Clinical Pediatric Endocrinology

Vol.31 / No.2
April 2022
pp 98–100

Mutation-in-Brief

A novel nonsense variant (p.Arg1293Ter) of the immunoglobulin superfamily 1 (IGSF1) associated with congenital hypogonadotropic hypogonadism and central hypothyroidism

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Highlight

- IGSF1 may be the cause in patients with congenital hypogonadotropic hypogonadism and central hypothyroidism.

Key words: IGSF1, hypogonadotropic hypogonadism, central hypothyroidism, novel variant

Introduction

Individuals with deletions and/or pathogenic variants of the *Immunoglobulin superfamily 1* (*IGSF1*) gene may show congenital central hypothyroidism (CCH) (1–3). In addition, these individuals may have PRL deficiency and, in a small number of cases, GH deficiency. Furthermore, the onset of puberty tends to be delayed, and is often accompanied by giant testes. Despite the early replacement of thyroid hormone, CCH may be accompanied by developmental disorders and attention deficit hyperactivity syndrome (2, 3). However, asymptomatic cases have also been reported.

We report the identification of a novel nonsense variant (p.Arg1293Ter) of *IGSF1* in a young male patient with congenital hypogonadotropic hypogonadism (CHH), CCH, and GH deficiency.

Case Report

Our patient was a 17-yr-old boy born after 36 wk of gestation by normal vaginal delivery (weight: 2150 g; length: 45 cm). Family history showed no indication of endocrine disorders. Cryptorchidism was noted at birth, but no follow up or endocrinological tests were done at that time.

During a health examination at 18 mo of age, a delay in psychomotor development was noted, and he was followed up at our neurodevelopmental department as an outpatient. At 5 yr of age, he was diagnosed with a pervasive developmental disorder.

He was of a short stature at about 6 yr of age, and when 9, he was referred to endocrine outpatient department. At that time, he was 116.2 cm tall (–2.6 SD for a normal Japanese boy), and weighed 24 kg (–1 SD for normal Japanese boy) (**Fig. 1A**). Endocrinological examination showed IGF-1 in the normal range (106 ng/mL; normal range for his age, 84–350 ng/mL), while GH provocative tests of arginine and clonidine showed low responses of GH (0.6 to 2.4 ng/mL and 1.2 to 3.0 ng/mL, respectively) (**Table 1**). Thyroid function was as follows (normal range in parentheses): TSH 1.45 mU/L (0.24–3.50 mIU/L), FT3 2.45 pg/ml (2.45–4.6 pg/mL), and FT4 0.89 ng/dL (1.07–2.10 ng/dL). Based

