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

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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

Highlights

● A case of combined pituitary hormone deficiency with an FGFR1 missense variant.
● Review on cases of combined pituitary hormone deficiency with FGFR1 variants.
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 an 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 μg/mL (2.20–4.30 μg/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, GSF1, KISSIR, 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 KISSIR (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...
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/; 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 score 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/ Ensembl69); a score close to 1 indicates an identified variant to be disease causing.
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.
| Case | Age | 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      | NE       | Mother with irregular menses | GH, LH FSH, TSH | Normosmia | No micropenis | Short stature (~ 4.1 SD) | Anterior pituitary hypoplasia | This study |
| 2    | 0 mo | F   | c.1447C>T     | Impaired | Father with oligospermia | GH, LH FSH, TSH | NE | Not described | SOD, Cleft lip/plate Microphthalmia Coloboma Learning difficulties | Anterior pituitary hypoplasia | (2) |
| 3    | 3 mo | M   | c.336C>T      | Unknown  | GH, LH, FSH | NE | Not described | SOD, Seizures Hyperbilirubinemia | Absent corpus callosum | (2) |
| 4    | 19 mo| M   | c.1349C>T     | Impaired | Unaffected mother | LH, FSH, AVP | NE | No micropenis | 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     | Impaired | Unaffected father | GH, LH FSH, TSH | Normosmia | No pubertal signs at 13 yr old | Short stature (~ 3.0 SD) | Anterior pituitary hypoplasia | (4) |
| 6    | 16 yr| M   | c.1864C>T     | NE       | Unknown | GH, LH FSH | Normosmia | Small undescended testes Micropenis | Short stature (~ 2.7 SD) | Normal | (3) |
| 7    | 20 yr| F   | Large deletion (~ 8.5 Mb) | 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) |

*Age at initial investigation. 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). 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.
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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