### Title
Screening for OPTN mutations in amyotrophic lateral sclerosis in a mainly Caucasian population

### Author(s)
Sugihara, Katsunobu; Maruyama, Hirofumi; Kamada, Masaki; Morino, Hiroyuki; Kawakami, Hideshi

### Citation
Neurobiology of Aging, 32 (10) : 1923.e9 - 1923.e10

### Issue Date
2011

### DOI
10.1016/j.neurobiolaging.2011.03.024

### Self DOI

### URL
http://ir.lib.hiroshima-u.ac.jp/00034789

### Right
(c) 2011 Elsevier Inc. All rights reserved.
Screening for *OPTN* mutations in amyotrophic lateral sclerosis in mainly Caucasian.

Katsunobu Sugihara, Hirofumi Maruyama*, Masaki Kamada, Hiroyuki Morino, Hideshi Kawakami

Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8553, Japan

*To whom correspondence should be addressed:

Hirofumi Maruyama, M.D., Ph.D.

Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University,

1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8553, Japan

Tel: (81) 82-257-5850

FAX: (81) 82-257-5848

E-mail: hmaru@hiroshima-u.ac.jp
Abstract

Mutations in the optineurin (OPTN) gene cause amyotrophic lateral sclerosis (ALS). We previously reported three types of OPTN mutation in Japanese ALS subjects. Here, to identify the OPTN mutations in individuals of different ethnicity, we screened 563 sporadic ALS (SALS) subjects and 124 familial ALS (FALS) subjects who were mainly Caucasian. We found a c.964T>C synonymous variation in exon 8. However, we could not find the meaningful OPTN mutations. The results indicate that OPTN mutations causing ALS are rare, especially in mainly Caucasian ALS subjects.

Key words: ALS (amyotrophic lateral sclerosis), polymorphism, optineurin (OPTN)

1. Introduction

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease. It is a progressive disorder that involves degeneration of upper and lower motor neurons at all levels of the motor system, from the cortex to the anterior horn of the spinal cord. Population-based epidemiological studies of the disease show that 1.6 % to 5.7 % of the cases are familial in nature; the remaining 95% occur sporadically within the population. Various genes that may cause familial ALS (FALS), including superoxide dismutase-1 (SOD-1), angiogenin, TARDBP, and FUS/TLS, have been identified, and the frequency of their mutation is about 30% in total.
Optineurin (OPTN) is the gene that causes primary open-angle glaucoma (POAG) (Rezaie et al., 2002). We detected three types of OPTN mutation in Japanese subjects: homozygous deletion of exon 5, homozygous Q398X nonsense mutation and heterozygous E478G missense mutation in Japanese ALS subjects. A patient with the E478G mutation showed OPTN-immunoreactive cytoplasmic inclusions (Maruyama et al., 2010). Another group also reported OPTN mutations in ALS (Iida et al., 2011). In the present study, we sequenced OPTN in mainly Caucasian ALS subjects to investigate the presence and frequency of OPTN mutations.

2. Materials and Methods

The subjects were 563 sporadic ALS (SALS) (mean age at onset 57.0 years; age range 21-88 years) and 124 FALS (mean age at onset 57.8 years; age range 32-83 years) from the Coriell Institute for Medical Research. Most subjects were Caucasian. The PCR products were sequenced using Applied Biosystems BigDye Terminator v3.1 sequencing chemistry and examined using an ABI PRISM 3130 Genetic Analyzer. We did not check the large deletion or other structural variation.

3. Results

The results are shown in Table 1. In total, 266 variations in 563 SALS, and 66 variations in 124 FALS cases were observed. However, we could not find the meaningful OPTN mutations that may cause ALS.
4. Discussion

We identified for the first time the c.964T>C synonymous variation in exon 8 in SALS. The c.799 A>G variation in exon 6 in SALS and the c.1273C>T variation in exon 10 in FALS do not have “rs” numbers, but have already been reported (Rezaie et al., 2002, Nemesure et al., 2003). We identified some variations, but most of the identified variations had already been reported.

In mainly Caucasian subjects, we did not find any of the three types of mutation; we therefore conclude that OPTN mutations causing ALS are rare in mainly Caucasian ALS subjects. TDP-43 or SOD1-positive inclusions of sporadic ALS and SOD1-ALS were also noticeably immunolabeled by anti-OPTN antibodies. In addition, OPTN mutations abolished the inhibition of activation of nuclear factor kappa B (Maruyama et al., 2010). These previous results showed that OPTN may be involved in the pathogenesis of a wide range of types of ALS, although the mutation rate is low. Further investigations, such as pathological or biochemical studies are needed.

Acknowledgements

HMa is supported by the Uehara Memorial Foundation and HK is supported by the Takeda Science Foundation.

Disclosure statement

Conflicts of interest: none.

The study was approved by the review boards of the Hiroshima University.
References


Table 1. Variations of Optineurin.

<table>
<thead>
<tr>
<th>Location</th>
<th>Variation</th>
<th>Protein</th>
<th>Status</th>
<th>FALS</th>
<th>SALS</th>
<th>Hapmap frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 4</td>
<td>c. 412G&gt;A</td>
<td>p. T34T</td>
<td>rs2234968</td>
<td>48</td>
<td>209</td>
<td>0.434</td>
</tr>
<tr>
<td></td>
<td>c. 433G&gt;A</td>
<td>p. L41L</td>
<td>rs11591687</td>
<td>2</td>
<td>11</td>
<td>N/A</td>
</tr>
<tr>
<td>Exon 5</td>
<td>c. 603T&gt;A</td>
<td>p. M98K</td>
<td>rs11258194</td>
<td>5</td>
<td>14</td>
<td>N/A</td>
</tr>
<tr>
<td>Exon 6</td>
<td>c. 799A&gt;G</td>
<td>p. E163E</td>
<td>reported</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Exon 8</td>
<td>c. 964T&gt;C</td>
<td>p. S218S</td>
<td>new</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Exon 10</td>
<td>c. 1273C&gt;T</td>
<td>p. S321S</td>
<td>reported</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. 1274G&gt;A</td>
<td>p. E322K</td>
<td>rs523747</td>
<td>10</td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

N/A: not available