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Case Report

Combined pituitary hormone deficiency in a patient with an *FGFR1* missense variant: case report and literature review

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Highlights

- A case of combined pituitary hormone deficiency with an *FGFR1* missense variant.
- Review on cases of combined pituitary hormone deficiency with *FGFR1* variants.

Abstract. Recent studies have indicated that heterozygous loss-of-function variants in fibroblast growth factor receptor 1 (*FGFR1*) are involved in the development of congenital hypogonadotropic hypogonadism and combined pituitary hormone deficiency (CPHD). We encountered a Japanese boy with short stature and pubertal failure. Endocrine studies showed GH, TSH, and LH/FSH deficiencies, and brain magnetic resonance imaging delineated hypoplastic anterior pituitary and ectopic posterior pituitary. The patient was treated with GH, *l*-thyroxine, and hCG/rFSH. Next-generation sequencing panel for pituitary dysfunction identified a probably weak disease-associated heterozygous missense variant in *FGFR1* (NM_023110.3:c.176A>T:p.(Asp59Val)), together with a probably non-deleterious heterozygous missense variant in *KISS1R* (NM_032551.5:c.769G>C:p.(Val257Leu)). We also review six previously reported CHPD patients with probably deleterious *FGFR1* variants. The data, in conjunction with the previously reported cases, argue for the relevance of *FGFR1* variants to the development of CPHD.

Key words: combined pituitary hormone deficiency, fibroblast growth factor receptor 1 (*FGFR1*), pituitary hypoplasia, genetic overlap

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Introduction

Heterozygous loss-of-function variants of fibroblast growth factor receptor 1 (*FGFR1*) (MIM# 136350) are known as the major underlying factor for the development of congenital hypogonadotropic hypogonadism (CHH) with normosmia and Kallmann syndrome (KS) with anosmia/hyposmia (1). Indeed, they are identified in ~ 10% of patients with CHH/KS. Notably, such *FGFR1* variants are associated with variable expressivity and incomplete penetrance (1). In addition, oligogenicity has also been identified in ≥ 20% of patients with CHH/KS, and *FGFR1* is involved in oligogenicity (1). These findings suggest that *FGFR1* variants are regarded as disease-causing factors and disease-associated factors.

Furthermore, heterozygous loss-of-function variants of *FGFR1* have occasionally been identified in combined pituitary hormone deficiency (CPHD) (1–5). This condition is accompanied by variable expressivity and incomplete penetrance, although oligogenicity has not been reported in CPHD (1–5). Such *FGFR1* variants are associated with various combinations of affected pituitary hormones and are shared by apparently healthy subjects and CPHD patients. In addition, *FGFR1* variants are often accompanied by midline brain anomalies including, septo-optic dysplasia (SOD) (1–5). Thus, genetic overlap has been observed between CHH/KS and CPHD with and without midline brain anomalies (2).

Here, we report a Japanese boy with CPHD and a probably disease-associated *FGFR1* variant, and review previously reported cases of CPHD and *FGFR1* variants.

Patient and Methods

Case description

Our patient was naturally conceived and was born at 35 weeks of gestation after an uncomplicated pregnancy and delivery. At birth, his length was 45.0 cm (– 0.25 SD), and his weight was 1.9 kg (– 1.47 SD). There were no descriptions of abnormal genitalia in the neonatal hospital records.

At 7 yr and 2 mo of age, the patient was referred to our hospital because of growth failure. His height was 100.0 cm (– 4.0 SD), and his weight was 17.4 kg (– 2.1 SD) (**Fig. 1A**). He had proportionate short stature and lacked abnormal genital findings such as micropenis and cryptorchidism. Routine laboratory test results were normal, and endocrine studies showed definitely low serum IGF-I level and central hypothyroidism (**Table 1**). Thus, the patient was immediately treated with *l*-thyroxine (2.5 μg/kg/day). Subsequently, pituitary hormone provocation tests were performed, indicating severe GH deficiency and probable gonadotropin (LH/FSH) deficiency (**Table 1**). Furthermore, the basal cortisol level and peak ACTH level indicated the possibility of central adrenal insufficiency. Thus, the patient was carefully observed without glucocorticoid replacement, and no adrenal crisis occurred during the follow-up period. His bone age was assessed as 3 yr and 5 mo. Brain magnetic resonance imaging delineated hypoplastic anterior pituitary hypoplasia and ectopic posterior pituitary (**Fig. 1B**). Thus, GH replacement therapy was started with a dosage for childhood GH deficiency (0.175 mg/kg/wk) until 16 yr and 4 mo of age and with that for adult GH deficiency (0.08 mg/kg/wk) thereafter, improving statural growth (**Fig. 1A**).

