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The Therapeutic Effect of Recombinant Human Growth Hormone (rhGH) on a Child with X-Linked Intellectual Disability Caused by HUWE1 Gene Mutation: A Case Report

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Abstract

Background: X-Linked Intellectual Disability (XLID) is caused by pathogenic variation of genes on X chromosome, accounting for approximately 15% of all intellectual disability cases.

Case Report: A 6-year and 6-month-old girl had one seizure each at 9 and 10 months of age, and both the seizure episodes were generalized seizures, with or without fever. The girl's motor and language development are delayed. Her lower limbs are of unequal length. Meanwhile, her height is growing slowly and lower than the 3rd percentile of children of the same age and sex. There were no obvious abnormalities in her head Computed Tomography (CT) and Electroencephalogram (EEG). A *de*-novel heterozygous mutation of *HUWE1* gene exon 82 (c.12702T>G, p.Ile4234Met) was identified by whole-exon sequencing (Trio-WES). There was no variation at this locus in her parents. The peak of her growth hormone is 10.6 ng/ml. She began receiving the recombinant human Growth Hormone(rhGH) therapy at the age of 4 years and 6 months and continued for two years, her height showed improvement.

Conclusion: We reported a girl with XLID caused by *HUWE1* gene mutation, she carried the novel heterozygous *HUWE1* mutation, and there are only a few reports of X-linked intellectual disability caused by *HUWE1* mutation worldwide. In clinical work, for children with intellectual disability and growth retardation, or with a clear family history of abnormalities, gene testing should be actively carried out to clarify the reason.

Keywords: *HUWE1* gene; Mutation, X-linked intellectual disability; Recombinant human growth hormone

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Introduction

Intellectual Disability (ID) refers to the decline of cognitive ability or social adaptability, which is mostly caused by genetic factors. X-Linked Intellectual Disability (XLID) is caused by pathogenic variation of genes on X chromosome. At present, about 15% of genes related to intellectual disability are known to come from X chromosome [1].

HUWE1 gene is located in Xp11.22, encoding E3 ubiquitin ligase. In recent years, it has been found that *HUWE1* gene is highly expressed in the whole brain, such as olfactory bulb, cerebral cortex, hippocampus and cerebellum. *HUWE1* gene plays a very important role in the development, proliferation and synaptic formation of human neurons. The mutation of *HUWE1* gene is significantly related to the occurrence of nervous system diseases [2].

In this paper, a girl with XLID, carried the *de*-novel heterozygous *HUWE1* mutation, is reported. The girl received the recombinant human Growth Hormone (rhGH) treatment and achieved ideal height growth. After our literature search, there are only a few reports of X-linked intellectual disability caused by *HUWE1* mutation worldwide, and we have not found any reports of rhGH therapy for such patients.

Case Presentation

A 6-year-old 6-month Chinese Han girl had growth retardation and multiple convulsions after birth. The child was found to cry less after birth, look up after the age of 4 months, sat alone after 7

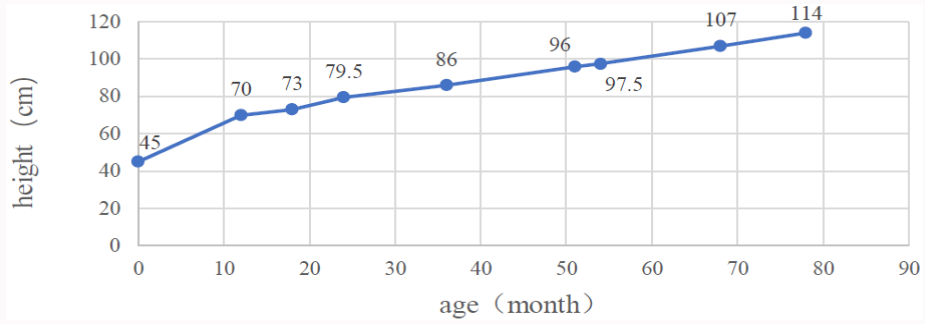

Figure 1: The growth trend of height of the proband.

