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Spastic paraplegia as the predominant phenotype in a cohort of Chinese patients with adrenoleukodystrophy

Wen-Jiao Luo[1] | **Qiao Wei**[1] | **Hai-Lin Dong**[1] | **Yang-Tian Yan**[1,2] | **Mei-Jiao Chen**[1] | **Hong-Fu Li**[1]

[1]Department of Neurology and Research Center of Neurology in Second Affiliated Hospital, and Key Laboratory of Medical Neurobiology of Zhejiang Province, Zhejiang University School of Medicine, Hangzhou, China

[2]Department of Neurology, Wenling Hospital of Traditional Chinese Medicine, Wenling, China

Correspondence
Hong-Fu Li, Department of Neurology and Research Center of Neurology in Second Affiliated Hospital, and Key Laboratory of Medical Neurobiology of Zhejiang Province, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou 310009, China.
Email: hongfuli@zju.edu.cn

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Abstract

Background: X-linked adrenoleukodystrophy (ALD) is one of the most common peroxisomal disorders characterized by abnormal accumulation of very long-chain fatty acids (VLCFA) in plasma and tissues and caused by mutations within *ABCD1*. Clinically, ALD present with various phenotypes, ranging from asymptomatic type to rapidly progressive childhood cerebral form. However, no remarkable abnormality in cerebral white matter usually makes it difficult to distinguish adult ALD from hereditary spastic paraplegia (HSP).

Methods: We analyzed the features of seven Chinese ALD patients who had a primary phenotype of spastic paraplegia. Sequencing was performed in the probands and their familial members. Detailed clinical, VLCFAs test, hormone test, magnetic resonance imaging, and electromyogram are presented.

Results: We reported seven ALD patients from a Chinese cohort of 142 HSP patients. Genetic investigations revealed five known *ABCD1* mutations (c.346G>C, c.521A>G, c.829G>T, c.1415_1416delAG, and c.1849C>T) and two novel mutations (c.454C>G, c.1452_1482del). Further auxiliary testing revealed that they had higher VLCFA and/or adrenal insufficiency.

Conclusions: Our findings expand the mutation spectrum of *ABCD1* and indicate that ALD represent a significant portion (4.9%, 7/142) of the spastic paraplegia entities. ALD should be considered in male patients with spastic paraplegia, even if there was no positive family history.

KEYWORDS

ABCD1, hereditary spastic paraplegia, peroxisomal disease, very long-chain fatty acids, X-linked adrenoleukodystrophy

1 | INTRODUCTION

X-linked adrenoleukodystrophy (ALD) is one of the most common peroxisomal disorders caused by mutations within *ABCD1* (OMIM 300371) gene (Berger & Gartner, 2006). It is characterized by abnormal accumulation of the very long-chain fatty acids (VLCFA) in white matter, adrenal glands, fibroblasts, and plasma (Berger & Gartner, 2006). Clinically, ALD present

Wen-Jiao Luo and Qiao Wei authors are contributed equally to this work.

various phenotypes, including childhood cerebral adrenoleukodystrophy, adolescent cerebral adrenoleukodystrophy, adult cerebral adrenoleukodystrophy, adrenomyeloneuropathy (AMN), olivo-ponto-cerebellar ALD, Addison's only, and asymptomatic ALD (Niu, Ni, & Wu, 2013). In clinical practice, no remarkable abnormality in cerebral white matter usually makes it difficult to distinguish adult AMN from hereditary spastic paraplegia (HSP). In this study, we reported seven Chinese ALD patients with *ABCD1* mutations and a phenotype mimicking HSP.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by the Ethics Committees of Second Affiliated Hospital, Zhejiang University School of Medicine. Written informed consent was obtained from each participant.

2.2 | Clinical and genetic analysis

A total of 142 Chinese participants with clinically diagnosed HSP were consecutively recruited from the Second Affiliated Hospital of Zhejiang University School of Medicine from April 2015 to June 2019. The clinical evaluations were performed by at least two senior neurologists. Genomic DNA was extracted from the peripheral blood, using QIAamp genomic DNA kits (Qiagen). Targeted next-generation sequencing (NGS), Sanger sequencing, and cosegregation analysis were carried out in every proband and available familial members, as previously described. Five hundred individuals without neurological disorders were collected as controls. Variant analysis was based on the American College of Medical Genetics and Genomics (ACMG) guidelines. Patients detected to carry *ABCD1* mutations were further underwent VLCFAs test, hormone test, magnetic resonance imaging (MRI), and electromyogram. Variants were described at cDNA and protein level using reference sequences NM_000033.4 and NP_000024.2, respectively.

