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Genetic mutation analysis of hereditary spastic paraplegia

A retrospective study

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Abstract

Hereditary spastic paraplegias are heterogeneous disorders with diversified clinical manifestations, and genetic testing is important for the diagnosis and typing of hereditary spastic paraplegias.

Gene panel sequencing containing 55 hereditary spastic paraplegias-related genes was performed to screen the pathogenic genes for hereditary spastic paraplegias. Sanger sequencing was adopted to validate if the family member carried the same pathogenic gene as the proband.

Fifteen out of 53 patients carried mutation(s) in the screened hereditary spastic paraplegias-related genes. Among the 23 identified mutations, only one mutation had been previously reported as a pathogenic mutation. In the pedigree of case 6, the proband, his mother and uncle all carried the same novel deletion mutation (c.1459delA) at *SPAST* gene. Based on the pedigree, the disease was inherited in an AD pattern. In the pedigree of case 53, the family disease may be in an X-linked recessive inheritance pattern. The proband (case 53) carried two novel mutations in *ALT1* gene and *L1CAM* gene (c.2511C>A), respectively. The *L1CAM* gene is the causative gene for the SPG1 X-linked recessive—hereditary spastic paraplegias.

Our data confirm the genetic heterogeneity of hereditary spastic paraplegias, and SPG4/SPAST were the most frequent forms. The pathogenicity of the novel mutations is worth to be further investigated.

Abbreviations: AD = autosomal dominant, AMN = adrenal spinal cord neuropathy, AR = autosomal recessive, HSP = hereditary spastic paraplegias, PLS = primary lateral sclerosis, SNPs = single nucleotide polymorphisms, XR = X-linked recessive.

Keywords: gene panel sequencing, hereditary spastic paraplegias (HSP), *L1CAM* gene, Sanger sequencing, *SPAST* gene

1. Introduction

Hereditary spastic paraplegias (HSPs) are clinically and genetically heterogeneous disorders characterized by progressive spasticity, extremities weakness and dorsal column impairment.[1] Based on the clinical manifestations, HSPs are divided into pure and complicated forms. The inheritance patterns of HSP include autosomal dominant (AD), autosomal recessive (AR), X-linked recessive (XR), and mitochondrial maternally inheritances.[2] An epidemiological study has shown that the global prevalences of AD-HSP and AR-HSP are roughly equal, ranging from 0.0 to 5.5 per 100,000 individuals.[3] In Western countries, however, AD-HSPs accounts for about 70% to 80% of all HSPs.[4] Although XR-HSP is extremely rare, its molecular genetic mechanism is relatively clear. Up to now, two subtypes of XR-HSPs have been identified, namely SPG1 and SPG2. These two subtypes usually manifest as complicated HSPs.[5]

The pure HSPs are mainly transmitted in an AD pattern, while the complicated HSPs are mostly transmitted in an AR pattern.[6] At present, more than 70 genetic types of HSP have been reported.[7] Common subtypes of AD-HSPs include SPG4, SPG3, SPG6, SPG8, SPG9, and SPG10 subtypes, while the common subtypes of AR-HSPs are SPG5, SPG7, and SPG11.[8] Many AR-HSP patients are considered as sporadic cases due to their small pedigrees or unknown family history.[5] HSP-related gene mutations are usually point mutations, commonly resulting in missense mutation, nonsense mutation, stop codon mutation, and splicing mutation.

Due to the high clinical heterogeneity, HSPs lack specificity of clinical manifestations, and are difficult to be differentially diagnosed from primary lateral sclerosis (PLS) and adrenal spinal cord neuropathy (AMN). In addition, there are many overlaps in the clinical manifestations among each HSP subtypes. Therefore, genetic testing is important for the diagnosis and typing of HSP.

Our previous study has reported the clinical manifestations of 56 HSP patients treated in our hospital.[9] The purpose of this

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study was to further report the results of genetic test of these HSP patients.

2. Experimental procedures

2.1. Patients

A total of 53 patients diagnosed with HSP in our previous study underwent genetic test to identify the potential pathogenic mutation for HSP.[9] To this end, 2 mL of peripheral blood were collected and subjected to extract its genomic DNA using QIAmp DNA Blood Mini kit according to manufacturer's protocol. This study was approved by the ethics committees of the Chinese PLA General Hospital. Written informed consent was obtained from each patient.