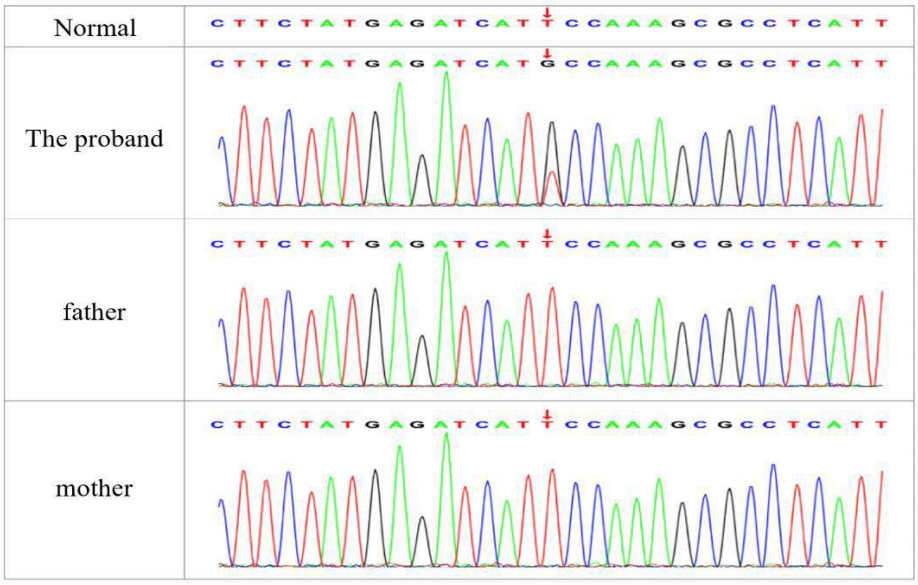

Figure 2: Sanger sequencing of the proband and her family members.

months, could walk after 23 months but unstable, at the age of 3 years old, she shouts "Mama", without a sentence. She had a history of two seizures at the age of 9 months, 10 months. She was the first fetus and the first delivered by natural childbirth at 40+5 week of pregnancy, with no history of asphyxia rescue. The Apgar score is 10 points/1 minute-9 points/5 minute-10 points/10 minute. The birth weight is 2.9 kg and the body length is 45 cm. During the prenatal examination, the child was found to be slightly smaller than the normal fetus. The length of both lower limbs was different after birth. The left lower limb was 3.8 cm shorter than the right lower limb (by measuring height). At the age of 3 years and 10 months, the child underwent temporary block of right distal femur + proximal tibial epiphysis and 8-shaped plate fixation. Her height is growing slowly, the length of her left leg is less than two standard deviations of normal children of the same age, her height growth trend is shown in Figure 1. She has binocular strabismus, high jaw arch and limb muscle strength grade I-IV.

Clinical Findings

After obtaining parental informed consent, we conducted whole-exome genetic testing on them. The whole-exome sequencing was performed using the IDT xGen Exome Research Panel v2.0 for exon capture, followed by sequencing on an Illumina NovaSeq 6000 series sequencer (PE150). The target sequence sequencing coverage was no less than 99%. The genetic testing confirmed that the *HUWE1* gene c.12702 (exon82) T>G (p.Ile4234Met). There was no variation at this locus in her parents (Figure 2). The brain magnetic resonance examination showed widened perivascular space in the white matter area of the cerebral hemisphere, obvious at the top of the forehead, and the ventricles and aqueducts were not enlarged. There is no obvious abnormality in her brain EEG. At the age of 4 years and 6 months, she underwent an X-ray examination of her left wrist to assess bone age, there are three ossification centers. At the age of 5 years and 5 months old, her spinal X-ray indicates scoliosis deformity, but she didn't stand straight during the examination; At the age of 5 years and 9 months old, her lower limb X-ray showed that the unequal length of her lower limbs is more pronounced (Figure 3).

