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BRIEF COMMUNICATION

An adolescence-onset male leukoencephalopathy with remarkable cerebellar atrophy and novel compound heterozygous AARS2 gene mutations: a case report

Qing Dong[1] · Ling Long[1] · Yan-yu Chang[1] · Yan-jun Lin[1] · Mei Liu[1] · Zheng-qi Lu[1]

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Abstract

Mutations in the mitochondrial alanyl-transfer (t)RNA synthetase 2 (AARS2; OMIM 612035) have been linked to leukoencephalopathy recently. Until now, there have been only 13 cases reported in the literature. Hence, the clinical and genetic characteristics of this disease are not fully understood. Here, we reported an adolescence-onset male leukoencephalopathy patient characterized by progressive limb tremor at the age of 17 years. He had no signs of a cardiomyopathy. Magnetic resonance imaging scanning demonstrated severe cerebellar atrophy and white matter abnormalities involving descending tracts. Focused exome sequencing revealed he had novel compound heterozygous mutations in *AARS2* gene (c.2265dupA; p.Arg756fs and c.650C>T; p.Pro217Leu). The patient was diagnosed with *AARS2* mutation-related leukodystrophy (AARS2-L). We report a case with novel AARS2 gene mutations with developed striking cerebellar atrophy and leukoencephalopathy, which helps to further understand the clinical and genetic heterogeneity of AARS2-L.

Introduction

Adult-onset leukoencephalopathies are a group of rare neurological diseases, characterized by degeneration of the white matter of the central nervous system and a generally progressive clinical course [1]. The differential diagnosis of adult-onset leukoencephalopathies is often challenging due to the high heterogeneity of etiologies [2]. With advances in the understanding of the genetic basis, several causative gene mutations have been shown to be responsible for the etiology of adult-onset leukoencephalopathies [3], such as colony-stimulating factor 1 [4], eIF2B family [5] and alanyl-transfer (t)RNA synthetase 2 (AARS2) [6].

AARS2 is a nuclear gene, accounting for AARS2 loading of alanine onto tRNA during mitochondrial translation [7]. Recently, autosomal recessive mutations in *AARS2* gene have been linked to *AARS2* mutation-related leukodystrophy (AARS2-L) [8]. Since first identified in 2014, only 13 AARS2-L cases have been reported in English literature until now [6, 9–11]. Here we report a male leukoencephalopathy patient with remarkable cerebellar atrophy and novel compound heterozygous *AARS2* gene mutations.

Case presentation

Patient history and clinical data

A 23-year-old male visited our hospital due to deteriorating neurological symptoms, including severe limb tremor, gait impairment, and slurred speech in 2016. He was the fourth child of his non-consanguineous parents. No similar symptoms occurred in his parents or his three older sisters. He and his second sister had thalassemia. He had normal physical development, except for congenital strabismus, and he had received several strabismus surgeries. He had mild clumsiness since childhood. At the age of 17 years, he had gradually developed a mild, asymmetric, and coarse upper limb tremor at certain posture and during movement. He consecutively visited three hospitals in the following 3 years

These authors contributed equally: Qing Dong, Ling Long.

✉ Zheng-qi Lu
LuZQ_zssy@163.com

[1] Department of Neurology, The Third Affiliated Hospital of Sun Yat-sen University, No. 600 Tianhe Road, Guangzhou 510630, China