At 14 yr and 3 mo of age, he was examined for lack of secondary sexual development. He had bilateral intrascrotal testes of 3 – 4 mL and lacked pubic hair. He had a normal sense of smell. Serum testosterone was undetectable, and a GnRH test revealed gonadotropin (LH/FSH) deficiency (**Table 1**). His bone age was evaluated as 12.5 yr. Thus, he received subcutaneous injections of hCG with a dosage gradually increased from 500 IU/wk to 1,500 IU/wk and recombinant FSH (rFSH) with a dosage gradually increased from 75 IU/wk to 300 IU/wk (**Fig. 1A**). On the last examination at 18 yr and 3 mo of age, his height was 172.2 cm (+ 0.2 SD), his weight 62.5 kg (+ 0.2 SD), his testis size was 20 mL bilaterally, and pubic hair development at Tanner stage 5. Basal serum IGF-I was 268 ng/mL (age- and sex-matched reference range: 142–526 ng/mL), free T4 1.10 ng/dL (0.80–1.60 ng/dL), free T3 3.27 pg/ml (2.20–4.30 g/ml), and testosterone 9.6 ng/mL (2.8–8.0 ng/mL).

The parents were non-consanguineous and healthy with normal heights. The mother had menarche at 14.5 yr of age (+ 1.8 SD) and irregular menses thereafter. His sister was also conceived naturally, with menarche at 11.5 yr of age (– 0.6 SD) and regular menses thereafter.

Molecular studies

Leukocyte genomic DNA of this patient was subjected to next-generation sequencing panel, to examine multiple genes for pituitary dysfunction including *HESX1*, *LHX3*, *LHX4*, *OTX2*, *POU1F1*, *PROK2*, *PROP1*, *SOX2*, *SOX3*, *CHD7*, *FGF8*, *FGFR1*, *GLI2*, *IGSF1*, *KISS1R*, *SOX10*, and *WDR11* (Kazusa DNA Research Institute).

Ethical consideration

This study was approved by the Institutional Review Board Committee of Shizuoka Children's Hospital and was performed after obtaining written informed consent from the patient and the parents.

Results

We identified two variants with frequencies of ≤ 0.01 in all the databases utilized in this study, *i.e.*, a heterozygous missense variant in *FGFR1* (NM_023110.3: c.176A>T, p.(Asp59Val)) (**Fig. 1C**) and a heterozygous missense variant in *KISS1R* (NM_032551.5: c.769G>C, p.(Val257Leu)). Both variants were confirmed by Sanger direct sequencing, and were found to be of maternal origin (**Fig. 1D**). The *FGFR1* variant was registered