The girl was given levetiracetam oral liquid 15 mg/(kg.d) from the age of 1 year to 2 and a half years old, with the increase of body weight, the oral dose was not added. Moreover, she had been undergoing language and sports rehabilitation training. At the age of 3 years and 10 months, the girl underwent temporary block of right distal femur + proximal tibial epiphysis and 8-shaped plate fixation. At the age of 4 years and 6 months, her height is 97.5 cm, and the peak of growth hormone is 10.6 ng/ml by the growth hormone challenge test. From February 2022, she began to receive rhGH treatment. At the age of 6 years and 6 months, her height is 114 cm, she grows by about 8 cm in height every year. We conduct follow-up every three months to evaluate the effectiveness and safety of rhGH therapy,

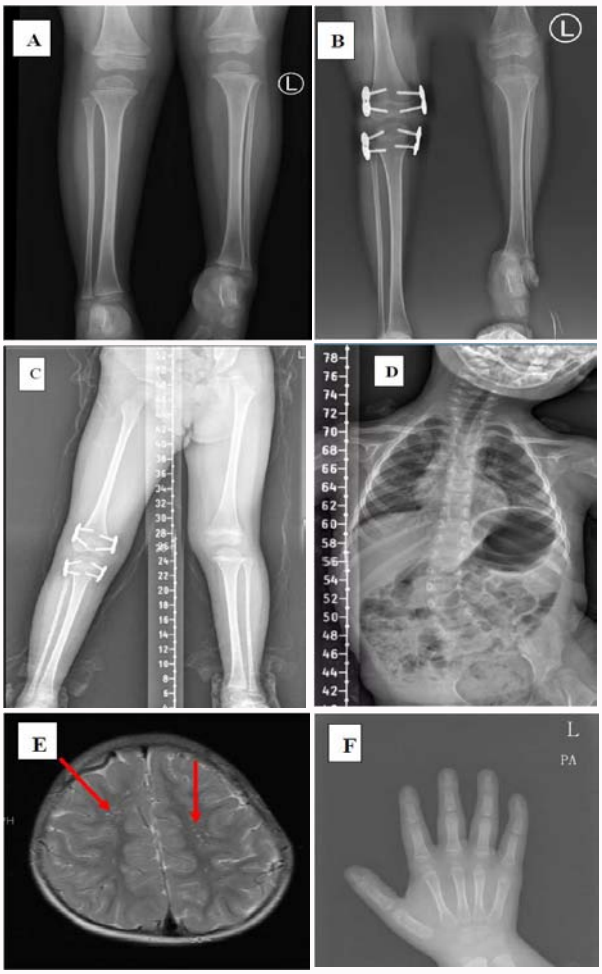

Figure 3: A) The lower limb X-ray before surgery; B) The lower limb X-ray after surgery, C) The X-ray film results at 5 years and 9 months old; D) At the age of 5 years and 5 months old, she underwent a full length X-ray examination of her spine; E) Brain magnetic resonance imaging of the proband revealed that fine dot long T2 signal shadow in the white matter of cerebral hemisphere; F) At the age of 4 years and 6 months old, she underwent an X-ray examination of her left wrist to assess bone age.

including the thyroid function, IGF-1, blood glucose, and other tests. We found that she does not have obvious scoliosis through physical examination. Due to the child's extreme fear of X-ray examination, the bone age film was not completed as instructed by the doctor. The girl had no convulsion attack in recent 2 years. She could remember simple sentences, understand and complete simple instructions, but her pronunciation was not accurate. She liked to play with children. During standing and walking, her right lower limb occasionally bent her hip and knees, and she was unstable when climbing stairs.

