NEW FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS WITH BENIGN PROGRESSION AND MYOCLONUS IN LOWER EXTREMITIES

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INTRODUCTIONS

Amyotrophic lateral sclerosis (ALS) is one of adult-onset neurodegenerative diseases characterized by progressive loss of the lower and upper motor neurons, which progress to paralysis of almost all skeletal muscles of extremities and bulbar muscles, and eventually to respiratory failure typically within 2 to 3 years of the symptom onset.

The clinical phenotypes including age at onset and rate of progression of fALS are substantially heterogeneous.

We herein report a Japanese family in which five siblings presented slowly progressing upper and lower motor neuron deficits, characterized with benign clinical course and myoclonus of lower extremities.

OBJECTIVES

To elucidate the phenotype-genotype correlation of this atypical fALS, clinical and genetic investigations were performed.

METHODS

Five sibling patients (three males, two females) from a Japanese family and one healthy sibling (female) were clinically interviewed and examined. Genetic analyses including genome-wide linkage analysis and whole exome sequence analysis were performed using genomic DNAs extracted from peripheral blood samples of these siblings.

RESULTS

The family tree of the patients is shown in Fig. 1 and clinical history, neurological findings and neurophysiological findings of the patients in generation III is summarized in Table 1. According to the El Escorial criteria, III-4, III-5 and III-6 who presented positive Babinski sign were diagnosed as possible ALS. III-2 and III-3 were diagnosed as suspected ALS because they had lower motor neuron symptoms but no upper neuron symptoms.

The clinical features of this fALS are characterized with slow progression (duration of the disease: 19.6 ± 3.9 years (mean ± S.D.)), lower extremities-predominant late-onset muscle weakness and atrophy (onset of muscle weakness: 52.8 ± 2.6 years (mean ± S.D.)) (Fig. 2) and myoclonus of lower extremities which could develop in childhood.

Mutational analysis revealed no mutations of well-known candidate fALS or FTLD/ALS genes. Genome-wide linkage analysis and whole exome sequence analysis revealed possible new candidate genes.

CONCLUSIONS

We reported a new benign fALS family accompanied with myoclonus in lower extremities. Linkage and exome analyses suggest novel causative genes.

Figure 1 A family tree of the patients.

Figure 2 Photographs of legs of the patients. A. III-6 (proband) B. III-3 C. III-4 D. III-5

Table 1 Summary of History, Neurological findings and Neurophysiological findings of the patients in generation III

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Duration (years)</th>
<th>Clinical Neurological findings</th>
<th>Neurophysiological Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Examination</td>
<td>At Onset</td>
<td>Onset to</td>
<td>Onset to</td>
<td>Tongue</td>
</tr>
<tr>
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</tr>
<tr>
<td>III-6</td>
<td>66</td>
<td>52</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

EMG: B: bilateral; R: right; L: left; L/E: lower extremities U/E: upper extremities NE: not examined or not identified from clinical history; S: suspected from history of having myoclonus O: myoclonus was observed during examination. C: Chronic denervation pattern (high amplitude motor unit potential was observed) P: prolonged MEP latency and CMCT

COI Disclosure Name of first author: Jumpei Togawa I have no COI to disclose concerning the presentation.