2.2. Exon sequencing for HSP-related genes

To screen the potential pathogenic genes for HSP, gene panel sequencing containing 55 HSP-related genes (GenCap Enrichment technologies, MyGenostics Inc, Beijing, China) was performed using HiSeq 2000 high-throughput sequencing system (Illumina Inc, USA). In addition, the following four genes were also included in the gene panel because they account for the inherited diseases with clinical manifestations similar to HSP: *ABCD1* (adrenoleukodystrophy-related gene), *MARS2* (hereditary spastic ataxias-related gene), *ACADVL* (very long-chain acyl-CoA dehydrogenase deficiency-related gene), and *ETFDH* (multiple acyl-CoA-dehydrogenase deficiency-related genes).

2.3. Bioinformatics analysis

After filtering the contaminant sequences using the Solexa QA package and cutadapt (https://cutadapt.readthedocs.io/en/stable/), the sequences were aligned to the reference genome by SOAPaligner (http://soap.genomics.org.cn/index.html) to obtain a unique alignment sequence. PCR duplicates were removed by Picard software (http://broadinstitute.github.io/picard/).

First, single nucleotide polymorphisms (SNPs) were identified using the SOAPsnp program (http://soap.genomics.org.cn/soapsnp.html), and were searched in 1000 Genomes Project database (www.1000genomes.org), followed by the Human Genome Mutation Database (http://www.biobase-international.com/product/hgmd HGMD) and the dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP) to determine whether the variant has been reported as a pathogenic mutation.

2.4. Sanger sequencing validation of family members

After the candidate pathogenic genes mutations were obtained in the exon sequencing, Sanger sequencing was adopted to validate if the family member(s) of the patient carried the same candidate pathogenic gene mutations as the proband according to the standard protocols.

3. Results

3.1. Genetic test

Of the 53 patients underwent genetic testing, 9 cases had a family history of HSP, while 44 cases were sporadic patients. The gene panel testing showed that 15 out of 53 patients carried at least one mutation in the screened HSP-related genes, including 23 mutations (Table 1). According to the inheritance patterns of the mutated genes, there were 9 cases with mutated genes in AD inheritance pattern, including four SPG4 subtypes (case 4, 6, 23, 26 in Table 1), two SPG31 subtypes (case 9, 13), 1 case of SPG3 (case 53), SPG6 (case 20), and SPG10 (case 7), respectively. There were 6 cases with mutated genes in AR inheritance, including 3 cases of SPG11 (case 27, 30, 49), 1 case of SPG15 (case 39), SPG58 (case 14), and SPG69 (case 25), respectively. In addition, case 53 also carried a mutation in *L1CAM* gene, which is the causative gene for SPG1 HSP (XR inheritance pattern).[10]

Among the 15 cases with mutation, there were 12 sporadic patients (case 4, 7, 9, 13, 14, 23, 25, 26, 27, 30, 39, 49) and 3 patients with a family history (case 6, 20, 53). The pedigree trees of case 6, 20, 53 were shown in Figure 1.

3.2. Bioinformatic analysis

Bioinformatic analysis revealed that among the 23 identified mutations, one mutation at *SPG11* gene (case no. 27) has been reported as a pathogenic mutation. The other cases of variants have not been reported as a pathogenic mutation in the literature, including one case of start codon mutation (case no. 13), frameshift mutation (case no. 26), nonsense mutation (case no. 30), splicing mutation (case no. 25), as well as 12 cases of missense mutations.

3.3. Sanger sequencing validation of family members

Among the 15 patients with mutation gene, Sanger sequencing was performed in the family members in 7 patients (case 4, 6, 7, 14, 20, 30, 39) to validate if their relatives carried the same mutation as the proband. The mother and uncle of case 6 both carried the same mutation (c.1459delA) in *SPAST* gene as the proband. The father of case 7 carried the same mutation (c.1816C>T) in *KIF5A* gene. The mother of the case 14 carried the same *KIF1C* gene mutation (c.2819G>A) as the proband. The brother of the case 20 patient carried the same mutation in *NIPA1* gene (c.8C>T). The mothers of case 30 and case 39 also carried the same mutations in the *SPG11* gene (c.6517C>T, Fig. 2) and *ZFYVE26* gene (c.4529C>T) as the corresponding proband.