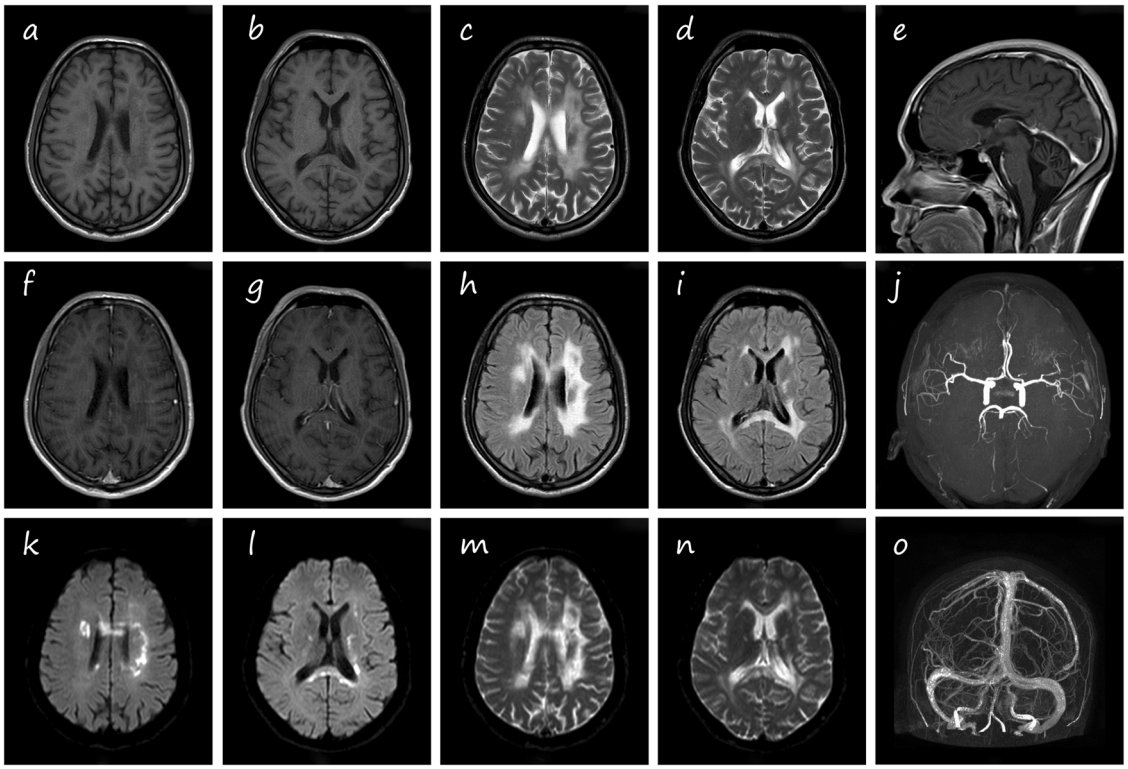

Fig. 1 Brain MRI images of the patient. **a**, **b** Axial T1-weighted imaging (T1WI): Confluent T1 hypointensity was observed in the deep white matter, centered in the frontoparietal areas, periventricular regions, and corpus callosum. **c**, **d** Axial T2-weighted imaging (T2WI): Bilateral, asymmetric, and confluent high signal intensity in the same regions was found in T1WI. **e** Sagittal T1WI: Remarkable atrophy of the cerebellum was observed. **f**, **g** Contrast enhancement of axial T1WI: Contrast enhancement of the lesions was absent. **h**, **i** Axial T2FLAIR: There was asymmetric subcortical high signal in the supratentorial white matter involving the frontal and parietal lobes, periventricular, coronal radiate, and corpus callosum. **k**, **l** Diffusion-weighted imaging (DWI): Punctate, linear, and partly confluent areas of restricted diffusion in the abnormal white matter. **m**, **n** Apparent diffusion coefficient (ADC): A high signal of the corresponding areas on the DWI was shown. **j** Magnetic resonance angiography (MRA): No stenosis of the major vessels was observed. **o** Magnetic resonance venography (MRV) showed no signs of cerebral venous sinus thrombosis

due to decreased frequency of morning erections, but the cause remained unknown. At the age of 22 years, he developed severe limb tremor and weakness, nystagmus, anarthria, ataxia, gait impairment, and cognitive decline. At admission, he had no difficulty with urination and defecation and had no obvious psychological and behavioral abnormalities. His Mini-Mental State Examination (MMSE) score was 17/30. The missing values of MMSE test were orientation to time (1/5), orientation to place (4/5), attention and calculation (1/5), recall (2/3), and complex commands (3/6), while the patient retained the function of registration (3/3), repetition (1/1), and language (2/2). Neurologic physical findings included wide-based gait, vertical nystagmus, tongue extended towards the right, spastic tetraparesis, brisk deep reflexes of all limbs, bilateral patella clonus and Babinski sign, extremity ataxia, and Romberg sign. He could not cooperate when we performed the sensory examination. He had no signs of a cardiomyopathy. General physical examination revealed no obvious abnormality. Written informed consents were obtained from the patient's elder sister for publication of this case report and any accompanying images. Because the patient had cognitive impairment, and the patient's elder sister had higher education than the patient's parents, thus the patient's parents asked her to sign the written informed consent. However, the patient's parents were also informed and consent was obtained.

