A 42-year-old woman with 4H leukodystrophy caused by a homozygous mutation in *POLR3A* gene

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To the Editor: Leukodystrophies are a heterogeneous group of inherited neurological disorders characterized by impairing myelin of the white matter. Based on the original definition of the leukodystrophy, Timmons *et al*[1] described four patients with hypomyelination, hypogonadotropic hypogonadism, and hypodontia, and proposed naming this disease as 4H syndrome. Several years later, it was identified that mutations in *POLR3A* or *POLR3B* genes, encoding for the two largest sub-units of the RNA polymerase III, were shown to cause 4H leukodystrophy.[2] We here report a woman with 4H leukodystrophy carried the c.1911+18 C>T mutation in POLR3A in a homozygous state, which is the first report with this mutation site in China.

A 42-year-old woman, born to non-consanguineous parents with no family history of neurological diseases, suffered from ataxia for 3 years. After a normal psychomotor development, the patient first presented dental eruption at 1-year-old and with absence at 5 years of age. She stopped growing when she was 15 years old, and remained heights under 150 cm. Intellectual impairment became evident at 35 years old. Approximately 4 years ago (38 years old), she appeared secondary amenorrhea. Ataxia aggravated in the following 3 years and gradually affected daily life. On examinations, she has short stature [Supplementary Figure 1, http://links.lww.com/CM9/A61], tooth dysplasia and ataxia-related syndrome. There were no nystagmus, papilla atrophy or other visual problems. Her Mini-Mental State Examination (MMSE) score was 19, indicating mild intellectual disability. No contraceptives were used. She gave birth to a boy by making a cesarean section at 23-year-old, and her son was without any neurological symptom so far. Her parents died of other internal medicine diseases. Their gonads developed normally when they were alive. Only one brother who showed normal appearance and cognition was in her family.

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Doppler ultrasound revealed abnormal uterus in post-menopausal women. Detailed endocrine assessment confirmed hypogonadotropic hypogonadism by the low levels of follicle-stimulating hormone and luteinizing hormone [Supplementary Table 1, http://links.lww.com/CM9/A61]. Brain magnetic resonance imaging (MRI) described whole brain cortical atrophy on T1-weighted images and diffuse white matter hypomyelination in the bilateral cerebral hemispheres on T2-weighted images and fluid attenuated inversion recovery (FLAIR) [Figure 1A and 1B]. Dental panoramic radiographs showed abnormality of eruption of teeth and short tooth roots [Supplementary Figure 2A and 2B, http://links.lww.com/CM9/A61], suggesting the presence of hypodontia. Extensive genetic sequencing and Sanger verification detected revealed homozygous mutation in *POLR3A* gene sited in c.1911+18C>T [Supplementary Figure 3A, http://links.lww.com/CM9/A61]. The *POLR3A* genes of her son and brother were shown to be heterozygous [Supplementary Figure 3B and 3C, http://links.lww.com/CM9/A61]. Based on these clinical features, a diagnosis of 4H leukodystrophy was considered.

Our patient was diagnosed with 4H syndrome based on much evidence. First, from a biological point of view, this mutation has been contained in the Online Mendelian Inheritance in Man (607694) and could be judged as "pathogenic" according to the American College of Medical Genetics and Genomics. Second, from the heritage point, although we are unable to obtain gene samples from her parents, it can be inferred that her parents are heterozygous from her brother's genotype (heterozygous mutation) and parents' normal phenotype, which is eligible to autosomal recessive inheritance. Finally, the clinical characteristics of our case are consistent with the typical manifestations of 4H syndrome. Therefore, our patient was definitively diagnosed as 4H syndrome with a mutation of *POLR3A* gene. 4H leukodystrophy is

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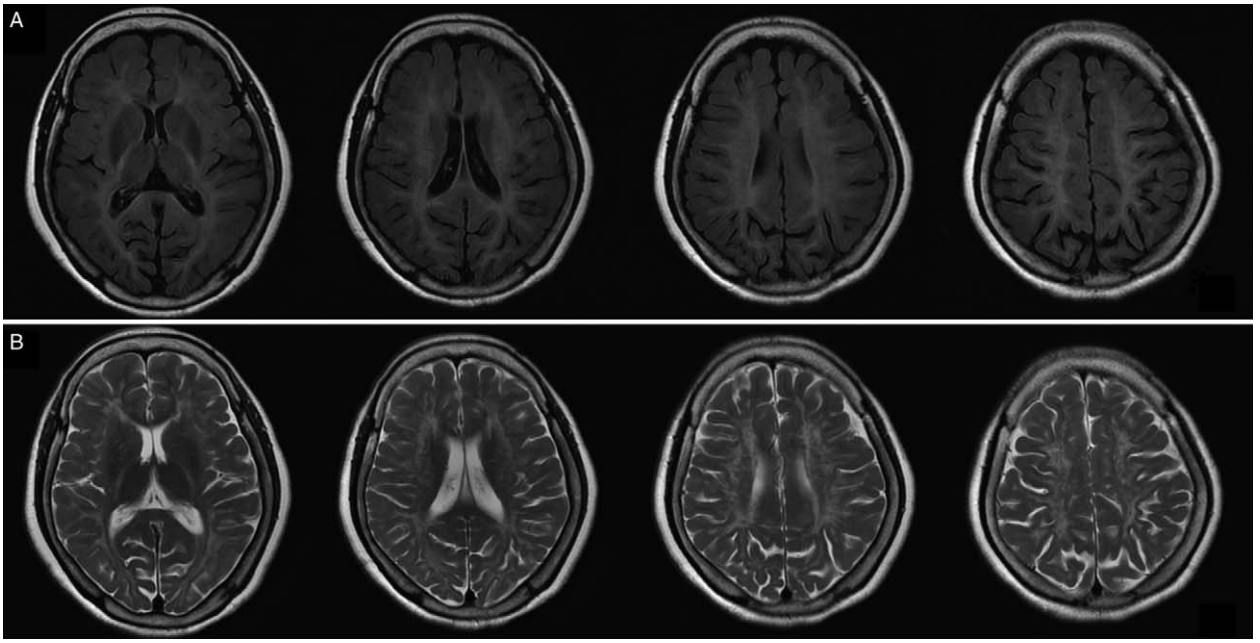

Figure 1: Diffuse white matter hypomyelinations in bilateral cerebral hemispheres. Axial FLAIR images (A); Axial T2WI images (B). FLAIR: Fluid attenuated inversion recovery.

considered to be an infantile disease and also seems to be observed at adolescence. In a previous report, the onset age of 4H leukodystrophy varied from 1 to 13 years of age.[3] Our patient presented with progressive ataxia as initial symptom 3 years ago, but with abnormal dental development since childhood. It means that the patient started from hypodontia at 4 to 5 years of age and had a long course of the disease without other clinical symptoms. The diagnosis of 4H leukodystrophy needs the examinations of endocrine, brain MRI, dental tests, and extensive genetic sequencing. Hormone replacement therapy can be used in patients with decreased gonadal hormones and achieve the desired effect.[4] Therefore, early diagnosis can help improve the quality of patients' life.

Declaration of patient consent

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

Conflicts of interest

None.

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