3 | RESULTS

3.1 | Identification of mutations by NGS and Sanger sequencing

Among the 142 patients with diagnosis of HSP, we found seven index patients carrying *ABCD1* mutations, including five known pathogenic mutations (c.346G>C, c.521A>G, c.829G>T, c.1415_1416delAG, and c.1849C>T) and two novel mutations (c.454C>G, c.1452_1482del). The pedigrees of these seven probands were shown in Figure 1. The mutation c.454C>G (p.R152G) was absent in the ExAC, 1000G, genomAD, and our 500 in-house controls. It was predicted to be deleterious by SIFT, Polyphen-2, Mutation Taster, and CADD. According to ACMG, it was classified as "likely pathogenic." The truncating mutation c.1452_1482del (p.P487Wfs*61) was also absent in the above database and should be classified as "pathogenic." Among the five identified missense mutations, four mutations (c.346G>C, c.454C>G, c.521A>G, and c.829G>T) were localized in exon 1 of *ABCD1*. The two truncating mutations (c.1415_1416del, c.1452_1482del) were localized in exon 5. Interestingly, in the case with c.346G>C mutation, we did not detect the mutation in either of his parents, implying a possible de novo mutagenesis in this family. Unfortunately, functional studies of these novel mutations were not performed due to condition limitations.

3.2 | Clinical features of patients carrying *ABCD1* mutations

The detailed clinical features for seven patients were summarized in Table 1. One patient had a positive history, while the others were sporadic cases. All seven cases were male and had an initial diagnosis of HSP. The mean age at onset was 32 years (ranging from 24 to 45 years). None of them showed cognitive deficit or obvious evidence of white matter lesions in brain MRI. The level of VLCFA was increased in five patients, and not available in two patients (Table S1). Cortisol levels were normal in all patients. However, there was a definite increase in ACTH level in two cases carrying c.521A>G and c.1452_1482del.

Case 1, a 31-year-old male, had 5-year history of rigidity and weakness in lower limbs, gait difficulty, and urination dysfunction. Neurological examinations revealed enhanced muscle tone, brisk tendon reflexes, positive Babinski signs and clonus. Hypesthesia of topesthesia and vibration sense was also observed. Brain MRI and whole spine MRI revealed no obvious lesion. Electromyography showed impaired peripheral nerves injury of upper and lower limbs.

Case 2 was a 49-year-old man who developed progressive gait difficulties over the past 8 years. Neurological examinations revealed increased muscle tension, hyperreflexia, positive ankle clonus, and Babinski sign. The sensory system examination and coordination were intact. Brain MRI revealed no abnormality. Electromyography showed decreased the sensory conduction velocity of bilateral median nerve and left ulnar nerve. The levels of VLCFA were high: C26:0 level was 3.41 nmol/ml, C24:C22 was 1.79, C26:C22 was 0.067.

Case 3 was a 34-year-old male who complained numbness of lower limbs at the age 23 years. Five years after the onset, he required assistance to walk and had a problem with urinary incontinence. No remarkable change was observed in brain and lumbar MRI. The results of the VLCFAs were