Laboratory and auxiliary examinations

Hematological and biochemical examinations showed mild thalassemia, hyperuricemia, hypolipidemia, and 25-hydroxyvitamin D deficiency. Examination of cerebrospinal fluid and serum levels of sex hormone (testosterone, follicle-stimulating hormone, prolactin, progesterone, luteinizing hormone, estradiol) were both normal. Electromyography showed nerve injuries in the sensory branches of right tibial nerve and right median nerve. Evoked potentials were normal. Electroencephalogram exhibited moderate abnormalities. The dominant wave was 7–9 Hz, 20–60 μv, α/θ. There was few β waves, and many scattered θ waves (5–7 Hz, 20–100 μv),

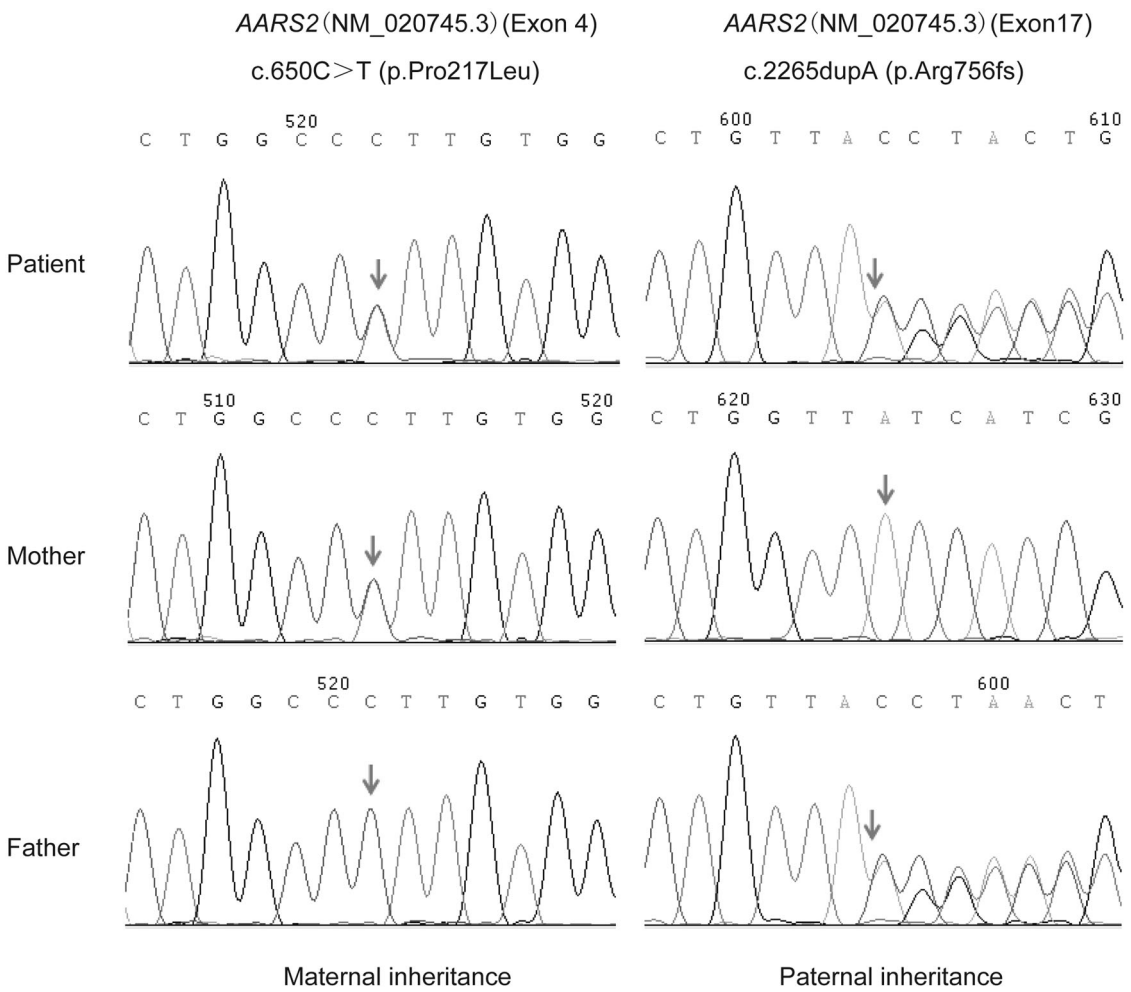

Fig. 2 Focused exome sequencing of the patient and his parents. C650C>T (p.Pro217Leu) was inherited maternally, and c225dupA (p.Arg756fs) was inherited paternally

part of which appeared paroxysmally, mainly in the frontal lobe. The 24-h ambulatory electrocardiogram showed sinus wandering pacemaker and early repolarization syndrome. Mild tricuspid regurgitation was observed by echocardiogram. No abnormal findings of abdominal organs and genitourinary system were revealed by duplex ultrasound scanning.

MRI examination

Brain MRI findings showed that asymmetric hyperintense signal on T2-weighted imaging, fluid-attenuated inversion recovery and low signal on T1-weighted imaging could be observed throughout the supratentorial white matter involving the frontal and parietal lobes, periventricular, coronal radiate, corpus callosum, and descending connections. Subcortical U fibers were spared (Fig. 1a–d, h, i). No contrast enhancement was detected (Fig. 1f, g). Diffusion-weighted imaging and apparent diffusion coefficient showed that punctate, linear, and partly confluent regions of restricted diffusion were roughly parallel to the lateral ventricles (Fig. 1k–n). The most obvious characteristic was remarkably cerebellar atrophy (Fig. 1e). Magnetic resonance angiography and magnetic resonance venography seemed normal (Fig. 1j, o).

