Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3318-23
Intern Med 64: 575-580, 2025
http://internmed.jp

【 CASE REPORT 】

A Japanese Boy with Dysmorphic Syndrome with Multiple Pituitary Hormone Deficiency and Gingival Fibromatosis Due to a Pathogenic *KCNQ1* Variant

Hisakazu Nakajima[1-3], Kazuki Kodo[1], Hidechika Morimoto[1,2], Shinsuke Hori[4] and Satoru Sugimoto[1,2]

Abstract:

A six-year-old boy presented with short stature and gingival fibromatosis (GF). Dysmorphic features included slant optic fissures, a high-arched palate, thick earlobes, and an edematous face. Laboratory tests showed low levels of serum insulin-like growth factor-1 and serum free thyroxine but normal serum thyrotropin levels. Provocative tests suggested growth hormone deficiency, central hypocortisolemia, and hypothalamic hypothyroidism. At 12 years old, hypogonadotropic hypogonadism was observed. Next-generation sequencing revealed a heterozygous missense variant, *KCNQ1* p.(P369L), in the proband and mother. The coexistence of multiple pituitary hormone deficiencies and GF helps diagnose *KCNQ1*-variant dysmorphic syndrome through genetic testing.

Key words: *KCNQ1*, short stature, gingival fibromatosis, multiple pituitary hormone deficiency

(Intern Med 64: 575-580, 2025)
(DOI: 10.2169/internalmedicine.3318-23)

Introduction

KCNQ1 encodes the alpha subunit of the voltage-gated ion channel Kv7.1, which has been previously implicated in familial long or short QT syndrome (1-3). From 2017 to 2019, two missense variants, c.347G>T: p.(R116L) and c.1106C>T: p.(P369L), were found in *KCNQ1* from four unrelated families with childhood-onset growth hormone (GH) deficiency (4, 5). These variants cause isolated GH deficiency, multiple pituitary hormone deficiency (MPHD), and gingival fibromatosis (GF) (4, 5).

Interestingly, *KCNQ1* messenger RNA (mRNA) and protein are expressed in somatotrophs and gonadotrophs of mice and humans, as well as in embryonic murine hypothalamic growth hormone-releasing hormone neurons and in the human hypothalamus (4). Currents through voltage-gated potassium channels in pituitary cells suggest that ion channels may be pivotal regulators of the pituitary function (4).

Patients with both pituitary insufficiency and *KCNQ1* variants are rare. To our knowledge, no such case has been reported in Japan. We herein report a pediatric case of MPHD caused by a pathogenic *KCNQ1* variant.

Case Report

A six-year-old boy (proband II-1) was referred to our pediatric endocrinology clinic with a short stature and possible developmental delay (Fig. 1A). Intrauterine fetal distress resulted in delivery at a gestational age of 40 weeks via Caesarean section. At birth, his height and weight were 45 cm and 2,652 g, respectively. His parents (I-1 and I-2) were healthy, of standard height, and lacked arrhythmia (Fig. 1A). His younger brother (II-2) was healthy and had no short stature (Fig. 1A). Consanguinity was absent in his parents. GF had been observed since 11 months old and required repeated surgical intervention. At 2 years 9 months old, the patient's K-type developmental test (new edition) score was

[1]Department of Pediatrics, North Medical Center Kyoto Prefectural University of Medicine, Japan, [2]Department of Pediatrics, Kyoto Prefectural University of Medicine, Japan, [3]Department of Pediatrics, Midorigaoka Hospital, Japan and [4]Department of Oral and Dental Surgery, Kyotango City Kumihama Hospital, Japan
Received: December 6, 2023; Accepted: May 27, 2024; Advance Publication by J-STAGE: July 11, 2024
Correspondence to Dr. Hisakazu Nakajima, hisakazu@koto.kpu-m.ac.jp

