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Mutation-in-Brief

A novel missense variant of *FGFR1* in a Japanese girl with Kallmann syndrome and holoprosencephaly

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Highlight

- A novel missense variant of *FGFR1*, p.Glu531Lys, is associated with Kallmann syndrome and holoprosencephaly.

Key words: fibroblast growth factor receptor 1 (FGFR1), Kallmann syndrome, holoprosencephaly, novel variant

Introduction

Fibroblast growth factor receptor 1 (FGFR1), a receptor tyrosine kinase, acts as a cell surface receptor for fibroblast growth factors and plays an essential role in the regulation of embryonic neurogenesis. Pathogenic variants of *FGFR1*, the gene encoding FGFR1, have been reported in cases of Kallmann syndrome (KS) (1) or holoprosencephaly (HPE) (2). Herein, we report the case of a Japanese girl with KS and HPE, carrying a novel pathogenic variant of *FGFR1*.

Case Report

The proband was a Japanese girl who was born at term after an uneventful pregnancy. She was the first child of phenotypically normal parents with no significant family history. Her birth weight and length were 3060 g (+ 0.59 SD) and 49.7 cm (+ 0.49 SD), respectively. She had no cleft lip, hypotelorism, nor absence of the nasal septum. Her development was almost normal except for walking. She needed orthotics for bilateral clubfoot from the age of 1 yr and 6 mo and was able to walk by herself at the age of 2 yr. She had neither polydipsia nor polyurea. At 3 yr of age, medical attention was sought for diarrhea and vomiting of three days durations. Her height and weight were 91.0 cm (–1.43 SD) and 12.8 kg (–0.90 SD), respectively. She did not show any facial dysmorphic features except for a flat nasal tip. Her serum sodium and urea nitrogen levels were 162 mEq/L, 49.2 mg/dL, respectively. The urine specific gravity was 1.029. Intravenous fluid therapy was initiated. On the third day of admission, her serum sodium, osmolality, and arginine vasopressin

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levels were 154 mEq/L, 306 mOsm/L, and 1.2 pg/mL, respectively. Her urine osmolality was 376 mOsm/L. Brain MRI revealed a continuous frontal cortex across the midline and the absence of the septum pellucidum, corpus callosum, and olfactory bulbs (**Fig. 1**). Loading tests with insulin, gonadotropin-releasing hormone, and thyrotropin-releasing hormone, after improvement in dehydration, revealed gonadotropin insufficiency (**Table 1**). After discharge, her serum sodium level remained within normal limits except for a few episodes of hypernatremia in the case of gastroenteritis. We diagnosed her with KS and lobar-type HPE, presenting with partial diabetes insipidus and bilateral clubfoot. With age, dyscalculia and dysgraphia became apparent, and she scored 55 on a preschool intelligence test. She could not distinguish the scents in her daily life. She also experienced hyperacusis. She was enrolled in a support class for children with special needs in an elementary school.

After genetic counseling, written informed consent was obtained from her mother. The study was approved by the Ethics Committee of Keio University School of Medicine (IRB number: 20140289; date of approval: May 25, 2015). Genomic DNA was extracted from peripheral blood samples of the proband. Next-generation sequencing-based screening of the major causative genes of KS and HPE (*CCDC141*, *CHD7*, *DUSP6*, *FEZF1*, *FGF17*, *FGF8*, *FGFR1*, *FLRT3*, *GLI2*, *HS6ST1*, *IL17RD*, *KAL1*, *NELF*, *POLR3B*, *PROK2*, *PROKR2*, *SEMA3A*, *SEMA3E*, *SIX3*, *SOX10*, *SPRY4*, and *WDR11*) identified a novel heterozygous variant, c.1591G>A, p.Glu531Lys, in *FGFR1*. We verified the presence of this variant using PCR-based direct sequencing (**Fig. 1**). No genetic testing of the parents was performed.

p.Glu531Lys variant is not found in the Human Genetic Variation Database (HGVD; http://www.