Before confirmed diagnosis, the patient was given intravenous infusion of oxiracetam (4 g per day), buspirone (5 mg po tid), and methylprednisolone (1 g per day) for 5 days, followed by oral Medrol (24 mg per day) for 1 week. Symptoms were slightly relieved during hormone therapy, presented by a slight improvement in muscle strength (up to grade 5), Romberg sign negative, gait improvement, and with self-care ability. However, after stopping the hormone treatment, the symptoms rapidly deteriorated.

Genetic tests

To investigate the potential genetic etiology of the disease, high-throughput gene panel sequencing containing 4811

hereditary disease-related genes (Kingmed Diagnostics, Guangzhou, China) was performed. The gene panel included those accounting for spinocerebellar ataxia, Friedreich's ataxia, hereditary diffuse leukoencephalopathy with axonal spheroids, dentatorubral-pallidoluysian atrophy, Bassen-Kornzweig syndrome, Hartnup disease, Joubert's syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and ataxia with vitamin E deficiency. As shown in Fig. 2, the patient was found to carry novel compound heterozygous mutations in *AARS2* (NM020745.3), a frameshift (c.2265dupA, p.Arg756fs) mutation (paternal inheritance) and a missense (c.650C>T, p.Pro217Leu) mutation (maternal inheritance). The patient was diagnosed with AARS2-L. Patient's three older sisters also received *AARS2* gene sequencing. Only his eldest sister carried the c. 2265dupA frameshift mutation. The family tree was shown in Fig. 3.

Prognosis

At 8 months after discharge, the patient had no self-care ability, with walking difficulty, extremely high muscle tension in bilateral limbs, and emotional instability. He was unable to straighten the right upper limb, and his cognitive function markedly declined. He had stopped Western medical treatment, and had switched to traditional Chinese medical treatment. However, the therapeutic efficacy was poor.