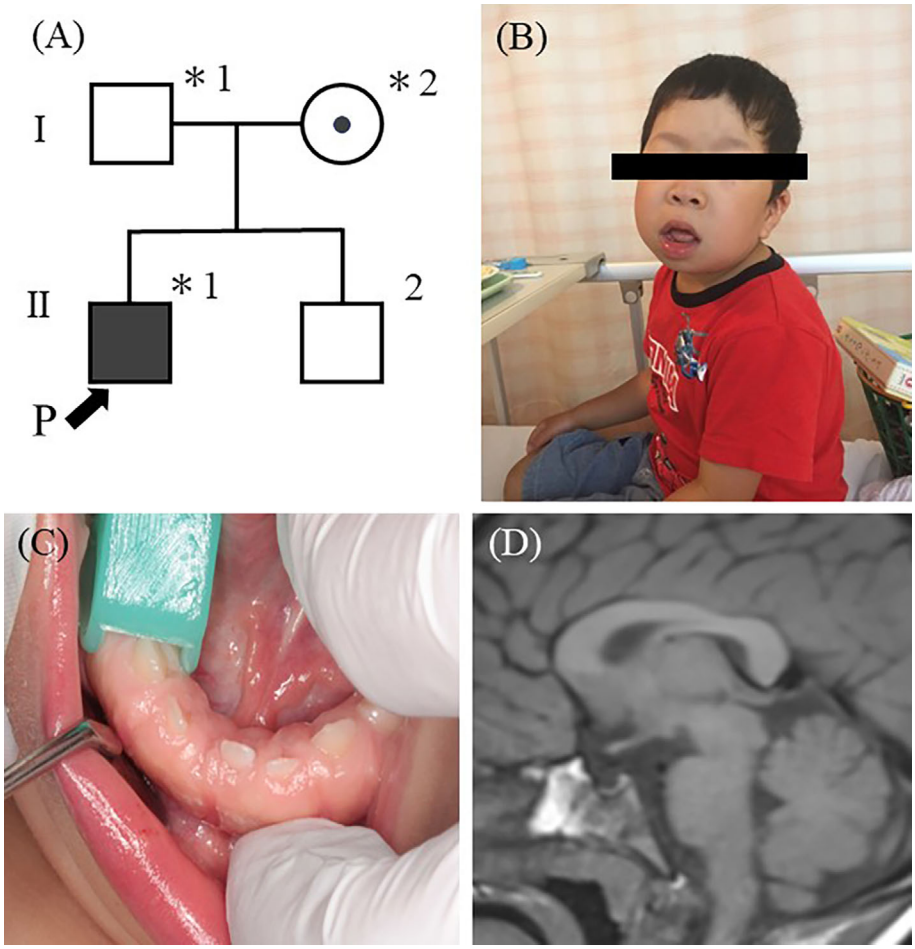

Figure 1. **(A) Proband (II-1) family tree. The arrow (P) shows the proband, and asterisk (*) indicates the individual who received genetic testing. (B) The general appearance of the proband. Parental permission was obtained to publish the photograph. (C) Image of the oral findings of the patient, demonstrating gingival fibromatosis. (D) Magnetic resonance imaging of the brain and pituitary, showing pituitary hypoplasia and a thin pituitary stalk.**

88.

At the first referral, his height and weight were 100.7 cm [-2.65 standard deviation (SD)] and 15.4 kg (-2.07 SD), respectively. His appearance was characterized by a short neck, slanted optic fissures, high-arched plate, thick earlobes, and edematous face (Fig. 1B). We also confirmed the presence of GF (Fig. 1C). Therefore, dysmorphic syndrome was suspected.

His growth seemed to have been on an unfavorable trajectory since three years old (Fig. 2). Laboratory test revealed decreased levels of serum insulin-like growth factor-1 (IGF-1; <10 ng/mL; normal range, 55-215 ng/mL) and free triiodothyronine (0.67 ng/dL; normal range, 0.9-1.7 ng/dL) but normal thyrotropin levels [thyroid stimulating hormone (TSH), 3.90 μIU/mL; normal range, 0.34-3.88 μIU/mL]. Serum blood urea nitrogen and creatinine levels were within the normal ranges. Blood tests did not detect electrolyte abnormalities or hypoglycemia. His bone age was estimated to be 3.0 years using the Greulich-Pyle standard. Magnetic resonance imaging revealed a hypoplastic pituitary gland with a thin stalk (Fig. 1D).