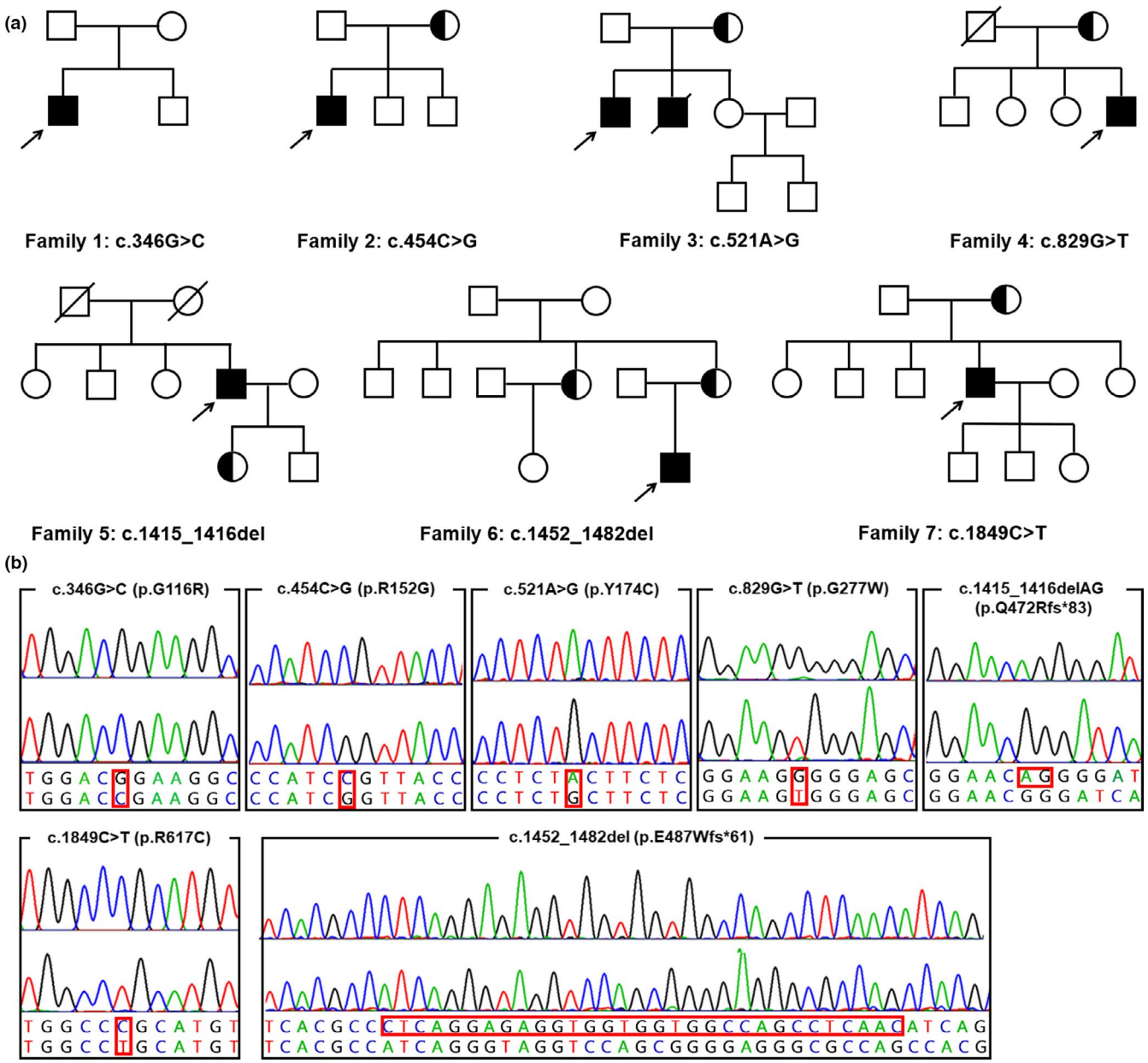

FIGURE 1 Pedigrees and chromatograms of seven ALD families in our cohort. (a) Squares indicate males; circles indicate females; the black symbols indicate affected individuals; arrows indicate the probands; the half black symbols indicate carriers. (b) The mutations of *ABCD1* in seven probands. The upper chromatogram in each frame represents the reference sequence, and the lower one depicts the mutant sequence. ALD, adrenoleukodystrophy

increased. The pituitary gland also produced high levels of adrenocorticotropic hormone, luteinizing hormone and prolaction, which are listed in Table S1. His affected brother developed gait difficulty at age 18 years and died in bed at the age 28 years.

Case 4 was a 28-year-old male who experienced weakness of lower limbs and sexual dysfunction for 2 years. Neurological examinations revealed slight nystagmus, brisk tendon reflex, positive ankle clonus. MRI of the brain and whole spine revealed unremarkable findings. Electromyography revealed peripheral neuropathy in both lower limbs. His levels of VLCFAs were elevated: C26:0 level was 4.92 nmol/ml, C24:C22 was 1.59, C26:C22 was 0.092.

Case 5 was a 52-year-old male who experienced weakness of lower limbs starting from 7 years ago. Neurological examination revealed scissors gait, increased muscle tension, hyperreflexia, and ankle clonus in lower limbs. Babinski sign and Hoffmann's sign were positive bilaterally. He did not show paresthesia or cognitive impairment. MRI showed no obvious abnormality. Electromyography showed reduced conduction velocity of sensory and motor nerve in lower limbs. There were no data about adrenocorticotropic hormone, serum cortisol, and plasma VLCFA.