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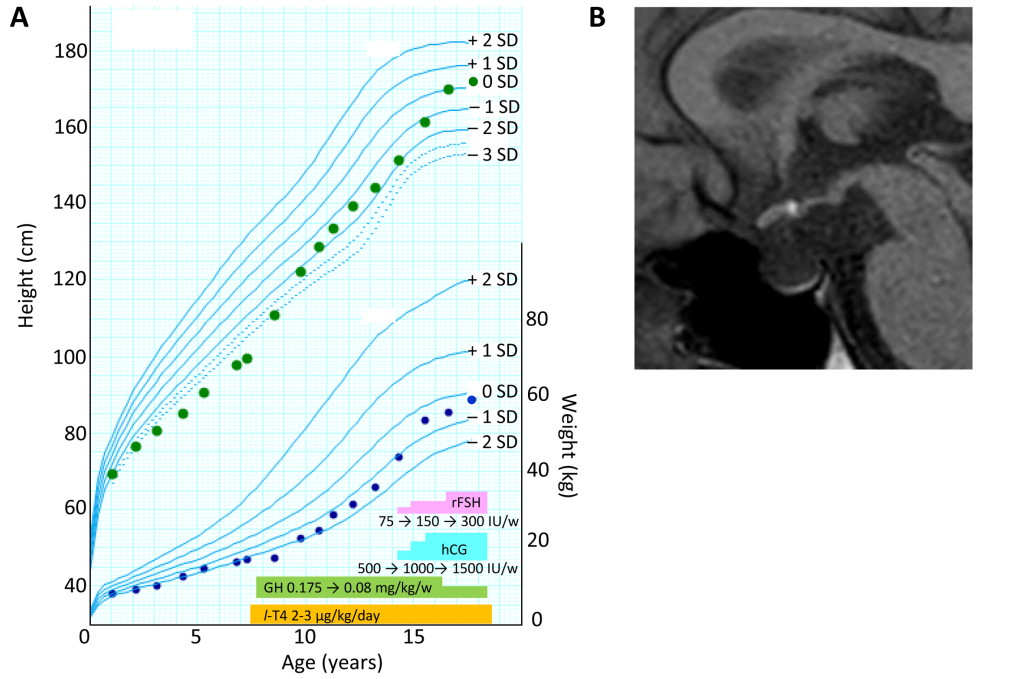
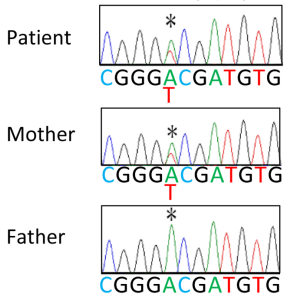


D

FGFR1
c.176A>T, p.(Asp59Val)



E

Frequency in databases

	gnomAD genome_EAS	gnomAD exome_EAS	HGVD	14KJPN	In-house
FGFR1	None	0.000109	0.0051	0.0049	None
KISS1R	None	None	None	0.0001	None

In silico pathogenic predictions

	CADD score	PP2_HVAR Score	SIFT score	MutationTaster score
FGFR1	1% most Deleterious 25.2	Possibly damaging 0.857	Damaging 0.018	Disease causing 1.000
KISS1R	Deleterious 13.5	Benign 0.009	Tolerated 0.295	Polymorphism 0.911

Fig. 1. Clinical and genetic findings of this boy. **A.** The growth chart of this boy plotted on the sex- and age-matched growth curves of Japanese boys. Painted circles indicate actual heights/weights. Hormone replacement therapies are shown. **B.** T1-weighted sagittal magnetic resonance image, showing anterior pituitary hypoplasia and ectopic posterior pituitary. **C.** Structure of *FGFR1* cDNA and FGFR1 protein and the position of the p.(Asp59Val) variant. For cDNA, the coding and non-coding regions are shown in light purple and white, respectively. *FGFR1* encodes multiple domains including signal peptide (SP) domain, immunoglobulin-like domains 1, 2, and 3 (Ig1, Ig2, and Ig3), acidic domain (AD), transmembrane (TM) domain, and tyrosine kinase domains 1 and 2 (TK1 and TK2). **D.** Direct sequencing showing the missense variant identified in this study (asterisks). **E.** Frequencies of the *FGFR1* and *KISS1R* variants in the public and in-house databases, and *in silico* pathogenic predictions for the two variants. The URLs are: (1) gnomAD (the Genome Aggregation Database), http://gnomad.broadinstitute.org/; (2) HGVD (Human Genetic Variation Database), http://www.hgvd.genome.med. kyoto-u.ac.jp/; (3) 14KJPN (Whole-genome sequences of 14,000 healthy Japanese individuals and construction of the highly accurate Japanese population reference panel), https://jmorp.megabank.tohoku.ac.jp/ (4) CADD (Combined Annotation–Dependent Depletion), http://cadd.gs.washington.edu/ score; PHRED scores of > 10–20 are indicate as deleterious, and those of > 20 gives the 1% most deleterious; (5) Polyphen-2 Hum Var, http://genetics.bwh.harvard.edu/pph2/; the scores range from 0.000 (most probably benign) to 1.000 (most probably damaging); (6) SIFT (Sorting Intolerant From Tolerant), http://sift.jcvi.org/; a scores below 0.05 predicts as negative effect on amino acid and those above 0.05 indicates as tolerated; and (7) MutationTaster, http://www.mutationtaster.org/ (MutationTaster2, GRCh37/ Ensembl 69); a score close to 1 indicates an identified variant to be disease causing.