3.4. Exclusion diagnosis of HSP

The genetic test data showed that there were 3 patients had no mutations in the HSP-related genes but had a point mutation in *ABCD1* gene (case 1, 3, 36). The 3 cases were male, onset at 18 to 32 years old, without a family history of HSP. The mutation of case 3 was a frameshift mutation (c.1415_1416del), while the mutation of the case 36 was a nonsense mutation (c.1715C>A), both of which have been reported as a disease-causing mutation of adrenoleukodystrophy (ALD)–adrenomyeloneuropathy (AMN) in HGMD database. Thus, these two cases could be diagnosed with ALD–AMN. The mutation (c1166G>A) of case 1 was a missense mutation, which has also been reported as a pathogenic mutation. In addition, the patient had long-term fatigue and sexual dysfunction, therefore could be diagnosed with ALD.

4. Discussion

In this study, 28.3% (15/53) patients were found to carry mutation(s) in HSP-related genes. The results showed that the

Table 1

HSP patients found to carry mutations in HSP-related genes panel screening.

Case no.	Onset age	Type	Clinical manifestations	Inheritance pattern based on the pedigree	Gene name	Subtypes based on the mutated gene	Inheritance pattern based on the mutated gene	Nucleotide change	Mutation type	Amino acid change
4	31	Complicated	Weak lower extremities, scissors gait, increased muscle tone of lower extremities, reduced deep sense, increased reflexes of lower extremities, positive Babinski sign	Sporadic	*SPAST*	SPG4	AD	c.1571C>T	Missense	524 alanine → valine
					SPAST			c.1588C>T	Nonsense	530 arginine → stop codon
6	17	Pure	Stiff lower extremities, scissors gait, increased muscle tone of lower extremities, active reflexes of lower extremities, positive Babinski sign	AD	*SPAST*	SPG4	AD	c.1459delA	Frameshift	487 reading frame shift
7	16	Pure	Stiff lower extremities, scissors gait, increased muscle tone of lower extremities, lower extremities hyperreflexia, positive Babinski sign	Sporadic	*KIF5A*	SPG10	AD	c.1816C>T	Missense	606 arginine → tryptophan
9	20	Complicated	Mental decline, weak lower extremities, scissors gait, slightly increased muscle tone Upper limb, lower extremities hyperreflexia, positive Babinski sign	Sporadic	*REEP1*	SPG31	AD	c.274G>A	Missense	92 valine → methionine
13	19	Complicated	Mental decline, stiff lower extremities scissors gait, arched foot, increased muscle tone of lower extremities, lower extremities hyperreflexia, positive Babinski sign	Sporadic	*REEP1*	SPG31	AD	c.2T>G	Start codon	1 methionine → arginine
14	11	Complicated	Reduced hearing, stiff lower extremities, scissors gait, increased muscle tone of all four extremities, active reflexes of upper extremities, lower extremities hyperreflexia, positive Babinski sign	Sporadic	*KIF1C*	SPG58	AR	c.2819G>A	Missense	940 arginine → histidine
