A novel ABCD1 gene mutation causes adrenomyeloneuropathy in a Chinese family

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Abstract

Background: Adrenomyeloneuropathy (AMN) is a rare genetic disease. In this study, a case of AMN was uncovered in a Chinese family.

Methods: Clinical manifestations were collected and observed through medical records, physical examination, laboratory tests, and magnetic resonance imaging (MRI). Generation sequencing of the ABCD1 gene was performed, and the pedigree of the family was analyzed.

Results: The proband suffered from adrenocortical insufficiency at 8 years old and presented with a slowly progressive gait disorder at 21 years old. Physical examination, laboratory tests, and MRI showed that he had adult-onset AMN manifestations, including spasticity and hyperactive tendon reflexes with Hoffman and Babinski signs in the limbs, difficulty in performing the heel-to-shin test, hyperpigmentation, increased levels of adrenocorticotropic hormone and very long-chain fatty acids, decreased levels of corticosteroid and serum gesterol, and salient atrophy of the cervical and thoracic spinal cord. DNA analysis revealed a missense variant, c.290A>C (p.His97Pro) in exon 1 of the ABCD1 gene, in the proband. Sanger sequencing confirmed that the proband's mother was heterozygous for the same variant. The ABCD1 gene mutation transmitted in an X-linked inheritance manner.

Conclusion: A novel missense mutation in the ABCD1 gene was identified in a Chinese family, which caused an unusual manifestation of adult-onset AMN. This discovery is beneficial for the genetic counseling of patients with X-linked adrenoleukodystrophy.

KEYWORDS
ABCD1, adrenomyeloneuropathy, Chinese family, missense mutation, X-linked

1 | INTRODUCTION

X-linked adrenoleukodystrophy (X-ALD) is a metabolic disorder characterized by impaired oxidation of very long-chain fatty acids (VLCFAs), which leads to the accumulation of VLCFAs in tissues, such as the brain white matter, spinal cord, and adrenal cortex. It is caused by mutations in the ABCD1 gene, which codes for the peroxisomal transporter protein ALDP (Engelen et al., 2012). The ABCD1 gene has been mapped to Xq28 (Migeon et al., 1981). More than 750 different variants in the ABCD1 gene have been identified, and 343 are missense mutations (Kemp et al., 2001).

Adrenoleukodystrophy (ALD) can begin at different ages with a variety of manifestations, depending on the extent to which organs are affected (Moser et al., 1999). Among them, childhood cerebral
ALD and adult-onset adrenomyeloneuropathy (AMN) are the two main phenotypes of X-linked ALD (Moser et al., 2000). Adult-onset AMN usually begins at a later age and affects the spinal cord pyramidal tracts, dorsal columns, and peripheral nerves (Engelen, Kemp, & Poll-The, 2014). Approximately 20% of AMN patients show cerebrodemyelination in the late stage of the disease, occasionally with Wallerian degeneration of the corticospinal tract or cerebellar atrophy (de Beer, Engelen, & Geel, 2014).

Here, we present a Chinese family with adult-onset AMN that was caused by a novel mutation in the \textit{ABCD1} gene.

2 | METHODS

2.1 | Subjects

The present study was approved by the local Ethics Committee of Jilin University, Changchun, China. The proband and the proband’s mother were studied after they signed a written informed consent form.

2.2 | Magnetic resonance imaging (MRI)

The brain and spinal cord of the proband and the proband’s mother were examined by MRI.

2.3 | Identification of the \textit{ABCD1} mutation

Blood specimens were obtained from the proband and the proband’s mother, and the DNA was isolated. Generation sequencing was performed on ABI 9700 PCR and ABI 3730XL instruments (Life Technologies). The \textit{ABCD1} mutation was identified through comparison with known human genome sequences and was defined as pathological mutation according to Human Gene Mutation Database (PMID: 27779215).

