Journal of the Neurological Sciences 357 (2015) 167–172

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Mutational spectrum of the *SPAST* and *ATL1* genes in Korean patients with hereditary spastic paraplegia

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ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form 14 July 2015
Accepted 15 July 2015
Available online 17 July 2015

Keywords:
Hereditary spastic paraplegia
SPAST
ATL1
Pathogenic variants
Sequencing
Gene

ABSTRACT

Hereditary spastic paraplegia (HSP) is a genetically heterogeneous group of diseases characterized by insidiously progressive lower-extremity weakness and spasticity. Spastic paraplegia 4 (*SPAST*) is the most common type of uncomplicated autosomal dominant HSP (40% of such cases), and spastic paraplegia 3A (*ATL1*) is the second most common. Here, we conducted mutational analysis of the *SPAST* and/or *ATL1* genes in 206 unrelated patients with HSP. DNA sequencing and multiplex ligation-dependent probe amplification was used to analyze *SPAST* or *ATL1* pathogenic variants. To confirm splice-site pathogenic variants, mRNA transcripts were analyzed by reverse transcription-polymerase chain reactions and sequencing. Among the 52 patients with medical records and *SPAST* or *ATL1* gene pathogenic variants or novel unclassified variants, 50 showed spasticity or weakness in their lower extremities. We identified 16 known and 18 novel *SPAST* pathogenic variants and 2 known and a novel splicing pathogenic variants in *ATL1*. We also identified 4 unclassified *SPAST* variants in 5 patients and an unclassified *ATL1* variant in 1 patient. Further, a novel leaky-splicing variant (c.1537-11A>G) was found in *SPAST*, which caused skipping of exon 13 or exons 13–14. Among the 206 unrelated patients with HSP, *SPAST* or *ATL1* pathogenic variants and potentially pathogenic variants were identified in 52 patients, a low pathogenic variant rate compared to previous results. Results from our study suggest that other genes may be involved in HSP in the Korean population.

1. Introduction

Hereditary spastic paraplegia (HSP) is a genetically heterogeneous group of diseases characterized by insidiously progressive lower-extremity weakness and spasticity [1,2]. Spastic paraplegia 4 (SPG4) is the single most common type of HSP, accounting for about 40% of such cases and spastic paraplegia 3A (SPG3A) is the second most common type of autosomal dominant HSP (AD-HSP) [3]. Other clinical features include lower extremity hyper-reflexia, extensor plantar responses, loss of vibration senses in both lower extremities, and voiding difficulties. These symptoms result from length-dependent axonal degeneration of the descending corticospinal tracts and the ascending dorsal columns [4]. HSP is classified as "complicated" or "pure," depending on whether gait disturbance is accompanied by the respective presence of other symptoms, such as seizure, dementia, cognitive dysfunction cerebellar ataxia, or neuropathy. HSP can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. HSP is genetically heterogeneous, with 77 loci and 55 genes associated with HSP [5]. In autosomal dominant HSP, 11 loci and 19 HSP-related genes have been identified elsewhere [6].

The spastin protein consists of 616 amino acids and 4 major domains: a transmembrane domain, a microtubule-interacting and trafficking (MIT) domain, a microtubule-binding domain (MTBD), and an ATPase associated with various cellular activities (AAA) domain [7]. The *SPAST* gene product, spastin, associates with microtubules through its adenosine triphosphate binding domain associated with diverse cellular activities (AAA domain) [8,9]. Altered spastin proteins are defective in their ability

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http://dx.doi.org/10.1016/j.jns.2015.07.024
0022-510X/

for normal microtubule interactions, which disrupts organelle transport and leads to the abnormal localization of intracellular organelles, such as mitochondria and peroxisomes [8,10,11]. The AAA domain (amino acids 342 to 599) regulates the function of the protein through an ATPase associated pathway, and this region is highly conserved between species. Most pathogenic variants affect the AAA domain, suggesting a possible loss of function of spastin in HSP [10].