Received: December 2, 2021 Accepted: December 20, 2021 Advanced Epub: January 14, 2022
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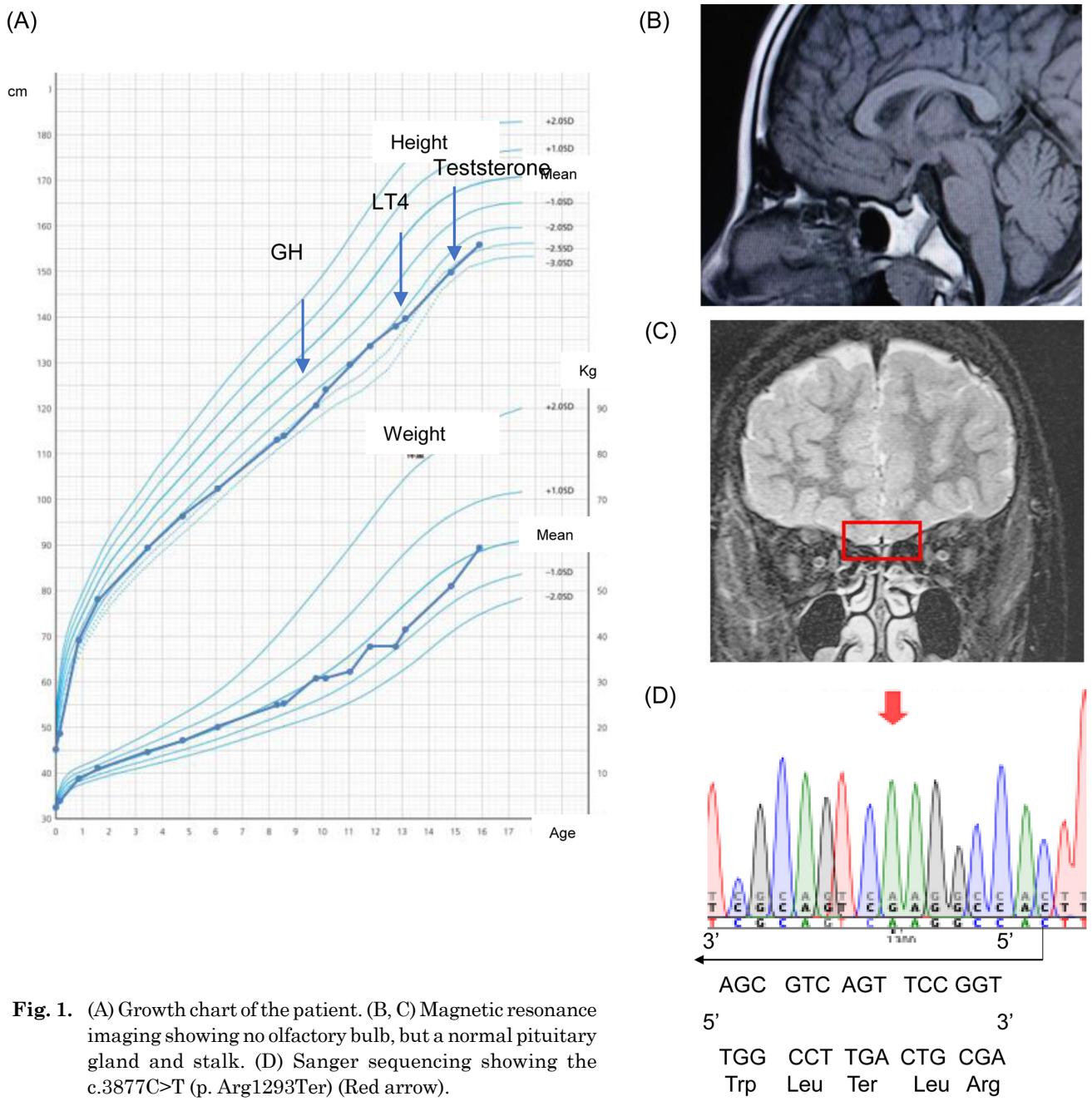

Fig. 1. (A) Growth chart of the patient. (B, C) Magnetic resonance imaging showing no olfactory bulb, but a normal pituitary gland and stalk. (D) Sanger sequencing showing the c.3877C>T (p. Arg1293Ter) (Red arrow).

on these findings, the patient was diagnosed with GH deficiency, and GH supplementation was initiated, but CCH was not noted. At 13 yr of age, he had not developed secondary sexual characteristics, and showed a bilateral testicular volume of 2 mL and a micropenis (penile length, 2 cm). A detailed interview revealed that he had a reduced sense of smell. Endocrine tests are summarized in **Table 1**. Magnetic resonance imaging of the brain showed no olfactory bulb, but a normal pituitary gland and stalk (**Fig. 1B, C**). His testosterone level did not respond (< 0.03 to < 0.03 ng/mL) in the hCG loading test. Based on the above results, the patient was diagnosed with hypogonadotropic hypogonadism, central hypothyroidism, and PRL deficiency. Thyroid hormone replacement was initiated at this time, and testosterone replacement was started at 15 yr of age.