An arginine provocation test showed a low response to pituitary GH release (Table 1). A growth hormone releasing peptide-2 provocative test also revealed GH deficiency and adrenocorticotropic hormone (ACTH) insufficiency with a low peak serum cortisol (Table 1) (6). A thyrotropin-releasing hormone provocative test revealed a significant increase in TSH secretion (Table 1).

We diagnosed the index patient with MPHD: GH deficiency, hypothalamic hypothyroidism due to TSH insufficiency, and ACTH deficiency. At 6.6 years old, the patient was treated with injection therapy of recombinant human (rh) GH (0.175-0.20 mg/kg/week), and oral administration of levothyroxine (0.5-2 μg/kg/day) and hydrocortisone (5-10 mg/day). These two treatments successfully improved the growth trajectory of the patient (Fig. 2). The bone age was 5.0 years old when the chronological age was 9.3 years old. At 7 years old, an electrocardiogram showed a QTc interval of 402 ms (normal range, 360-440 ms). At 10.3 years old, pubarche had reached grade 2, whereas serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels were less than 0.1 mIU/mL, 1.1 mIU/mL,

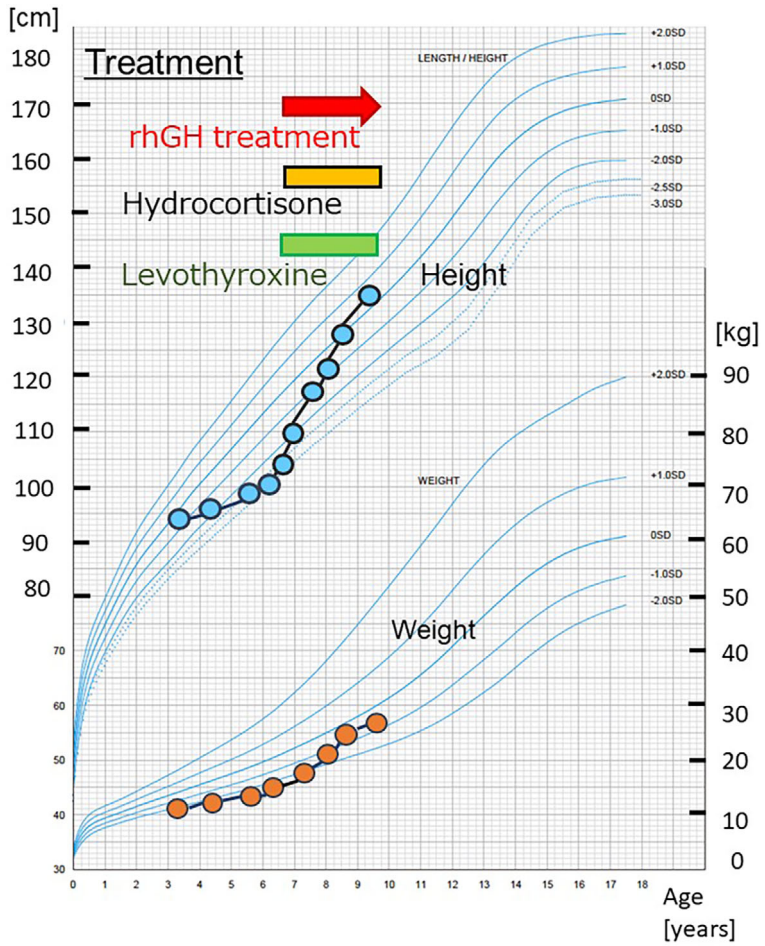

Figure 2. **Growth chart and clinical course of the patient. Hormonal treatment with levothyroxine (0.5-2.0 μg/kg/day, per os), hydrocortisone (5-10 mg/day, per os), and human recombinant growth hormone (rhGH; 0.175-0.20 mg/kg/week, by daily subcutaneous injection) improved patient growth trajectory. rhGH: recombinant human growth hormone**