Discussion

AARS2-L is an extremely rare disease. Only 13 AARS2-L cases have been documented in the literature thus far (Table 1). According to the previous reports [6, 9–11], characteristics of AARS2-L include: (1) Female patients usually have ovarian failure, while male patients have no endocrine disease or hypogonadism. Our patient had normal serum sex hormone level even though having decreased frequency of morning erections. Hence, the clinical characteristics of male AARS2-L remain to be further investigated in more cases. (2) The neurologic expression is a variable combination of upper motor neuron signs, ataxia, and dementia. (3) Pathological findings may include myelin loss with rarefaction and gliosis in the white matter and numerous axonal spheroids [9]. (4) MRIs show a slightly asymmetric hyperintense T2 signal in the frontoparietal and periventricular white matter with the involvement of pyramidal tracts. Corpus restricted diffusion locates in the corona radiata and centrum semiovale, which are mainly consistent with the brain MRI findings of our patient. No enhancement and ventricular abnormalities are detected. Brain atrophy is generalized and mild except one case with serious cerebellar atrophy. Nevertheless, our patient exhibited remarkable cerebellar atrophy. (5) Most cases carry compound heterozygous mutations of *AARS2*. On the other hand, our patient had a congenital eye problem and mild clumsiness since childhood, which is similar to case 2 in Table 1 [6]. In this report, although hormone therapy slightly relieved patient's symptoms, however, the symptoms rapidly deteriorated after stopping the hormone treatment, indicating that hormone therapy may be not an effective treatment for AARS2-L. It has been shown that the symptoms of mitochondrial diseases may become more severe under physiological stress conditions [12].

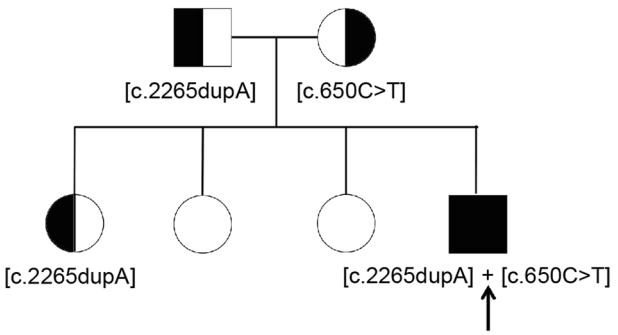

Fig. 3 Pedigree and inheritance of the mutations c.2265dupA and c.650C>T of the *AARS2* gene. The arrow marks the proband

AARS2 gene consists of 22 exons and encodes a mitochondrial alanyl-tRNA synthetase protein with 985 amino acids [1, 9, 13]. In this study, the focused exome sequencing showed that our patient had novel compound heterozygous *AARS2* mutations, c.2265dupA (p. Arg756fs) and c.650C>T (p. Pro217leu), which was located in the aminoacylation domain. Both mutations were inherited as an autosomal recessive trait. The c.2265dupA frameshift mutation was predicted to cause frameshift from codon 756 and premature termination at codon 805, which may disrupt the entire protein. The frameshift mutation (c.2265dupA) was not registered in the dbSNP147, ESP6500siv2_all, and 1000g2015aug_all databases. The missense mutation (c.650C>T) was predicted to change the highly conserved Pro (amino acid 217) to Leu. The missense mutation was registered in dbSNP147 (rs# rs529993647) database but not registered in ESP6500siv2_all and 1000g2015aug_all databases. The missense mutant is found in the ExaC database twice, both in South Asian individuals. Bioinformatics software (PolyPhen2 (polymorphism phenotype)) predication showed that this missense mutation was a potential pathogenic mutation. Given that c.650C>T is a rare variant, changing a highly conserved amino acids, and segregating in the family with the AARS2-L type of phenotype, it is likely to be disease-causing. Euro et al. [14] have suggested that all *AARS2* mutations may reduce the aminoacylation activity of the synthetase. However, we

Table 1 Clinical and genetic characteristics of *AARS2* mutation-related leukodystrophy reported in the literature