3 | RESULTS

3.1 | Clinical manifestations

The proband, a 21-year-old male college student, presented with a 1-year history of slowly progressive gait disorder. He suffered from adrenocortical insufficiency when he was 8 years old. On neurological examination, spasticity and hyperactive tendon reflexes with Hoffman and Babinski signs in the limbs were observed. He was unable to perform the heel-to-shin test due to spasticity of the lower limbs, but he could still walk without assistance. He was alert without any intellectual disabilities. He could speak fluently and clearly without a detectable dysarthria. His hearing and vision were normal. There was no nystagmus or ophthalmoplegia. Both superficial and proprioception sensations were intact. Physical examinations showed hyperpigmentation, especially in the gingiva, tongue, areolae, creases of the hand, and elbow joint (Figure 1). The respiratory, cardiovascular, and abdominal examinations were unremarkable. The sphincter function was normal.

Laboratory investigations, including full blood counts, blood electrolytes, thyroid function, sex hormones, liver and renal function, and pituitary hormone levels (except gesterol), were normal.

\textbf{FIGURE 1} The patient showed hyperpigmentation in the gingiva (a), tongue (b), areolae (c), creases of the hand (d), and elbow joint (e)
The adrenocorticotropic hormone (ACTH) levels were markedly increased (379.70, 440.40, and 288.40 pM, at 0:00, 8:00, and 16:00, respectively), and the corticosteroid levels were decreased (<1 µg/dl, normally 1.40–6.30 µg/dl, at 0:00, 8:00, and 16:00). The serum gonadotropin level was decreased (0.11 ng/ml, normally 0.28–1.22 ng/ml). In addition, the VLCFAs were measured in the plasma. The hexadecanoic acid (C26:0) level was 2.519 µM (normally < 1.20 µM), the hexadecanoic acid and docosane acid ratio (C26:0/C22:0) was 0.06 µM (normally < 0.03 µM), and the tetradecanoic acid and docosane acid ratio (C24:0/C22:0) was 1.38 µM (normally < 0.62 µM).

Brain MRI was normal, and the spinal cord MRI showed salient atrophy of the cervical and thoracic regions (Figure 2), without any compression. Electrophysiological studies, including nerve conduction, visual evoked potentials, brainstem auditory evoked potentials, and somatosensory evoked potentials, did not reveal any abnormal findings. Based on these results, a diagnosis of X-ALD was made.

3.2 Genetic analysis

Genetic analysis of the family members exhibited the missense mutation A>C at the 290th bp of the encoding region (c.290A>C), which led to a change in the 97th amino acid (from histidine to proline) in exon 1 of ABCD1 gene (Figure 3). Sanger sequencing confirmed the ABCD1 point mutation in the proband. He was homozygous, and his mother was heterozygous for this variant. His father died several years ago; therefore, no blood sample could be obtained and tested. Based on the clinical manifestations and genotypic analysis results, a pedigree of the family with X-ALD was constructed (Figure 4). The ABCD1 point mutation followed an X-linked inheritance pattern (Figure 4).

4 DISCUSSION

In the present study, the medical history, physical examination, laboratory tests, and MRI indicated that the proband had the clinical manifestations of ALD. Genetic analysis uncovered the missense mutation A>C at the 290th bp of the encoding region (c.290A>C) of the ABCD1 gene, which was X-linked. These results indicated that a point mutation in the ABCD1 gene caused AMN in a Chinese family.