Table 1. **Results of Pituitary Hormone Provocative Tests.**

Arginine provocative test		0’	30’	60’	90’	120’
GH	(ng/mL)	0.66	0.33	0.52	0.97	1.07
GHRP-2 provocative test		0’	15’	30’	45’	60’
GH	(ng/mL)	0.69	1.53	1.55	1.13	0.92
ACTH	(pg/mL)	18.7	34.2	26.1	19.9	17.9
Cortisol	(μg/dL)	3.6	4.9	5.9	4.5	4.1
TRH provocative test		0’	30’	60’	90’	120’
TSH	(μIU/mL)	3.9	17.03	24.46	31.22	43.08
Free triiodothyronine	(pg/mL)	2.87	-	-	-	2.94
Free thyroxine	(ng/dL)	0.69	-	-	-	0.74

ACTH: adrenocorticotropic hormone, GH: growth hormone, GHRP-2: growth hormone releasing peptide-2, TRH: thyrotropin-releasing hormone, TSH: thyrotropin (thyroid stimulating hormone)

and 0.03 ng/mL, respectively. At 12.5 years old, delayed puberty was found at grade 2, as serum LH and FSH levels were <0.1 mIU/mL and 0.8 mIU/mL, respectively. Thus, the low levels of serum FSH at baseline diagnostically suggest hypogonadotropic hypogonadism (7).

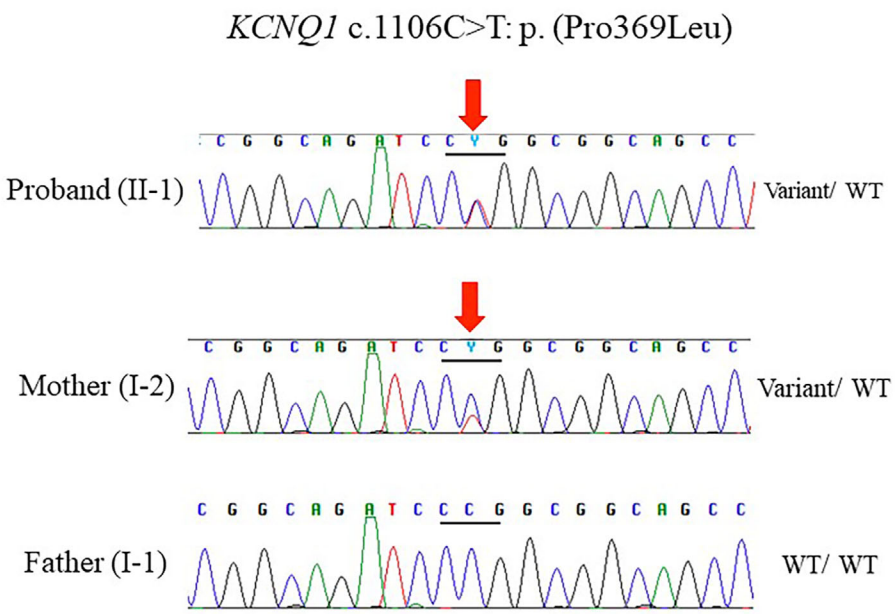

Figure 3. Genetic testing using genomic DNA of the proband and his parents. Chromatographs show a part of the *KCNQ1* sequence by Sanger sequencing. The proband (II-1) and his mother (I-2) harbor a heterozygous variant of c.1106C>T: p. (P369 L). The father (I-1) has the homozygous wild type. WT: wild type

A genetic analysis of the KCNQ1 gene

Genetic tests were performed on the proband and his parents after informed consent was obtained from the patient. This genetic analysis study was approved by the Kyoto Prefectural University of Medicine Medical Ethics Committee (approval number: ERB-G-90).