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Table 1. Endocrine data of this patient

	Stimulus (dosage)	Basal	Peak *
At 7 yr of age			
IGF-I (ng/mL)		12.7 (63–247)	
Free T4 (ng/dL)		0.53 (1.07–1.61)	
Free T3 (pg/mL)		2.63 (3.10 –5.10)	
TSH (μIU/mL)		2.15 (0.53– 5.16)	
Testosterone (ng/mL)		0.13 (0.03–0.68)	
GH (ng/mL)	Arginine (0.5 g/kg)	0.4 (< 3.0)	0.1 (> 6.0)
ACTH (pg/mL)	CRH (1.5 μg/kg)	28.8 (15.2 ± 12.8)	152.7 (28.0–130.6)
Cortisol (μg/dL)	CRH (1.5 μg/kg)	6.9 (2.51–22.9)	25.2 (10.6–26.9)
LH (mIU/mL)	GnRH (100 μg/m^2)	< 0.05 (0.02–0.15)	0.23 (1.70–3.77)
FSH (mIU/mL)	GnRH (100 μg/m^2)	0.14 (0.38–1.11)	0.64 (1.38–9.18)
At 14 yr of age			
Testosterone (ng/mL)		< 0.1 (0.28–11.1)	
LH (mIU/mL)	GnRH (100 μg/m^2)	< 0.1 (0.44–1.63)	0.24 (10.9–20.6)
FSH (mIU/mL)	GnRH (100 μg/m^2)	< 0.1 (1.73–4.27)	0.1 (1.68–10.8)

* Peak values during provocation tests; blood sampling at 0, 30, 60, 90, and 120 min. Values in parentheses indicate age-matched reference values in Japanese boys.

with an allele frequency of ~ 0.005 (*i.e.*, ~ one allele per 100 persons) in the Japanese databases (HGVD and 14KJPN), whereas the *KISS1R* variant was extremely rare in the databases (**Fig. 1E**). *In silico* pathogenicity predictions indicated high pathogenicity for the *FGFR1* variant but not for the *KISS1R* variant (**Fig. 1E**).

Discussion

We identified two maternally derived heterozygous missense variants in a boy with CPHD (GH, TSH, and LH/FSH deficiencies). According to the ACMG criteria (6), both variants are assessed as uncertain significance, because the *FGFR1* variant is positive for PM1 (located in a functional domain), PP2 (missense variant in a gene with a low rate of benign missense variation), PP3 (multiple lines of *in silico* pathogenicity predictions in support of a deleterious effect), and BS1 (allele frequency greater than expected for the disorder), and the *KISS1R* variant is positive for PP2 and BP4 (multiple lines of *in silico* pathogenicity predictions against a deleterious effect). However, the *FGFR1* variant would be assessed as a probably weak disease-associated variant with variable expressivity and incomplete penetrance, because: [1] high pathogenicity was consistently predicted by the *in silico* analyses; [2] the same missense variant has been identified in a Japanese patient with KS (7); [3] the maternal phenotype (irregular menses) would be regarded as a mild phenotype reflecting variable expressivity; and [4] the relatively high frequency of this variant in the databases would be explained by assuming that most variant-positive subjects exhibit an apparently normal phenotype due to reduced penetrance. By contrast, the *KISS1R* variant, although it was extremely rare, would be non-deleterious, because it was evaluated as non-deleterious by the *in silico* analyses. Collectively, the *FGFR1* variant would have played a certain role in the development of CPHD in this patient, although the relevance of the *KISS1R* variant has not been formally excluded. In addition, there might be an undetected disease-related variant(s) in a non-coding region(s) of the examined genes or in unexamined gene(s).

Gonadotropin-related phenotypes observed in this patient are noteworthy. First, he was free from micropenis and cryptorchidism at 7 yr of age (probably since birth) and had somewhat enlarged testes (3 – 4 mL) at 14 yr of age. Second, gonadotropin secretion was more severely affected at 14 yr of age than at 7 yr of age. Third, hCG/rFSH therapy successfully induced testosterone production and testicular enlargement. These findings would imply that gonadotropin deficiency worsened with age and that his testes retained the capacity to respond to hCG/rFSH therapy at the pubertal age.