TABLE 1 The clinical features of patients with *ABCD1* mutations

Patient	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Variants	c.346G>C (p.G116R)	c.454C>G (p.R152G)	c.521A>G (p.Y174C)	c.829G>T (p.G277W)	c.1415_1416delAG (p.Q472Rfs*83)	c.1452_1482del (p.P487Wfs*61)	c.1849C>T (p.R617C)
AAO (years)	26	41	23	26	45	24	36
DD (years)	5	8	11	2	7	7	4
Family history	No	No	Yes	No	No	No	No
Phenotype	AMN	AMN	AMN	AMN	AMN	AMN	AMN
Initial symptoms	Spasm	Weakness; unstable walk	Weakness; unstable walk	Weakness	Weakness	Weakness	Spasm
UL reflex	+++	+++	++++	+++	++++	++++	++
LL reflex	++++	++++	++++	++++	++++	+++	++++
Ankle clonus	+	+	NA	+	+	+	+
Babinski sign	+	+	−	+	+	+	+
Cognitive impairment	No	No	No	No	No	No	No
MRI	N/N/N/N	N/N/N/N	N/NA/NA/NA	N/N/N/N	N/N/N/N	N/N/N/N	N/Thinner/N/N
EMG	Yes	Yes	NA	Yes	Yes	Yes	N

Abbreviations: AAO, age at onset; AMN, adrenomyeloneuropathy; DD, disease duration; EMG, electromyography; LL, lower limbs; MRI, brain MRI/cervical spine MRI/thoracic spine MRI/lumbar spine MRI; MRI, magnetic resonance imaging; N, no obvious abnormality; NA, not available; UL, upper limbs.

Case 6 was a 31-year-old male who started the disease with a progressive gait difficulty at the age 24 years. On the neurological examinations, he showed spastic gait, weakness, and increased muscle tension in lower limbs. Hoffman sign, Babinski signs, and ankle clonuses were bilaterally positive. Vibration sensation and position sensation were weakened. Brain MRI revealed no obvious evidence of white matter lesions. His cortisol was normal, but his adrenocorticotrophic hormone at 8 a.m. was very high (891 pg/ml). The results of the VLCFAs also strongly suggested a diagnosis of ALD: C26:0 level was 2.96 nmol/ml, C24:C22 was 1.68, C26:C22 was 0.056.

Case 7 was a 40-year-old male who suffered from rigidity for more than 4 years. He complained about weakness, abnormal gait, and ankle pain at the age 39 years. His muscle tension was increased, with hyperreflexia in knee and ankle. Babinski sign was positive bilaterally. MRI indicated that the thoracic medulla was atrophic extensively. Electromyography of upper and lower limbs showed no peripheral nerve damage. His levels of adrenocorticotropic hormone, serum cortisol, and plasma VLCFA were also not obtained.

4 | DISCUSSION

ALD is a metabolic disease with high clinical heterogeneity. It is caused by defect in peroxisomal ATP-binding cassette-transporter adrenoleukodystrophy protein, which is coded by *ABCD1* and plays an important role in facilitating VLCFA to peroxisomes for β-oxidation (Berger & Gartner, 2006). A retrospective and international study suggests that adrenal insufficiency can occur in nearly 80% ALD patients (Huffnagel et al., 2019). Most men and women with ALD have a slowly progressive spinal cord disease, AMN, which typically begin in the 30's for men and postmenopausal for women. 35% of ALD males may develop a rapidly progressive inflammatory cerebral demyelination peaking in the ages 3–10 years of age. About 20% of adult males with AMN also develop cerebral disease that rapidly progresses to disability and death (Kemp et al., 2001). It is challenging to diagnose AMN when there is no evidence of adrenal insufficiency or accumulation of VLCFA. Recently, Chen et al. (2019) reported 7 ALD patients who had a phenotype of HSP and *ABCD1* mutations. Only four cases had adrenocortical insufficiency, whereas the other three presented normal adrenocortical function. Therefore, for sporadic spastic paraplegia, AMN should also be considered in addition to HSP. As a biochemical marker of ALD, VLCFA is an indispensable test, and ACTH and testosterone also need to be tested in patients with baldness or sexual dysfunction. Of course, genetic investigations are also an effective diagnostic method. Given the large number of genes and the relatively high diagnostic yield, whole-genome sequencing (WGS) may be particularly relevant to diagnosing spastic paraplegia (Kim et al., 2019). However, due to the high price of WGS, targeted gene panels and whole-exome sequencing (WES) is usual the preferred choice, followed by multiplex ligation-dependent probe amplification (MLPA). Of note, a significant proportion of HSP cases could not obtain a genetic diagnosis after WES and MLPA (Shribman, Reid, Crosby, Houlden, & Warner, 2019). WGS is then required to identify new causative gene or intronic variants.