Discussion

HUWE1 gene is located in Xp11.22, it encodes E3 ubiquitin ligase, which is composed of 4,374 amino acids with a molecular weight of about 481.9 KD and contains two N-terminal domains, similar to the "S" type. Due to its huge molecular weight, the full length of the gene was not fully determined until 2005 [3]. The protein encoded by *HUWE1* contains a domain HECT (Homologous to E6AP C Terminus) that catalyzes ubiquitin ligase, several domains related to substrate and ubiquitin binding, and a number of conserved domains with unclear functions. The most important one is HECT domain, which is located at the C-terminal, promoting the binding of ubiquitin to substrate [4,5]. Froyen et al. found the expression of *HUWE1* gene in many tissues of mouse model, such as cerebral cortex, hippocampus, tongue, eyes, kidney, liver, adrenal gland and fibroblasts. The mutation of *HUWE1* gene in neural stem cells or neuronal precursors and radial glial cells of embryonic mice can cause the death of mouse embryos in severe cases [6,7]. In recent years, it has been found that *HUWE1* gene is highly expressed in the whole brain, such as olfactory bulb, cerebral cortex, hippocampus and cerebellum. It plays a very important role in the development, proliferation and synaptic formation of human neurons [2,8,9].

Moortgat et al. reported 21 children with *HUWE1* gene mutation in 2018, including 14 women and 7 men. 15 different missense mutations and 1 splice site mutation were found. The clinical characteristics of these children include intellectual impairment, language impairment, short stature, epicanthus, short eyelid fissure and scoliosis, and the paper also showing that both *HUWE1* loss or gain of function are linked to ID [3]. Deng Jie et al. reported a case of early-onset epileptic encephalopathy with a new mutation in *HUWE1* gene. The child started 2.5 h after birth and was a focal seizure. Phenobarbital, levetiracetam and oxcarbazepine were successively used to control the seizure. After treatment for more than one month, it was relieved. At the last follow-up, the intellectual development was slightly backward [10].

Juberg-Marsidi syndrome is one of the most serious forms of XLID. Its clinical manifestations are acute cognitive impairment, short stature, microcephaly and seizures. Aprigliano R et al. found that X-linked Juberg-Marsidi syndrome is caused by *HUWE1* gene mutation [11]. Bosshard et al. pointed out that the clinical phenotype of X-linked intellectual disability caused by *HUWE1* gene mutation is highly heterogeneous, such as special face, microcephaly, different degrees of intellectual disability, growth retardation, deafness, joint contracture, eye diseases, urinary incontinence and so on, the relationship between different genotypes and clinical phenotypes is not yet clear [12].

Growth hormone is a peptide hormone secreted by the anterior pituitary gland of the human body. It is composed of various amino acids and can promote bone, visceral, and systemic growth. It promotes protein synthesis, affects fat and mineral metabolism, and plays a crucial role in human growth and development [13,14]. A small amount of literature indicates that the rhGH treatment pertains to improvement in mental development, but the clinical findings are not always consistent [15]. In recent years, studies have found that *HUWE1* gene plays a key role in tumorigenesis and tumor treatment, but the specific regulatory mechanism has not been clarified [16,17]. Some studies show that rhGH treatment may increase the incidence rate of cancer [18,19]. The patient we reported has a *HUWE1* gene mutation and has received rhGH treatment. While increasing height, we need to pay more attention to the occurrence of complications and actively evaluate the effectiveness and safety.

The mutation in the *HUWE1* gene identified in the girl with XLID were novel and unreported mutations. We did not search for any prior cases of rhGH therapy in children with *HUWE1* gene mutations. So far, the effect of rhGH treatment on this girl has been optimistic, and no adverse reactions have been found. We will continue to follow up on this case. At the same time, rehabilitation treatment is very important for these children. Professional rehabilitation training can improve their physical dysfunction and quality of life to a certain

extent. Children with epilepsy need anti epilepsy treatment under the guidance of neurologists. At present, the relationship between *HUWE1* gene type and phenotype is not clear, and further research is needed.

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