Genomic DNA was extracted from whole blood using a Genome Extraction Kit (GENOMIX; Biologica, Nagoya, Japan) by SRL (Tokyo, Japan). Gene panel testing using next-generation sequencing and Sanger sequencing was conducted at the Kazusa DNA Research Institute (Kisarazu, Japan). Genomic libraries were prepared using SureSelectXT Reagent Kit (Agilent Technologies, Santa Clara, USA) (8). Sequencing was performed using the NextSeq500 platform (Illumina, San Diego, USA) with 75-bp paired-end reads (8). Variant calling was conducted using the gold-standard Genome Analysis Toolkit (GATK) pipeline (8). Sequence reads were aligned to the human reference genome (GRCh38/hg38) using BWA-MEM (8). Single-nucleotide variants and small insertions/deletions have been identified using GATK (8). Sanger sequencing was performed on *KCNQ1*, using the genomes of family members. Current genetic testing identified a pathogenic *KCNQ1* variant in the proband, c.1106C>T: p.(P369L), which was previously reported by Tommiska et al. (4). This variant was estimated to be "likely pathogenic" according to variant interpretation using the ACMG-AMP guidelines (PS1, PS3, PP3, PP5, and PM2) (9). The same *KCNQ1* variant was found in his mother, whereas his father did not harbor any other pathogenic *KCNQ1* (Fig. 3).

The younger brother (II-2) did not undergo genetic testing because he was healthy and had neither short stature nor dysmorphic features, including GF.

Discussion

We encountered a pediatric case of a pathogenic *KCNQ1* variant presenting with short stature, MPHD, isolated GH deficiency, GF, and dysmorphic features. Our patient had the same variant as that previously reported *KCNQ1* p.(P369L) (4). To date, four families of pedigrees with multiple pituitary hormone deficiencies and GF due to *KCNQ1* mutations have been reported. Two families came from Finland, three from Switzerland, and four from the United States (Table 2) (4, 5). We believe that our index patient was the first diagnosed case of *KCNQ1* variant-stemming dysmorphic syndrome in Japan.

Only two *KCNQ1* variants (p.(R116L) and p.(P369L)) have been identified in previous cases of MPHD with or without GF (4, 5) (Table 2). *KCNQ1* p.(P369L) variant was present in three families (excluding our case), whereas p.(R116L) was present in one (4, 5). Our index case belongs to the majority of syndromes in previously reported family lines. We considered p.(P369L) to be a hotspot variant of *KCNQ1*-variant dysmorphic syndrome. In this context, genetic testing is useful for identifying dysmorphic syndromes according to the genetic specificity of the disease. However, the accumulation of further cases is essential to confirm that the two hotspot variants of *KCNQ1* are specifically responsible for the syndromic disease.

Uniquely, the index patient showed multiple pituitary hormone deficiencies, including GH, TSH, ACTH, and gonadotropin deficiencies. Table 2 summarizes the clinical mani-

Table 2. Profiles of Previously Reported Patients with KCNQ1 Pathogenic Variants and Pituitary Hormone Deficiency.