Previous studies have identified more than 450 different *SPAST* variants and 56 *ATL1* pathogenic variants (http://www.hgmd.cf.ac.uk/ac/index.php). A previous study with Korean HSP patients reported that the frequency of *SPAST* pathogenic variants in AD-HSP was 64% [12], which was higher than other reports [3,6]. Therefore, the aim of this study was to screen for and analyze *SPAST* and/or *ATL1* variants in 206 unrelated Korean HSP probands to better characterize *SPAST* and *ATL1* variants in the Korean population.

2. Patients and methods

2.1. Subjects

Two hundred and six unrelated patients were recruited for this study and referred for molecular analysis of HSP. *SPAST* variants were analyzed by direct sequencing of DNA samples from 185 patients, or by multiplex ligation-dependent probe amplification (MLPA) of DNA samples from 145 patients. Similarly, *ATL1* variants were analyzed by sequencing DNA from 141 patients, or by MLPA analysis of DNA samples from 140 patients. A total of 117 patients were evaluated for pathogenic variants in both genes. Family members of the probands were also evaluated clinically and genetically, when possible. Clinical evaluations were performed by a neurologist, who documented occurrences of weakness, spasticity, and sensory impairment in the lower extremities,

Table 1
Clinical aspects of *SPAST* and *ATL1* genes variants identified patients.

Patient	Gender	Age of onset	Familial history	LE weakness	LE spasticity	LE sensory impairment	Bladder symptom
1	M	10s	Y	N	Y	N	N
2	M	30s	Y	N	Y	N	N
4	M	50s	Y	Y	N	Y	N
5	M	40s	N	N	Y	N	N
6	F	10s	Y	N	Y	N	N
7	M	50s	N	Y	Y	N	N
8	M	3	Y	N	Y	N	N
9	F	30s	Y	Y	N	N	N
10	F	50s	Y	Y	Y	Y	Y
11	F	30s	N	Y	Y	Y	N
12	M	24	Y	Y	Y	N	N
13	M	40s	N	Y	Y	Y	N
14	F	40s	Y	Y	Y	N	N
15	F	45	Y	Y	N	N	N
16	M	10s	Y	Y	N	N	N
17	M	33	N	Y	N	N	Y
18	M	NA	Y	Y	Y	N	N
19	M	21	Y	N	Y	N	N
20	M	30s	N	Y	Y	N	Y
21	M	20s	Y	Y	Y	N	N
22	M	30s	Y	Y	Y	Y	N
23	M	38	Y	Y	Y	N	N
24	F	40s	Y	Y	Y	N	Y
25	M	50s	N	Y	Y	N	Y
26	F	42	Y	Y	N	N	N
27	M	30s	N	Y	Y	N	N
28	M	10s	Y	N	Y	N	N
29	M	10s	Y	Y	Y	Y	N
30	M	50s	Y	Y	Y	Y	N
31	F	30s	Y	Y	Y	N	N
32	F	30s	Y	Y	Y	N	N
33	M	30s	Y	Y	Y	N	N
34	M	40s	Y	Y	Y	Y	N
35	M	10s	Y	Y	Y	Y	N
36	M	39	Y	Y	Y	N	N
37	M	26	Y	N	Y	N	N
38	M	40s	N	Y	Y	Y	N
39	F	40s	N	Y	Y	N	N
40	M	40s	N	Y	Y	Y	Y
41	F	20s	Y	Y	Y	N	N
42	F	30s	Y	Y	N	Y	Y
43	M	40s	Y	Y	Y	N	N
44	M	6	Y	Y	Y	N	N
45	M	28	N	Y	Y	N	N
46	F	30s	Y	Y	Y	N	N
47	M	10s	Y	Y	Y	N	N
48	M	30s	Y	Y	N	N	N
49	M	30s	Y	Y	Y	N	Y
50	M	44	N	N	N	Y	Y
51	M	20s	Y	N	Y	N	N
52	F	10s	N	N	Y	N	N
53	M	10s	Y	Y	Y	N	N

No medical history was analyzed in one male patient.