					KIF1C	SPG58	AR	c.2987G>A	Missense	996 serine → aspartame
20	5	Pure	Stiff lower extremities, scissors gait, increased muscle tone of lower extremities, lower extremities hyperreflexia, positive Babinski sign	AD	*NIPA1*	SPG6	AD	c.8C>T	Missense	3 threonine → isoleucine
23	1	Pure	Stiff lower extremities, scissors gait, arched foot, increased muscle tone of lower extremities, active reflexes of lower extremities, positive Babinski sign	Sporadic	*SPAST*	SPG4	AD	c.226G>T	Missense	76 valine → leucine
25	16	Complicated	Mental decline, difficulty walking, stiff lower extremities with weakness, reduced deep sense, increased muscle tone of all four extremities, lower extremities hyperreflexia, positive Babinski sign	Sporadic	*RAB3GAP2*	SPG69	AR	c.2417-4A>G	Splicing	splicing change
					RAB3GAP2	SPG69	AR	c.2207C>T	Missense	736 alanine → valine
26	43	Pure	Stiff lower extremities, scissors gait, arched foot, mild weakness of all four extremities, increased muscle tone of lower extremities, lower extremities hyperreflexia, positive Babinski sign	Sporadic	*SPAST*	SPG4	AD	c.346delG	Frameshift	116 reading frame shift
27	16	Complicated	Mental decline, skin pigmentation, weak lower extremities, scissors gait, increased muscle tone of lower extremities, lower extremities hyperreflexia, positive Babinski sign	Sporadic	*SPG11*	SPG11	AR	c.4306C>T	Nonsense	1436 glutamine → stop codon
					SPG11	SPG11	AR	c.4306C>T	Nonsense	1436 glutamine → stop codon
30	30	Complicated	Mental decline, weak lower extremities, scissors gait, increased muscle tone of lower extremities, active reflexes of lower extremities, positive Babinski sign	Sporadic	*SPG11*	SPG11	AR	c.6517C>T	Nonsense	Arginine → stop codon
					SPG11	SPG11	AR	c.6602_6604del	Missense	2202 arginine del
39	24	Complicated	Dysarthria, stiff lower extremities, scissors gait, increased muscle tone of lower extremities, active reflexes of lower extremities, positive Babinski sign	Sporadic	*ZFYVE26*	SPG15	AR	c.4259C>T	Missense	1420 Ser → Phenylalanine
					ZFYVE26	SPG15	AR	c.2090A>G	Missense	697 aspartate → acid glycine
49	4	Complicated	Mental decline, weak lower extremities, arched foot, scissors gait, muscle atrophy, increased muscle tone of lower extremities, lower extremities hyperreflexia, positive Babinski sign	Sporadic	*SPG11*	SPG11	AR	c.5951G>A	Missense	1984 glycine → aspartic acid
					SPG11	SPG11	AR	c.5951G>A	Missense	1984 glycine → aspartic acid
53	2	Complicated	Mental decline, weak lower extremities, scissors gait, reduced deep sense, increased muscle tone of all four extremities, lower extremities hyperreflexia, positive Babinski sign	Possible XR	ALT1	SPG3A	AD	c.1408T>G	Missense	1408 threonine → glycine
					L1CAM	SPG1	XR	c.2511C>A	Missense	837 aspartic acid → glutamic acid

