Spastin gene mutation in Japanese with hereditary spastic paraplegia

I Yabe, H Sasaki, K Tashiro, T Matsuura, T Takegami, T Satoh

SUBJECTS AND METHODS

All of the subjects were neurologically evaluated by the present authors. The diagnosis was based on the neurological findings, a progressive course with an insidious onset, and a positive family history indicating dominant inheritance. Neuroimaging studies were done to exclude other causes of spastic paraplegia. Among the subjects, one was a member of an HSP family that was previously reported to have 2p linked AD-HSP (maximum lod score 3.53).11

All patients had progressive spasticity in the lower limbs bilaterally and their reflexes were hyperactive. All the patients showed an extensor plantar response. None of them showed extrapyramidal signs, ophthalmoplegia, retinal degeneration, skeletal muscle atrophy, or intellectual disturbance. Superficial sensation was intact, although some patients showed a slight reduction of vibration sensation. The mean age at onset was 35.3 years (SD 15.6, n=12), the range being 10-57 years. Spinal MRI showed no abnormalities or atrophy of the spinal cord.

After obtaining informed consent, high molecular weight genomic DNA was extracted from white blood cells or from lymphoblastoid cell lines. According to the method of Hazan et al,10 the 17 coding exons of the spastin gene were amplified by the polymerase chain reaction (PCR) using the original primer pairs, except those for exon 14 (http://www.genoscope.cns.fr/externe/English/Projets/Projet_U/primers.html). Since exon 14 was not amplified effectively using the reported pair of primers, we used two other primers (forward primer: 5′-TAACAGCCACAGACCTGTGC and reverse primer: 5′-GCTGTAAGATATAACGAAAATCCCA). The 5′ upstream 4.8 kb region from the initiator ATG codon or the 3′ non-coding region from the stop codon to the polyadenylation site. In the subjects with spastin mutation, the mean age at onset was 31.8 years (SD 18.1, n=5), the range being 10-54 years. There was no significant difference in the mean age at onset between the probands with and without spastin mutation by Student’s t test (p=0.53).

DISCUSSION

The present study showed that five out of 12 probands with AD-HSP (41.6%) had spastin gene mutations. In the remaining AD-HSP probands (58.4%), such mutations were not detected. This is the first report on the frequency of spastin gene mutation among Japanese patients with AD-HSP. Three out of five mutations, including Q347K and the two splice site mutations, were novel mutations.10,14,16,20 Each of these novel mutations was segregating with affected members in each family (data not shown). The variety of mutations in our subjects indicates that each pedigree had a different founder.

Recently, Fonknechten et al14 analysed 17 exons of the spastin gene in 87 AD-HSP probands from around the world, but mainly from Europe. They reported that SPG4 accounted for 37% of all AD-HSP. Our estimation of the prevalence of SPG4 in Japanese AD-HSP patients is compatible with their finding.

As in previous reports, the three missense mutations that we found were localised within the functional domain of spastin (the AAA cassette) and were therefore considered to interfere with the functioning of spastin. Two splice site mutations were also detected in the present study. Fonknechten et al14 suggested that the frequency of spastin splice site mutations
was significantly higher than in other human genetic disorders. These mutations are considered to be deleterious since the result is unstable aberrant transcripts that may lead to loss of function.

In the present study, we could not detect any specific mutation of the spastin gene in the proband of a 2p linked family. Svenson et al.16 and Fonknechten et al.14 also described similar cases where no mutation was detected in some 2p linked families. These findings may indicate that these AD-HSP patients have mutations in other regions of the spastin gene, for example, introns, or have mutations of other genes located nearby. Recently, Higgins et al.28 reported that spastic paraplegia could be caused by a 4 base deletion (del TAAT) near the splice junction in intron 3 of the spastin gene, but this mutation was not detected in our subjects. Further studies are needed to clarify the molecular mechanisms underlying SPG4.

ACKNOWLEDGEMENTS

We thank the AD-HSP patients for their participation in this study. This study was supported by a grant for Research on Ataxic Diseases from the Japanese Ministry of Health and Welfare.

Authors’ affiliations

I Yabe, H Sasaki, K Tsuchiro, Department of Neurology, Hokkaido University Graduate School of Medicine, N-15 W-7, Kita-ku, Sapporo 060-8638, Japan
T Matsusuka, Department of Neurology, Baylor College of Medicine, Houston, USA
T Takegami, Department of Neurology, Tajimi City Hospital, Tajimi, Japan
T Satoh, Department of Neurology, Kasai City Hospital, Kasai, Japan

Correspondence to: Dr H Sasaki, Department of Neurology, Hokkaido University Graduate School of Medicine, N-15 W-7, Kita-ku, Sapporo 060-8638, Japan; hsasaki@med.hokudai.ac.jp

REFERENCES

Spastin gene mutation in Japanese with hereditary spastic paraplegia
I Yabe, H Sasaki, K Tashiro, T Matsuura, T Takegami and T Satoh

doi: 10.1136/jmg.39.8.e46

Updated information and services can be found at:
http://jmg.bmj.com/content/39/8/e46

These include:

References
This article cites 21 articles, 5 of which you can access for free at:
http://jmg.bmj.com/content/39/8/e46#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
- Molecular genetics (1254)
- Neuromuscular disease (257)
- Peripheral nerve disease (97)
- Ethics (220)
- Eye Diseases (298)
- Genetic screening / counselling (887)
- Immunology (including allergy) (604)
- Clinical genetics (257)
- JMG Online mutation reports (168)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/