Genetic analysis was approved by the institutional review board of Jichi Medical University, and consents of the patient and his parents were obtained. A total of 25 genes (*CHD7, FGF8, FGFR1, GNRH1, GNRHR, ANOS1, KISS1R, PROKR2, TACR3, IGSF1, LKISS1, PROK2, SOX10, TAC3, WDR11, HESX1, LHX3, LHX4, OTX2, POU1F1, PROKR2, PROP1, SOX2, SOX3, GLI2*) were screened using a next-generation sequencer (Miseq system. Illumina). The identified variant of *IGSF1* was sequenced by the Sanger method, to find a novel pathological variant of *IGSF1*, with c.3877C>T (p. Arg1293Ter) in a hemizygous state (**Fig. 1D**). No other pathogenic variant was identified.

doi: 10.1297/cpe.31.2021-0071

Table 1. Endocrinological findings

Arginine test*	
GH (ng/mL)	0.6 → 2.4
Clonidine test*	
GH (ng/mL)	1.2 → 3.0
IGF-1 (ng/mL)*	106
TRH test**	
TSH (mIU/mL)	1.46 → 8.93
PRL (ng/mL)	< 0.5 → 1.6
FT4 (ng/dL)**	0.82
FT3 (pg/mL)**	2.52
GnRH test**	
LH (IU/L)	< 0.2→ 1.6
FSH (IU/L)	< 1.0 → 2.3
hCG test **	
Testosterone (ng/mL)	< 0.03 → 0.03
CRF test**	
ACTH (pg/mL)	12.4 → 97.9
Cortisol (mg/dL)	4.4 → 17.6

*Arginine and clonidine tests were done at the age of 9 yr. **, TRH, GnRH, hCG and corticotropin releasing factor (CRF) tests were done at the age of 13 yr. GH peak value exceeded 6 ng/mL. Reference range of IGF-1 for this age, 84–350 ng/mL. Basal reference range of PRL for this age, 1.3–10.8 ng/mL. Reference range of FT4 at this age, 1.10–1.67 ng/dL. Reference range of FT3 at this age, 2.90–4.81 pg/mL. LH peak value after GnRH stimulation exceeded 4.9 IU/L. FSH peak value after GnRH stimulation exceeded 6.4 IU/L. Testosterone peak value after hCG stimulation exceeded 2 ng/mL. Cortisol peak value after CRF stimulation exceeded 10 mg/dL.

Discussion

We identified a novel pathogenic nonsense variant of *IGSF1* in a young male patient with CHH, olfactory bulb hypoplasia, CCH, GH deficiency, and PRL deficiency.

Characteristics of IGSF1 abnormality, CCH and PRL deficiencies are consistent in this patient. IGSF1 dysfunction may be accompanied by GH deficiency, which was alleviated by thyroid hormone replacement. However, in this 9-yr-old patient, IGSF1 dysfunction was coexistent with CCH. In addition, the patient was diagnosed with a pervasive developmental disorder. Patients with IGSF1 abnormalities are known to have developmental disorders and attention deficit hyperactivity syndrome. IGSF1 abnormalities have also been reported to cause giant testes and high birth weight, however, in this case, the testicular volume was only 2 mL and birth weight was low.

In our patient, CCH was accompanied by CHH. While pathogenic variant of IGSF1 may underlie CCH, the exact cause of CHH has not been determined. Many genes that cause CHH have been identified, but the CHH-related genes analyzed in the present study are limited. However, a report of CHH with analysis of *IGSF1* had found 36 CHH-related genes in 130 patients with CHH from Brazil, and a rare variant of p.Pro237Ala of *IGSF1* was identified in one of them, who had a normal sense of smell (4). Further analyses of a large number of CHH cases is required.

Asakura *et al.* (5) have reported a case with anterior pituitary hypoplasia, ectopic posterior lobe, and invisible stalk, accompanied by CCH and GH deficiency due to an N-terminal pathogenic variant of *IGSF1*; however, LH and FSH levels were found to be normal.

In conclusion, IGSF1 abnormalities should be considered in patients with CHH and central hypothyroidism.

Conflict of interests: The authors declare no conflict of interest.

Ethical consideration: Written informed consent for publication and genetic testing was obtained from the patient and patient's parents.

Acknowledgments

This work was supported in part by the Japan Agency for Medical Research and Development (AMED) under grant number 20gk0110050h0001 (Chief Investigator: Go Tajima).

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