AD = autosomal dominant, AR = autosomal recessive, XD = X-linked recessive.

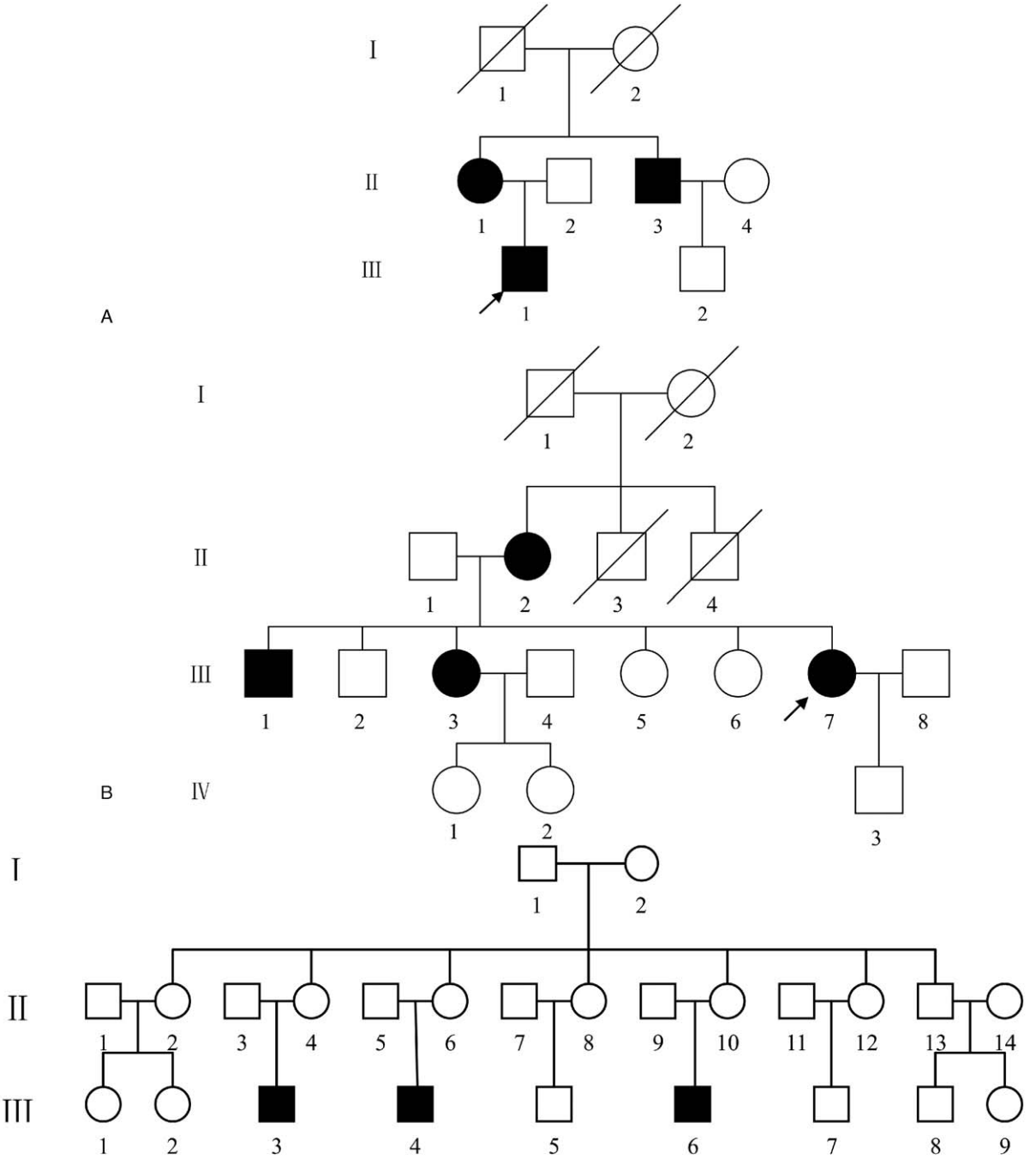

Figure 1. Pedigrees of three cases. The arrow marks the proband. (A) In the pedigree of case 6, the proband ((III1), his mother (II1) and uncle (II3) all carried the same novel deletion mutation (c.1459delA) at *SPAST* gene. (B) In the pedigree of case 20, both the proband (III7) and his brother (III1) carried a missense mutation at *NIPA1* (c.8C>T). (C) In the pedigree of case 53, the family disease may be in an X-linked recessive (XR) inheritance pattern. The proband (case 53) carried two novel mutations in *ALT1* gene and *L1CAM* gene (c.2511C>A), respectively.

detected mutation rate was higher in patients with a family history than in the sporadic patients (33.3% [3/9] *vs* 27.3% [12/44]), which is consistent with a Norwegian epidemiological study (49.2% [32/65] *vs* 14.7% [5/34]).[11] This phenomenon is due to the fact that the diagnosis of sporadic HSP is an exclusive diagnosis, therefore misdiagnosis in sporadic patients would decrease the rate of mutation detection in the following genetic testing. Thereby establishing a standardized diagnostic method for HSP is necessary for improving the accuracy of HSP diagnosis.

