

# Leukodystrophy without Ovarian Failure Caused by Compound Heterozygous Alanyl-tRNA Synthetase 2 Mutations

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To the Editor: Mutations in the mitochondrial alanyl-tRNA synthetase 2 gene (*AARS2*) have been recently found to lead to chronic progressive leukodystrophy or infantile cardiomyopathy. Up to date, there have been 15 patients reported with chronic progressive leukodystrophy. Notably, all the female patients (9/15) present with ovarian failure, described as “ovarioleukodystrophy.”<sup>[1-4]</sup> Herein, we report a female patient with progressive adult-onset leukodystrophy without ovarian failure due to compound heterozygous mutations in *AARS2*.

A 27-year-old female patient presented with progressive spastic-ataxic gait, declined memory, and calculating ability for 1 year. She had a normal physical and cognitive developmental milestone. There was no family history and known consanguinity. She has normal menstrual cycle and was devoided with no childbearing. Neurological examination revealed bilateral horizontal nystagmus and hypertonia in both legs with nearly normal muscle strength in the four limbs. The tendon reflexes were increased in both legs and positive Babinski’s sign was observed on both sides. The deep sensation was impaired below the T12 level. Heel-knee-tibia test and finger-nose test were not coordinated. Romberg’s sign was positive and heel-to-toe walk could not be performed. She got 26 points in the Mini-Mental state examination measuring scale.

The hormone levels including cortisol, adrenocorticotropic hormone, estrogen, follicle-stimulating hormone, and luteinizing hormone were totally normal. The blood lactate level in resting state and the cerebrospinal fluid test were not remarkable. Tandem mass spectrometry (MS-MS) in blood and gas chromatography-MS (GC-MS) in urine were also negative. The ultrasound of uterus and ovaries showed normal shape and size. Electromyography, cardiac ultrasound, and electrocardiography were normal. Magnetic resonance imaging (MRI) of the brain revealed nearly symmetric white matter lesions predominantly affecting regions adjacent to the posterior horn of lateral ventricle [Figure 1a–1e]. MR spectroscopy showed that the ratio of CHO/NAA was apparently elevated [Figure 1f].

By Sanger sequencing, compound heterozygous mutations in alanyl-transfer RNA (tRNA) synthetase 2 (*AARS2*) (OMIM\*612035) were detected [Figure 1g]. A previously described missense mutation (c.452T>C, p.M151T) was inherited from the father,<sup>[4]</sup> which is predicted to be probably damaging by both PolyPhen-2

(Harvard Medical School, Boston, Massachusetts, USA) and SIFT (J.Craig Venter Institute, California, USA) softwares, and a novel nonsense mutation (C.1871G>A, p.W624X) was inherited from the mother, which led to early termination of the peptide synthesis, determining the pathogenicity.

The reported patients with *AARS2* mutations have two autosomal recessive phenotypes, including fatal infantile cardiomyopathy and leukodystrophy. Patients with fatal infantile cardiomyopathy were found to have two missense mutations in *AARS2*, homozygous or compound heterozygous, except one case who carried one DNA base pair insertion mutation and a missense mutation.<sup>[5]</sup> However, the patients with leukodystrophy carried missense, splice-site, duplication, deletion, or nonsense mutations.<sup>[1-4]</sup> The molecular basis of the distinct tissue-specific phenotypes is supposed to be the varied degrees of impairment on *AARS* caused by different located mutations.

The mean age at onset of leukodystrophy is about 27 years old, ranging from 14 to 44 years. The disease was rapidly progressive, and mostly it took <10 years to develop to be bedridden. Cognitive and motor symptoms were the most common symptoms overall; other symptoms such as sensory disturbance, seizures, or depression can also present. Interestingly, the previously reported female patients presented ovarian failure at the mean age of 23 years.<sup>[1-4]</sup> The classic MRI features including frontoparietal predominant, confluent T1-weighted (T2W) hyperintense, and T1W-hypointense white matter signal abnormalities, especially for the periventricular and deep white matter, tend to spare the subcortical U fibers. Some cases showed atrophy of the corpus callosum or cerebellum.<sup>[2]</sup> Due to the similar phenotypes, leukoencephalopathy with colony-stimulating factor receptor 1-related axonal spheroids and pigmented glia cannot be easily distinguished from *AARS2*-related leukodystrophy. Therefore, genetic testing can be helpful in this circumstance.

