental retardation. Evidences for the SPG16 [6] locus, located in a large region at Xq11.2–q23 overlapping SPG2 locus, are weaker and based only in two small families.

In short, we identified in a large multigenerational family with pure spastic paraplegia a new locus (named SPG34) at Xq25 for an X-linked pure form of HSP, with onset in the
second or third decade of life and a slowly progressive course. This is the fourth locus for X-linked recessive HSP recognized so far.

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References


