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

Screening for *OPTN* mutations in amyotrophic lateral sclerosis in mainly Caucasian.

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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 32-83years) 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.

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Disclosure statement

Conflicts of interest: none.

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

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Table 1. Variations of Optineurin.

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

N/A: not available