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**Received:** 06-08-2017 **Edited by:** Qiang Shi  
**How to cite this article:** Sun J, Quan C, Luo SS, Zhou L, Zhao CB. Leukodystrophy without Ovarian Failure Caused by Compound Heterozygous Alanyl-tRNA Synthetase 2 Mutations. *Chin Med J* 2017;130:3021-2.

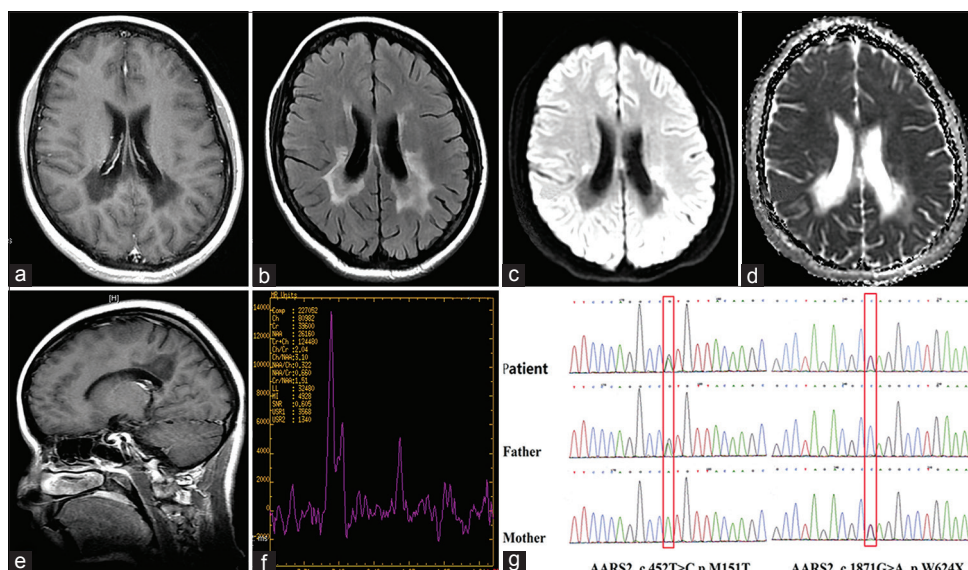
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**Figure 1:** Representative images of the patient. (a and e) Nearly symmetrical lesions in the regions adjacent to the posterior horn of lateral ventricle, T1W + C showed hypointense. (b) T2W-FLAIR showed hyperintense. (c) DWI showed some patch of high signals and (d) ADC showed hypointense. (f) The ratio of CHO/NAA was apparently elevated (1.7–3.1). (g) A novel nonsense heterozygous mutation (C.1871G>A, p.W624X, marked with red outline) inherited from the mother and a previously described missense heterozygous mutation (c.452T>C, p.M151T, marked with red frame) inherited from the father. T1W + C: Postcontrast T1 weighted; T2W-FLAIR: T2-weighted fluid-attenuated inversion recovery; DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient image.

Our case has leukodystrophy and similar symptoms as well as MRI features in line with those described earlier. However, she has normal menstrual cycle with normal sex hormone level. The difference may indicate a broadening of clinical phenotype or be due to the late onset of the ovarian failure, in view of the latest amenorrhea reported was at 33 years old. Notably, the nonsense mutation C.1871G>A, p.W624X has not yet been reported, further functional study of the pathogenic mechanism underlying the mutations should be investigated.

In conclusion, if a female patient presents with leukodystrophy, *AARS2* gene is supposed to be examined even though her menstrual cycle is normal. However, long-term follow-up is necessary to see whether the ovarian failure ultimately occurs or not.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that her name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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