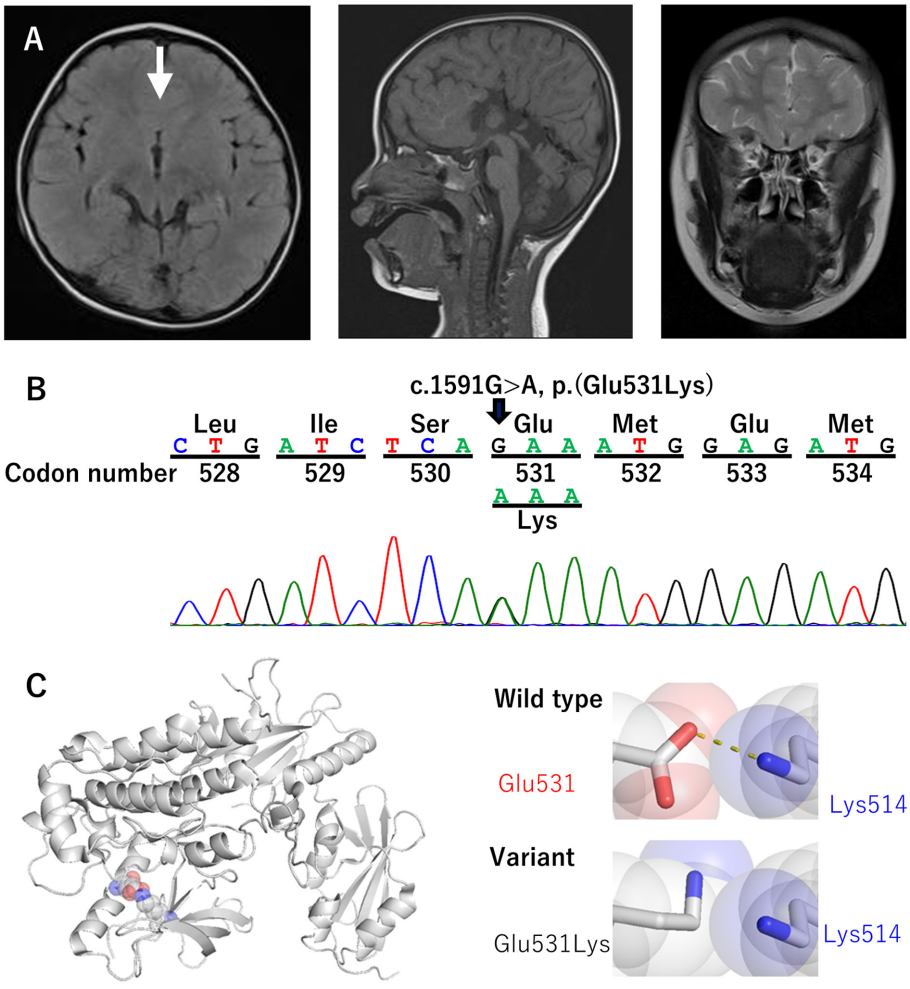

Fig. 1. (A) Axial flare (left), sagittal T1-weighted (center), and coronal T2-weighted MRI images (right) of the patient's brain at 3 yr of age. Frontal cortex is not fully separated and continuous on both sides (white arrow). Septum pellucidum and corpus callosum are completely absent. High-intensity signal is preserved in the posterior lobe. Olfactory bulb is not clearly identified. (B) Partial sequence chromatogram of exon 12 of the proband's *FGFR1* gene. A black arrow shows a variant of c.1591G>A, p.Glu531Lys. (C) Three-dimensional structure of the intracellular kinase domain of FGFR1 (left), and enlarged views of wild (upper right) and variant-type (lower right) salt-bridges. Residues corresponding to Glu531 and Lys514 are shown as spheres and sticks. Red and blue atoms show oxygen and nitrogen, respectively. The p.Glu531Lys was predicted to lose ionic bond formation (dotted line) in the salt-bridge.

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Table 1. Hormone levels after stimulation with insulin, gonadotropin-releasing hormone, and thyrotropin-releasing hormone

min	0	15	30	60	90	120
GH (ng/mL)	2.24	1.42	6.24	16.3		
ACTH (pg/mL)	10.1	7.7	196.8	74.0	28.7	23.1
Cortisol (μg/dL)	5.8	7.0	14.9	24.4	21.6	17.1
LH (mIU/mL)	< 0.20		< 0.20	0.22	< 0.20	< 0.20
FSH (mIU/mL)	< 0.20		1.92	2.37	2.25	2.30
TSH (μIU/mL)	1.27		10.43	9.39	7.47	5.72
PRL (ng/mL)	11.4		113.7	78.0	36.0	25.4

hgvd.genome.med.kyoto-u.ac.jp), Genome aggregation database (gnomAD; https://gnomad.broadinstitute.org/) or Japanese multi omics reference panel (jMorp; https://jmorp.megabank.tohoku.ac.jp/202206/). *In silico* analyses of p.Glu531Lys by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and PROVEAN (http://provean.jcvi.org/index.php) predicted "probably damaging" and "deleterious" with scores of 1.000 and –3.57, respectively. Glu531 forms a salt-bridge with Lys514 and interacts with the glycine-rich loop to facilitate binding of adenosine triphosphate and substrate in the tyrosine kinase domain (3, 4). In the three-dimensional model, the PyMOL Molecular Graphics System (http://www.pymol.org), the p.Glu531Lys loses the salt-bridge with Lys514 (**Fig. 1**).

Discussion

We identified a novel missense variant of *FGFR1* in a girl with KS and HPE. Although we did not determine whether the variant of the proband was *de novo*, we considered this variant as a "likely pathogenic variant" based on the recommendations of the American College of Medical Genetics and Genomics (5). First, p.Glu531Lys is not found in any genomic variation database of Japanese or other ethnic backgrounds. Second, two different computational predictions support the deleterious effect of p.Glu531Lys on FGFR1 protein function. Third, the three-dimensional model shows that Glu531of FGFR1 is an important residue for a salt-bridge with Lys514. Salt-bridge formation between Glu531 and Lys514 is highly conserved among vertebrate species and family members of the human FGFR (3). p.Glu531Lys changes the acidic amino acid with a basic one and loses the salt-bridge, potentially resulting in disruption of the interaction with the glycine-rich loop and eventual attenuation of FGF signaling. Fourth, *FGFR1* is the only gene responsible for the combination of KS and HPE, which is consistent with the phenotype observed in our patient. The partial diabetes insipidus in our patient was probably a condition related to HPE. Thus, p.Glu531Lys in *FGFR1* is likely a pathogenic variant that causes concurrent KS and HPE.

In conclusion, we identified a novel pathogenic variant of *FGFR1*, c.1591G>A, p.Glu531Lys, associated with KS and HPE. *FGFR1*-realted disorders should be considered in patients with KS and lobar-type HPE.

Conflict of interests: Tomonobu Hasegawa discloses the following financial relationships: receipt of scholarship donations from Novo Nordisk Pharma Ltd. and JCR Pharmaceuticals Co., Ltd.

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