In this study, 3 of the 9 cases with positive family history were detected with HSP-related gene mutation (case 6, 20, 53). In the pedigree of case 6 (Fig. 1A), there are 3 patients in two consecutive generations, and all members of the first generation had already passed away. It can be seen from the pedigree that the disease was inherited in an AD pattern. The proband (III1, case 6) was found to carry a novel deletion mutation in *SPAST* gene (c.1459delA) which is predicted to induce a frameshift mutation. It is known that the mutation of *SPAST* gene is transited in an AD pattern. Moreover, Sanger sequencing confirmed that the family

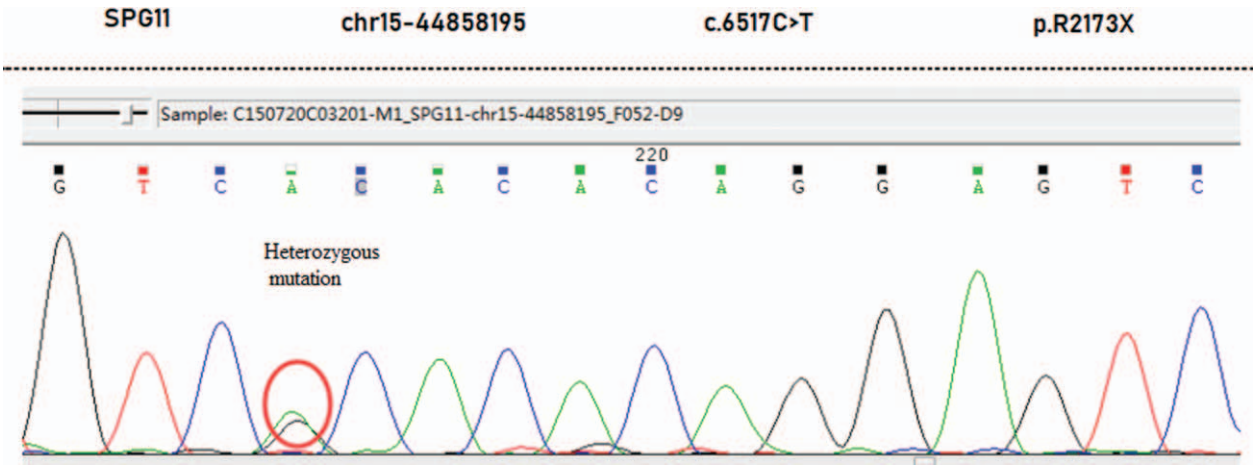

Figure 2. Sequence analysis of SPG11 detected a heterozygous mutation, c.6517C>T (circle).

members II1 and II3 with similar manifestations to the proband also carried the same mutation in *SPAST* gene. Taken together, the frameshift mutation at the *SPAST* gene was likely to be the pathogenic mutation and may result in SPG4 AD-HSP. Based on patient's recall, the first generation of the pedigree had no symptoms. Nevertheless, according to the pedigree analysis, it is speculated that the first generation might have the same mutation but it manifested as incomplete penetrance. However, following protein function analysis is needed to validate if the mutation is the pathogenic mutation.

In the pedigree of case 20 (Fig. 1B), there are 4 affected persons in two consecutive generations. The parents of the proband (II1 and II2) had 6 children, and three of them were affected, with a prevalence of 50%. Because there were only two consecutive generations of patients, map, the inheritance pattern cannot be determined according to the pedigree. Both the proband (III7) and his brother (III1) carried a missense mutation at *NIPA1* (c.8C>T). *NIPA1* gene is the causative gene for SPG6 HSP,[12] a rare type of AD-HSP. Currently, the pathogenic mechanism of SPG6 HSP remains unknown. SPG6 HSP can onset at any age, and progressed slowly. Most patients with SPG6 HSP manifests as pure HSP.[13] However, it is not yet confirmed if the mutation (c.8C>T) is the causative mutation. The Sanger validation results of the family members III2, III3, III5, and III6 are needed for further assessment.

As for the pedigree of case 53 (Fig. 1C), there were only 3 patients (III3, III4, III6) in the third generation, and all of them were males. The mothers (II4, II6, II10) of the 3 patients were sisters. Based on the pedigree, therefore, it is speculated that the disease may be inherited in an XR pattern. Genetic testing showed that the proband (III6) carried two novel mutations in *ALT1* gene (c.1408T>G) and *L1CAM* gene (c.2511C>A). The *L1CAM* gene is located on the X chromosome and is responsible for the SPG1 XR-HSP,[10] while the *ALT1* gene is associated with the SPG3 AD-HSP.[14] There were no affected persons in the first and second generations, therefore the familial disease is less likely to be caused by *ALT1* mutation. However, Sanger sequencing should be conducted in other family members for further validation.