The proband was diagnosed with adrenocortical insufficiency at the age of 8 years, and he presented with neurological symptoms 12 years later. These symptoms are in agreement with the disease progression of X-ALD, which is that adrenocortical insufficiency can be the presenting symptom in boys and men years or even decades before the onset of neurological symptoms (Hsieh & White, 2011) in as many as 35% of X-ALD patients (Laureti et al., 1996). He had higher serum ACTH and lower levels of corticosteroid; these levels are typical of approximately 50% of X-ALD patients (Laureti et al., 1996). His decreased serum gonadotropin level indicated that he had the subclinical sign of testicular insufficiency, which is common among X-ALD-affected males (Assies, Gooren, Geel, & Barth, 1997). His higher serum ACTH level, lower corticosteroid level, and hyperpigmentation in the gingiva, tongue, areolae, creases of the hand, and elbow joint indicated that he had the “Addison-only” phenotype of X-ALD (van Geel, Assies, Wanders, & Barth, 1997). The proband became gradually symptomatic over a 1-year period. After the initial clinical symptom of
spastic gait disturbance started, he still completed his education and lived independently. Then, the symptoms of myelopathy, including spasticity, hyperactive tendon reflexes with Hoffman and Babinski signs in the limbs, and salient atrophy of the cervical and thoracic spinal cord without any compression, manifested. The relatively mild and slow progression of the disease in the proband was in contrast to childhood cerebral ALD, and it followed the pattern of adult-onset AMN (Marino et al., 2007). Although the proband could still walk independently, it is likely that his disease will progress in 10–15 years with severe outcomes, such as wheelchair dependence (Qiu et al., 2018), progressive spastic paraparesis and sensory ataxia (Moser, Mahmood, & Raymond, 2007), and prominent spinal cord symptoms and axonopathy (Engelen et al., 2011; van Geel, Koelman, Barth, & Ongerboer de Visser, 1996), if he is not effectively treated. The MRI of the proband’s brain appeared normal, with salient atrophy of the cervical and thoracic spinal cord and without any compression. There were no abnormalities in nerve conduction, visual evoked potentials, brainstem auditory evoked potentials, somatosensory evoked potentials, or cognition. It has been found that approximately 20% of AMN patients develop additional cerebral demyelination and moderate cognitive deficits over a period of 10 years (van Geel, Bezman, Loes, Moser, & Raymond, 2001). Therefore, the brain and spinal cord of AMN patients need to be carefully monitored by MRI. In summary, the clinical, electrophysiological, and radiological features of the proband were in accordance with the clinical manifestations of the AMN form of X-linked ALD (Qiu et al., 2018).

In the present study, DNA analysis revealed the missense variant c.290A>C (p.His97Pro) in exon 1 of the \( \text{ABCD1} \) gene in the proband. The proband’s mother was heterozygous for the same variant, while the proband’s grandmother might also be heterozygous for the variant. The ALD symptoms in the male proband indicated that he had a mutated \( \text{ABCD1} \) allele on the X chromosome, which was confirmed by DNA sequencing. The transmission of the \( \text{ABCD1} \) mutation from his mother to the proband was also confirmed by the finding that his mother carried one allele of the \( \text{ABCD1} \) mutation and was heterozygous. Since the proband’s mother did not present with any ALD manifestations, the \( \text{ABCD1} \) point mutation is recessive; it might have been transferred from the proband’s grandmother to his mother. The \( \text{ABCD1} \) point mutation showed an X-linked inheritance, which is expressed in most cases of X-ALD (Kemp et al., 2001). The \( \text{ABCD1} \) gene encodes for the peroxisomal transporter protein ALDP (Engelen et al., 2012), which plays an important role in peroxisomal oxidation of VLCFAs (Engelen et al., 2012). Although some variations in the \( \text{ABCD1} \) gene, such as the “mis-sense mutations” N13T and H97L, do not affect protein function or cause disease but rather represent polymorphisms (Morita et al., 2013), most disease-causing mutations in the \( \text{ABCD1} \) gene cause loss of function of ALDP (Kemp et al., 2001), impairment of VLCFA oxidation, and accumulation of VLCFAs in tissues (Engelen et al., 2012). The higher levels of VLCFAs in the proband’s plasma support that this point mutation in the \( \text{ABCD1} \) gene causes a deleterious change in ALDP (Wiesinger, Eichler, & Berger, 2015), loss of function of ALDP (Kemp et al., 2001), impairment of VLCFA oxidation, and accumulation of VLCFAs in tissues (Engelen et al., 2012). In conclusion, a novel missense mutation in the \( \text{ABCD1} \) gene was identified, which caused an unusual manifestation of adult-onset AMN in a Chinese family. These findings further increase our knowledge about \( \text{ABCD1} \) mutations and their associated phenotypes, which is beneficial for the genetic counseling of patients with X-ALD.
CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Jingyao Liu carried out the molecular genetic studies, participated in the sequence alignment, and drafted the manuscript. Chao Wang and Hongchao Liu participated in the sequence alignment. Yanbo Hou participated in the design of the study. Hui Zhu conceived of the study, participated in its design and coordination, and helped to draft the manuscript. Chao Wang and Chunyu Dong wrote the paper. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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