Case no.	Sex	Age at onset (years)	First neurological symptom(s)	*AARS2* mutation	Amino acid change	Cerebellar symptoms	Cognitive deterioration	Psychiatric symptoms	Pyramidal signs	Epilepsy	Ovarian failure	References
1	F	15	Gait ataxia, tremor, cognitive decline, and psychosis	c.149T>G; c.1561C>T	p.Phe50Cys; p.Arg521[a]	+	+	+	−	−	+	[6]
2	M	Early teenage years	Hemiparesis and ataxia	c.2893G>A; c.1213G>A	p.Gly965Arg; p.Glu405Lys	+	+	−	+	−		[6]
3	F	33	Depression, cognitive decline, and psychosis	c.1609C>T and c.2350del; c.595C>T	p.Gln537[a] and p.Glu784Serfs*9; p.Arg199Cys	+	+	+	+	+	+	[6]
4	F	24	Tremor	c.230C>T; c.595C>T	p.Ala77Val; p.Arg199Cys	+	+	+	+	−	+	[6]
5	F	40	Depression and cognitive decline	c.595C>T; c.390_392del	p.Arg199Cys; p.Phe131del	−	+	+	−	−	+	[6]
6	F	22	Spastic paraparesis with ataxic signs and depression	c.595C>T; c.2611dup	p.Arg199Cys; p.Thr871Asnfs*21	+	−	+	+	−	+	[6]
7	F	30	Cognitive decline and psychosis	c.1145C>A; c.2255 +1G> A[a]	p.Thr382Lys;	−	+	+	+	−	+	[10]
8	M	18	Psychosis	c.578T>G; c.595C>T	p.Leu193[a]; p.Arg199Cys	+	+	+	+	−		[11]
9	F	40	Anxiety and cognitive decline	c.1041–1G>A[a]; c.595C>T	p. Arg199Cys	−	+	−	+	−	+	[9]
10	M	Late 30s	Obsessive behavior and hyperphagia; memory impairment	c.1188G>A[a]; c.1709delG	p. Gly570Afs*21					−		[9]
11	M	Mid-20s	Rapid motor decline	c.1188G>A[a]; c.1709delG	p. Gly570Afs*21	+	+	+	+	−		[9]
12	M	Middle adolescence	Cognitive decline and psychosis	c.892_894del; c.2234_2235 del	p.298_298delGln; p.Ser745Cysfs*60	+	+	+	+	−		[9]
13	M	Mid-40s	Right upper limb dystonia and dysarthria	c.595C>T (homozygous)	p. Arg199Cys	−	+	+	+	−		[9]
14	M	17	Tremor	c.2265dupA; c.650C>T	p.Arg756fs; p.Pro217Leu	+	+	+	+	−		The current report

F female, *M* male

[a] c.2255+1G>A, c.1041–1G>A, and c.1188G>A are splice site mutations which result in production of a nonfunctional protein

cannot assess the histopathological characteristics as the patient's family refused to consent to a biopsy. Hematological and biochemical examinations showed mild thalassemia, hyperuricemia, hypolipidemia, and 25-hydroxyvitamin D deficiency in this patient. However, up to now, there are no studies reporting that AARS2 is related to thalassemia, hyperuricemia, hypolipidemia, and 25-hydroxyvitamin D deficiency. It should be further investigated if these symptoms are related to mitochondrial dysfunction or AARS2-related disorders. The 24-h ambulatory electrocardiogram showed sinus wandering pacemaker and early repolarization syndrome. It has been shown that certain recessive mutations in AARS2 cause infantile mitochondrial cardiomyopathy [13], and severe cardiomyopathy can cause arrhythmia. However, previous studies show that patient with adult-onset leukoencephalopathy caused by compound heterozygous *AARS2* gene mutations do not have cardiomyopathy [6, 9, 10]. In this report, echocardiography revealed that the patient had no signs of cardiomyopathy, but it is unknown that if there was any tiny structural changes. It is worth to further investigate if *AARS* mutation causes myocardial autonomic neuropathy.

In summary, we describe a male case of leukoencephalopathy with novel compound heterozygous mutations in *AARS2* gene. The prominent characters of brain MRI were bilateral white matter lesion and cerebellum atrophy. This case is helpful for better understanding the clinical and genetic heterogeneity of AARS2-L.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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