Pedigree	Country	Case	Genetic variant/ Inheritance	Gender	Onset of GH treatment	Height SDS (SD)	Pituitary hormone deficiency	Brain MRI findings	GF	QTc interval	Dysmorphic features	Ref.
I	Finland	1	p.R116L (hetero.)/ Maternally	Female	15 yr	-4.5	GH, Gn	Normal	Present	Normal	N/A	(4)
		2	p.R116L (hetero.)/ Maternally	Female	12.4 yr	-3.4	GH, Gn	Normal	Present	Normal	N/A	
		3	p.R116L (hetero.)/ Maternally	Male	8.5 yr	-5.0	GH, Gn, ACTH	Pituitary hypoplasia	Present	Normal	Yes	
		4	p.R116L (hetero.)/ Paternally	Female	4.5 yr	-2.7	GH	Normal	None	N/A	No	
		5	p.R116L (hetero.)/ Paternally	Female	3.7 yr	-2.7	GH, TSH.	Normal	None	N/A	No	
		6	p.R116L (hetero.)/ Maternally	Male	15.9 yr	-2.6	GH, Gn	N/A	Present	Normal	Yes	
		7	p.R116L (hetero.)/ Maternally	Female	9 yr	-2.7	GH, Gn	N/A	Present	N/A	Yes	
		8	p.R116L (hetero.)/ Maternally	Male	6 yr	-1.8	GH, Gn	Pituitary hypoplasia	Present	Short QTc	Yes	
		9	p.R116L (hetero.)/ Maternally	Male	5 yr	-2.2	GH, Gn	Pituitary hypoplasia	Present	Short QTc	Yes	
		10	p.R116L (hetero.)/ Maternally	Female	13.4 yr	-2.3	GH	Normal	Present	Normal	Yes	
II	Finland	11	p.P369L (hetero.)/ N/A	Female	17 yr	-5.2	GH, Gn, ACTH, TSH	Normal	None	Short QTc	No	(4)
		12	p.P369L (hetero.)/ Maternally	Male	2.7 yr	-3.0	GH	Pituitary hypoplasia	Present	Normal	Yes	
		13	p.P369L (hetero.)/ Maternally	Male	No use	N/A	GH	N/A	None	Short QTc	Yes	
III	Swiss	14	p.P369L (hetero.))/ de novo	Female	N/A	N/A	GH	Normal	Present	Short QTc	N/A	(4)
IV	the United States	15	p.P369L (hetero.) / de novo	Male	9 yr	-2.34	GH	Normal	Present	Normal	Yes	(5)
V	Japan	16	p.P369L (hetero.)/ Maternally	Male	6 yr	-2.65	GH, Gn, ACTH, TSH	Pituitary hypoplasia	Present	Normal	Yes	This report

GH: growth hormone, SDS: standard deviation score, SD: standard deviation, GF: gingival fibromatosis, QTc: the corrected QT time in electrocardiogram, hetero.: heterozygous mutation, Gn: gonadotropin, ACTH: adrenocorticotropic hormone, TSH: thyrotropin, N/A: not available, Ref.: reference

festations of previously reported patients harboring a *KCNQ1* mutation, including our index case (4, 5). These *KCNQ1*-mutated syndromic individuals share common features, such as pituitary hormone deficiencies, GF, and short QT syndrome. Regarding pituitary hormone deficiencies, all individuals had GH deficiency, 50% developed gonadotropin deficiency, and 31% had pituitary hypoplasia (Table 2). In addition, all patients with *KCNQ1* p.(P369L) also showed GH deficiency, although two patients with *KCNQ1* p.(P369L) developed a combination of GH deficiency, gonadotropin deficiency, ACTH insufficiency, and TSH deficiency. These findings suggest the importance of monitoring the ACTH/cortisol and TSH/thyroid hormone axis in *KCNQ1* p.(P369L) patients, as well as gonadotropins. *KCNQ1* contributes to gonadotropin release in gonadotrophs, and *KCNQ1* mRNA and protein are expressed in human gonadotrophs (4, 10). Furthermore, in a transfection experiment using AtT-20 cells (derived from murine ACTH-releasing pituitary tumors), mutated *KCNQ1* (p.(R116L) and p.(P369L)) exhibited lower ACTH release than wild-type *KCNQ1* (4). These findings support the hypothesis that *KCNQ1* is a critical gene in the development of hypothalamic and pituitary hormone-releasing cells (11).

Of *KCNQ1*-variant patients with pituitary hormone deficiency, 31% had short QT syndrome (Table 2). Our index patient had neither short QT intervals on electrocardiograms nor arrhythmia attacks. However, the patient must be carefully followed up and monitored because previous research has suggested that he could develop sudden arrhythmia or changes in QT waves in the future (4). Patients with short QT syndrome are at risk of atrial fibrillation, ventricular fibrillation, or sudden death (12). A whole-cell patch-clamp analysis using HEK293 cells showed that the two mutated voltage-gated potassium channels (p.(P369L) and p.(R116L)) had higher voltage levels than the wild type (4).

