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More than three years' treatment response of recombinant human growth hormone in a patient with Coffin-Siris syndrome 7

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Coffin-Siris syndrome 7 (CSS7, OMIM #618027) is an extremely rare multisystemic autosomal dominant genetic disease caused by heterozygous mutation in the double PHD fingers 2 (DPF2), characterised by global developmental delay with mild to moderate intellectual disability, speech impairment, behavioural abnormalities, growth failure, coarse facial characteristics, and hypoplastic fifth toenails [1]. CSS7 is exceptionally rare, with only 10 cases reported worldwide [1–3].

The patient, a 5 years and 7 months old girl, was admitted to the hospital for the chief complaint of short stature. She was born as the second full-term child of unrelated and healthy parents. She has a sister who does not display similar symptoms. At birth, the weight was 2900 g. During the neonatal period, she was hospitalised for one week due to pneumonia. There were no unusual family or pregnancy histories. The father's height is 178 cm; the mother's height is 160 cm. Her sister's height falls within the normal range. Following her birth, she gradually exhibited motor retardation and speech impairment, achieving head control at 4 months, independent sitting at 12 months, autonomous walking at 20 months, and beginning to speak at the age of 2 years. Additionally, she has an allergy to seafood. Due to physical and neurodevelopmental delays, she underwent whole exome sequencing and cranial MRI when she was 5 years and 1 month old. The results showed that the girl carried a maternally inherited missense mutation in the DPF2 gene (c.283T>G, p.F95V, uncertain) and a spontaneous frameshift mutation in the ASH1L gene (c.8683dupA, p.T2895Nfs*5, pathogenic). Based on the clinical phenotype of the individual, the clinical diagnosis was confirmed as CSS7 with mental retardation autosomal dominant 52 (MRD52). The DPF2 gene of the patient was inherited from her mother, who did not manifest corresponding clinical symptoms. Cranial magnetic resonance imaging (MRI) revealed enlargement of the left temporal horn of the lateral ventricle, accompanied by bilateral microphthalmia and increased anteroposterior diameter of the skull (Fig. 1).

At the time of presentation, the patient's height was 99.0 cm (–3.55 SD) and weight was 13.5 kg (–3.10 SD). The patient exhibited self-injurious behaviour in the form of hair pulling but did not experience pain from this action. Characteristic features of the patient included microcephaly, small eye fissure with esotropia, microtia, low nasal bridge, broad nose, and high palatal arch. Additionally, brachydactyly was observed in the patient's second and fifth fingers. Furthermore, there was local hyperpigmentation of the skin (Fig. 1).

Due to her parents demanding height intervention, after carefully weighing the benefits against the risks, recombinant human growth hormone (rhGH) therapy was initiated at the age of 5 years and 7 months with a daily dose of 2 IU. No adverse effects related to the use of rhGH were observed. During treatment, the growth velocity was recorded as 9.8 cm/year, 6.5 cm/year, and 4.7 cm/year in the first, second, and third year, respectively. After 3 years and 3 months of rhGH treatment, the height standard deviation score (HtSDS) increased by 1.53 SD and weight standard deviation score (WtSDS) increased by 1.74 SD.

Similarly to previous reported patients, the individual described in this study also shows neurodevelopmental delay, encompassing speech delay, motor delay, and behaviour anomalies, accompanied by short stature, brachydactyly, and CSS-like facial features, such

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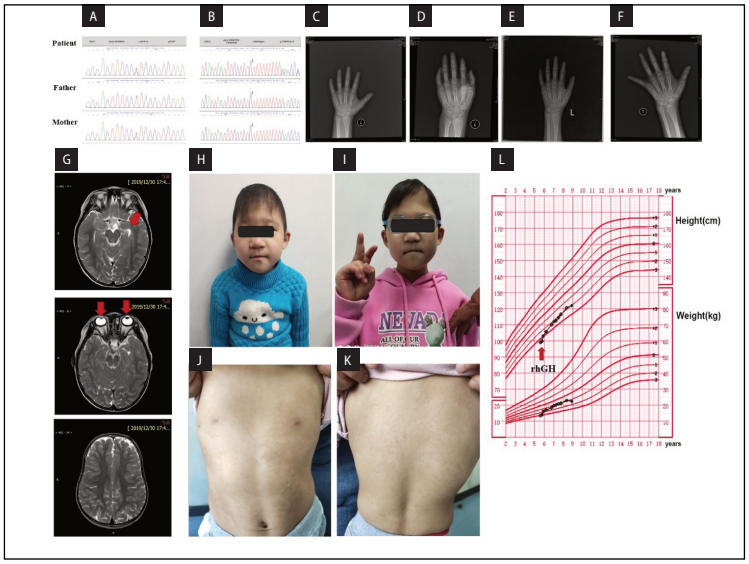

Figure 1. *The whole exome sequencing reveals heterozygous DPF2 gene and ASH1L gene variants and clinical characteristics in the patient.* **A.** *The heterozygous variant of c.283T>G (p.F95V) in the DPF2 gene was found in the patient and her mother, whereas her father had the wild type;* **B.** *The heterozygous variant of c.8683dupA (p.T2895Nfs*5) in the ASH1L gene was found in the patient, whereas her father and mother were wild type.* **C–F.** *The bone age (BA) of the patient. She also had brachydactyly in the second and fifth fingers. Her BA was 6 years and 10 months at the age of 6 years and 3 months (***C***); Her BA was 7 years and 10 months at the age of 6 years and 9 months (***D***); Her BA was 10 years at the age of 7 years and 8 months (***E***); Her BA was 11 years at the age of 8 years and 10 months (***F***). Cranial magnetic resonance imaging (MRI) at the age of 5 years and 7 months shows enlargement of the left temporal horn of the lateral ventricle, accompanied by bilateral microphthalmia and an increased anteroposterior diameter of the skull (***G***);* **H–I.** *The patient shows microcephaly, small eye fissure with esotropia, microtia, low nasal bridge, and broad nose;* **J–K.** *Local pigmentation of the skin;* **L.** *Growth chart of the patient after recombinant human growth hormone (rhGH) treatment*

as microcephaly, microtia, low nasal bridge, and broad nose [2–4]. However, the skeletal abnormalities documented in prior cases, including craniosynostosis and clinodactyly [2–4], were not observed in this patient. Distinctively, bilateral microphthalmia and local skin pigmentation were found in this patient. It is worth noting that the patient also carries a mutation in ASH1L gene, suggesting that the intellectual disability may be a result of the combined expression of the 2 genes.

Short stature is a common clinical feature in patients with CSS7, affecting approximately half of the patients diagnosed with this condition, yet the underlying mechanisms remains unclear. In previous reports, 80% of individuals with short stature were also found to have feeding difficulties [2–4]. Due to the desire to improve his height level, the parents sought growth hormone therapy. However, her growth velocity decreased annually. Despite this challenge, following the treatment, the height of the child increased from –3.55 SD to –2.02 SD, indicating that rhGH may indeed offer some degree of height improvement in patients with CSS7. However, BA progression accelerated during treatment — the difference between BA and chronological age was advanced from 0.7 years to 2.2 years, but because this individual carried a genetic variant that causes abnormal phalangeal development, the Greulich and Pyle method may not be applicable to her BA.

Ethics statement

Ethical approval is not required for this study.

Author contributions

Data collection: L.Y. and W.Q. Drafting manuscript: L.Y. and W.Q. G.C.X. critically reviewed the manuscript and provided significant input. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare.

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