To date, 812 nonrecurrent mutations in *ABCD1* gene have been reported including missense (46%), frameshift (23%), nonsense (13%), and amino acid insertions/deletions (6%) (https://adrenoleukodystrophy.info/). Mutations are distributed throughout the entire *ABCD1* gene unevenly and most missense mutations cluster in some exons (1b, 1c, 6, 7, 8, and 9) (Kemp et al., 2001). The amino acids encoded by exon 1b and 1c are located in transmembrane domain (TMD) and the amino acids encoded by exons 6, 7, 8, and 9 are located in nucleotide binding domain (NBD) (Kemp et al., 2001). TMD is associated to substrate binding, whereas NBD is involved in dimerizing and ATP binding, both two are necessary for the functional ABC transporters (Geillon et al., 2014).

In Chinese ALD patients, more than half of the mutations localized in exon 1 and 6 (Niu et al., 2013). And mutations in exon 6 are higher than that listed in the worldwide database, suggesting exon 6 is another possible hotspot exon in the Asian populations (Niu et al., 2013). The truncating mutation c.1415_1416delAG in family 5 was identified as the most frequent mutation in the word (Kemp et al., 2001), which resulted in a nonfunctional truncated protein by a premature stop codon at amino acid position 554 (Kemp et al., 1994).

Previous studies have shown that there was no clear genotype-phenotype correlation in ALD. Patients with the hotspot mutation (c.1415_1416delAG) in the world had presented a variety of phenotypes (Kemp, Huffnagel, Linthorst, Wanders, & Engelen, 2016). Apparent intrafamilial phenotypic variation had also been described within individual kindreds, even in identical twins (Wiesinger, Eichler, & Berger, 2015). Many nonrecurrent mutations, high de novo mutation rate, as well as environmental factors or modifying genes, make the genotype–phenotype correlation more difficult to research (Wiesinger et al., 2015). Unfortunately, no curative disease-modifying therapy has been found to prevent or slow the progression of spinal cord disease in AMN. There are only symptomatic treatments to relieve pain, spasm, and urinary incontinence. Hematopoietic cell transplantation (HCT) is effective at halting the progression of brain disease in males with ALD only if done at the first signs of progressive brain lesions and before neurological disability (Mahmood, Raymond, Dubey, Peters, & Moser, 2007). Allogeneic hematopoietic stem cell transplantation, with or without autologous *ABCD1* gene therapy, can halt the cerebral demyelination if done early before neurological symptoms or advanced brain disease occurs (Miller et al., 2011). Early diagnosis through

family screening of at-risk males, as of 2015 in the USA newborn screening, has provided hope for successful treatment for CALD (Moser et al., 2016). However, a retrospective study had shown that HCT failed to prevent the progression of myelopathy (Van Geel et al., 2015). Although Lorenzo's Oil, statins, and pioglitazone can reduce the levels of C26:0 in vivo, there is no evidence that they can bring clinical benefits in ALD patients (Berger & Gartner, 2006; Moraes, 2013). In addition, gene therapy is also not expected to have effect on AMN phenotype which is still under further evaluation (Eichler et al., 2017).

In conclusion, our study expanded the mutation spectrum of *ABCD1*. Our patients carrying *ABCD1* mutation all exhibited pure AMN, in line with the notion that myelopathy is the most common clinical manifestations in adults with ALD (Kemp et al., 2016). Laboratory test revealed higher VLCFA and/or adrenal insufficiency in these patients. Our results demonstrate that ALD represent a significant portion (4.9%, 7/142) of the spastic paraplegia entities. Genetic investigations and plasma VLCFA test are critical for the diagnosis. No correlation was found between genotype and phenotype (Niu et al., 2013). This is not surprising in view of the heterogeneous clinical expression often seen in ALD. The phenotypic variability of ALD is likely to be influenced by environmental factors and/or modifying genes. Adult ALD males with adrenal insufficiency and/or myelopathy have the risk to develop cerebral inflammation, as well as our patients (Kemp et al., 2016). Therefore, long-term follow-up and regular MRI examination are necessary. It had been reported that head trauma or cerebrovascular accident may trigger a sudden deterioration of the central nervous system (Raymond et al., 2010). We should attach importance to relieve spasticity of lower limbs to avoid the incidence of accidental falls.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS CONTRIBUTION

Dr. Luo: data acquisition, analysis, and interpretation of data, statistical analysis, drafting the manuscript. Dr. Wei: data acquisition, analysis, and interpretation of data, drafting the manuscript. Dr. Dong: data acquisition, interpretation of data. Dr. Yan: data acquisition. Dr. Chen: data acquisition. Dr. Li: funding, study design and conceptualization, data acquisition, analysis and interpretation of data, technical and material support, drafting and critical revision of the manuscript.

ORCID

Hong-Fu Li https://orcid.org/0000-0002-2203-0046

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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