In this study, 6 cases with a family history had no HSP-related gene mutation detected in the genetic testing. One possible explanation is that there are still some HSP-related genes which have not been found. In order to screen out the causative gene, whole exome or whole genome sequencing should be further performed. Another explanation is that some patients may have other hereditary disease but were misdiagnosed as HSP. For example, one of the six cases had onset after 30 years old and a short course of the disease. The clinical manifestations were simple spasmodic paraplegia of both lower extremities. Therefore, AD-PLS still could not be ruled out for this patient although it is extremely rare.

Among the 44 sporadic cases, 9 cases were detected with HSP-related gene mutations, of cases 27 have been reported as a pathogenic mutation.[15] Sporadic cases may be due to incomplete penetrance, unknown family history, AR/XR inheritance pattern, and small pedigree. Generally, single gene mutation in sporadic patients is difficult to be proven as a pathogenic mutation, especially the missense mutations; it is difficult to predict whether its protein product is functional. The previous study showed that about 10% to 20% of sporadic HSP patients are found to carry the mutation at *SPAST* gene (SPG4 subtype).[16] In the 5 non-sporadic patients with AD inheritance pattern, only one case (1/5 = 20%) was found to carry *SPAST* mutation. As for the 44 sporadic patients, there were only 3 cases with a mutation at *SPAST* gene (3/44 = 6.8%). The mutation rate was far lower in our study as compared with a previous report.[16] The discrepancy might be attributed to the small sample size of this study or there may be geographic variation in the mutation rate of the *SPAST* gene.

REEP1 gene mutation is responsible for the SPG31 HSP. It has been suggested that the pathogenic mechanism of SPG31 HSP is haploinsufficiency of the *REEP1* gene.[17] SPG31 accounts for about 2% to 8% of AD-HSP, and the SPG31 patients usually have onset before 20 years old. The majority of SPG31 are manifested as pure HSP, and some SPG31 patients with complicated HSP have white matter signal abnormalities.[8] In this study, 2 patients were found to carry *REEP1* gene mutation. One of the mutations occurred at the start codon (case 13), which may be more likely to be a pathogenic mutation. The other case is a missense mutation (case 9), and its pathogenicity is still unclear and further protein function prediction is needed.

KIF5A is the causative gene for SPG10 HSP,[17] and the pathogenic mutations in *KIF5A* are mainly missense mutation.[18] SPG10 accounts for 2% to 10% of AD-HSP and

sporadic patients, the age of onset is often >35 years. Clinically, SPG10 patients usually manifest as pure HSP.[18] One of our patient (case 7) carried a missense mutation (c.1816C>T) at *KIF5A* gene, but which has not been reported as a pathogenic mutation. Further protein functional prediction is necessary. In this study, three patients had homozygous (case 27) or compound heterozygous (case 30, 49) mutations in the *SPG11* gene. The homozygous mutation (c.4306C>T, nonsense mutation) in the case 27 has been reported as a pathogenic mutation.[15] However, the pathogenicity of the other two cases are unclear and needed to be further investigated. *SPG11* gene encodes the spatacsin protein.[19] SPG11 subtype accounts for about 20% of AD-HSP, and the majority of HSP with thinning corpus callosum (TCC) are associated with *SPG11* gene mutations.[20] HSP-TCC patients usually have mental retardation, and other common manifestations include sensor and motor axonal damage, cerebellar symptoms, extrapyramidal symptoms, and retinitis pigmentosa. The symptoms of SPG11 are typically more severe as compared with other subtypes. On average, two-thirds of patients become wheelchair-bound 15 years after disease onset.[21]

In summary, we reported the genetic testing results of our 53 HSP patients. Except for the three known pathogenic mutations (case 4, 12, 27), the pathogenicity of other novel mutations in HSP-related is worth to be further investigated in the following study, especially the c.1459delA mutation in *SPAST* gene (case 6) and the c.2511C>A mutation at *L1CAM* gene (case 53). Our report is helpful for the understanding of mutations in the HSP-related genes.

Author contributions

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