

# Genetic work-up of hereditary spastic paraplegias is crucial for classifying these disorders

O estudo genético das paraplegias espásticas hereditárias é crucial para classificar esses distúrbios

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Dear Editor,

We read, with interest, the article by Ortega et al. about the study of 35 Brazilian patients with hereditary spastic paraplegia (HSP), of whom 12 presented with a pure form of HSP and 23 with a complex form<sup>1</sup>. We have the following comments and concerns.

The main shortcomings of the study are that the trait of inheritance could be determined in only 5/12 of the pure HSPs and in only 8/23 of the complex forms, and that no genetic investigations were carried out in the 35 included patients<sup>1</sup>. Since the most common of the autosomal dominant forms are SGP4, SPG3A, SPG31, and SPG10 in Europe and the Americas<sup>2</sup>, the 12 patients with a pure form should be tested for mutations in the *SPAST*, *ATL1*, *REEP1*, and *KIF5A* genes respectively. Since the most frequent of the autosomal recessive forms are the SPG11, SPG15, SPG7, and SPG5 in the Americas<sup>2</sup>, the 23 patients with a complex form should thus be tested for mutations in the *SPG11*, *ZFYVE26*, *SPG7*, and *CYP7B1* genes, respectively. Not only should the index case be genetically screened, but also symptomatic and asymptomatic first-degree relatives. This is not only important for genetic counseling but also for assessing the prognosis in these patients.

We do not agree with the statement that currently “over 70 distinct loci and over 50 genes have been identified”<sup>1</sup>. According to a recent review by Roeben et al., currently at least 79 loci and at least 60 HSP genes have been identified<sup>3</sup> and the number of loci and causative genes is still increasing.

Since extrapyramidal manifestations were the second most frequent abnormality among the complex forms, in addition to spastic paraplegia, sensory disturbances, and bladder dysfunction, we should be informed which type of extrapyramidal manifestations these patients presented with and which treatment they received.

We also do not agree with the statement that neuropathy, in addition to spastic paraparesis and sensory disturbances, occurs in carriers of mutations in “*ATL1* and *BSCL2*”<sup>1</sup>. Axonal neuropathy particularly occurs in patients carrying mutations in *SPG11*, and *ZFYVE26*, as well as in *KIF4A*, *DDHD1*, *REEP1*, *GBA2*, *ATAD3A*, and *DNM2*. Nonspecific neuropathy has been reported particularly in patients carrying mutations in *PLP1*, *SPAST*, *SPG11*, *KIF1A*, *FA2H*, *KIAA0415*, and *CYP2U1*.

Finally, we propose to revise the statement that “pure HSPs are usually autosomal dominantly inherited and that complex HSPs are usually autosomal recessively transmitted”<sup>1</sup>. Depending on the region under investigation, currently only 70-90% of the pure HSPs follow an autosomal dominant trait and about 20% of the pure HSPs follow an autosomal recessive trait<sup>4</sup>.

Overall, this interesting study would be more meaningful if the trait of inheritance was determined in all patients, if the family history was taken more thoroughly, if the included patients were tested for mutations in appropriate genes, and if the discussion about neuropathy in HSP was extended.

## References

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