Interestingly, the proband's mother harbored the same het-

erozygous *KCNQ1* variant as the patient, although she has been asymptomatic to date without arrhythmia, short stature, dysmorphic features, or GF. *KCNQ1* is located in a cluster of imprinted genes mapped to chromosome 11p15.5 (13). This cluster is divided into centromeric and telomeric regions (10). The telomeric region harbors paternally expressed insulin-like growth factor-2 (*IGF2*) and maternally expressed *H19* (13). The centromeric region harbors paternally expressed potassium voltage-gated channel 1 opposite strand/antisense transcript 1 (*KCNQ1OT1*) as well as maternally expressed cyclin-dependent kinase inhibitor 1C (*CDKN1C*) and *KCNQ1* (13). *KCNQ1* is exclusively expressed in the maternal allele of the next generation (13). Thus, in our index case, the mutated allele with a methylated imprinted center was inherited from the mother. Given the mother's healthy phenotype, her *KCNQ1* variant was likely a *de novo* mutation or a result of a mutated paternal allele.

In conclusion, we reported a case of maternally inherited dysmorphic syndrome with MPHD and GF. The patient had a pathogenic mutant allele, p.(P369 L), of *KCNQ1*. His salient traits, short stature, dysmorphic features, and pituitary dysfunction associated with hypoplasia correspond to the characteristics presented in previous cases of *KCNQ1*-variant dysmorphic syndrome. We concluded that *KCNQ1* mutations may be responsible for syndromic MPHD. Genetic testing was feasible for confirming the diagnosis of syndromic disease. Physicians and pediatricians should be aware of this syndrome based on the current experience.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This work was supported by JSPS KAKENHI (grant number 21K11701).

Acknowledgements

We thank the patient and his parents for their participation in this diagnostic study.

References

1. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: *KVLQT1* mutations cause cardiac arrhythmias. Nat Genet **12**: 17-23, 1996.

2. Hedley PL, Jørgensen P, Schlamowitz S, et al. The genetic basis of long QT and short QT syndromes: a mutation update. Hum Mutat **30**: 1486-1511, 2009.

3. Bellocq C, van Ginneken AC, Bezzina CR, et al. Mutation in the *KCNQ1* gene leading to the short QT-interval syndrome. Circulation **109**: 2394-2397, 2004.

4. Tommiska J, Känsäkoski J, Skibobbed L, et al. Two missense mutations in *KCNQ1* cause pituitary hormone deficiency and maternally inherited gingival fibromatosis. Nat Commun **8**: 1289, 2017.

5. Dekelbab B, Chopra K. Growth hormone deficiency and gingival fibromatosis due to missense mutation of *KCNQ1*. J Endocr Soc **3** (Suppl 1): SUN-286, 2019.

6. Hayakawa T, Kitamura T, Tamada D, et al. Evaluation of hypothalamic-pituitary-adrenal axis by the GHRP2 test: comparison with the insulin tolerance test. J Endocr Soc **2**: 860-869, 2018.

7. Grinspon RP, Ropelat MG, Gottlieb S, Keselman A, Martinez A, Ballerini MG, et al. Basal follicle-stimulating hormone and peak gonadotropin levels after gonadotropin-releasing hormone infusion show high diagnostic accuracy in boys with suspicion of hypogonadotropic hypogonadism. J Clin Endocrinol Metab **95**: 2811-2818, 2010.

8. Fujiki R, Ikeda M, Yoshida A, et al. Assessing the accuracy of variant detection in cost-effective gene panel testing by next-generation sequencing. J Mol Diagn **20**: 572-582, 2018.

9. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med **17**: 405-424, 2015.

10. Stojilkovic SS, Bjelobaba I, Zemkova H. Ion channels of pituitary gonadotrophs and their roles in signaling and secretion. Front Endocrinol (Lausanne) **8**: 126, 2017.

11. Gregory LC, Dattani MT. The molecular basis of congenital hypopituitarism and related disorders. J Clin Endocrinol Metab **105**: dgz184, 2020.

12. Gaita F, Giustetto C, Bianchi F, et al. Short QT Syndrome: a familial cause of sudden death. Circulation **108** (8): 965-970, 2003.

13. Brioude F, Kalish JM, Mussa A, et al. Expert consensus document: clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. Nat Rev Endocrinol **14**: 229-249, 2018.