To our knowledge, six rare and probably deleterious *FGFR1* variants have been identified in patients with CPHD, in addition to the missense variant observed in this boy (**Table 2**) (2–5). They include a nonsense variant (case 6), a whole gene deletion (case 7), functionally confirmed missense variants (cases 2, 4, and 5), and a silent variant which probably affects splicing (case 3). The data of the total of seven patients suggest: [1] LH/FSH is invariably affected and GH is predominantly affected (6 of the 7 patients), while various combinations of CPHD affecting TSH, ACTH, and AVP have been reported; and [2] SOD has been observed in cases 2–4, and impaired pituitary development has been identified in cases 1, 2, and 5. These findings imply that *FGFR1* is involved not only in the development of the olfactory system and GnRH neurons but also in the formation of the midline brain structures such as the pituitary, optic region, and septum pellucidum (2). In addition, clinical findings of the carrier parents of cases 1, 2, 4, and 5 argue for the variable expressivity and reduced penetrance of the *FGFR1* variants.

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Table 2. Summary of probably disease-associated *FGFR1* variants in patients with CPHD

Case	Age [a]	Sex	*FGFR1* variant	Function	Inheritance	Affected hormone	Sense of smell	Reproductive phenotypes	Other clinical findings	MRI findings	Ref
1	7 yr	M	c.176A>T p.Asp59Val	NE	Mother with irregular menses	GH, LH FSH, TSH	Normosmia	No micropenis No cryptorchidism No pubertal signs	Short stature (– 4.1 SD)	Anterior pituitary hypoplasia Ectopic posterior pituitary	This study
2	0 mo	F	c.1447C>T p.Pro483Ser	Impaired	Father with oligospermia	GH, LH FSH, TSH ACTH	NE	Not described	SOD, Cleft lip/plate Microphthalmia Coloboma Learning difficulties	Anterior pituitary hypoplasia Undescended posterior pituitary	(2)
3	3 mo	M	c.336C>T p.Thr112Thr [b]	NE	Unknown	GH, LH, FSH	NE	Not described	SOD, Seizures Hyperbilirubinemia	Absent corpus callosum	(2)
4	19 mo	M	c.1349C>T p.Ser450Phe	Impaired	Unaffected mother	LH, FSH AVP	NE	No micropenis No cryptorchidism	SOD Low birth weight (< 3rd percentile) ASD, VSD Epicanthic folds Preauricular skin tags Brachydactyly Single central incisor Learning difficulties	Absent cavum septum pellucidum Dysgenetic corpus callosum	(2)
5	4 yr	F	c.1342C>T p.Arg448Trp	Impaired	Unaffected father	GH, LH FSH, TSH	Normosmia	No pubertal signs at 13 yr old	Short stature (– 3.0 SD)	Anterior pituitary hypoplasia Ectopic posterior pituitary Absent stalk	(4)
6	16 yr	M	c.1864C>T p.Arg622Ter	NE	Unknown	GH, LH FSH	Normosmia	Small undescended testes Micropenis No pubertal signs	Short stature (– 2.7 SD) Flat nasal root	Normal	(3)
7	20 yr	F	Large deletion (~ 8.5 Mb) [c]	NE	Unknown	GH, LH FSH	Normosmia	Primary amenorrhea Breast Tanner stage 3	Short stature (– 2.7 SD) Learning disability Epilepsy	Chiari malformation type I Syringomyelia	(5)

[a] Age at initial investigation. [b] This variant is predicted to generate a new exonic splicing enhancer binding site (TTACTTC) and/or disrupt an overlapping putative exonic splicing enhancer octamer (CCTACTTC). [c] The deletion involves *FGFR1* and 55 genes/pseudogenes; no gene except for *FGFR1* has been associated with brain development. MRI, magnetic resonance imaging; NE, not examined; SOD, sept-optic dysplasia; ASD, atrial septal defect; VSD, ventricular septal defect.

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Conclusions

We identified a probably weak disease-associated *FGFR1* missense variant in a boy with CPHD. Further studies will permit to clarify the pathogenic effect of this relatively common variant in Japan.

Conflict of Interests: The authors declare no conflict of interest associated with this report.

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