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NOTE

Insulin resistant diabetes mellitus in SHORT syndrome: case report and literature review

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Abstract. SHORT syndrome is a rare developmental disorder frequently associated with growth failure and insulin resistant diabetes mellitus (IRDM). Since GH has a diabetogenic effect, GH therapy has been regarded as a contraindication. We observed a Brazilian girl with SHORT syndrome who received GH therapy from 4 6/12 years of age for SGA short stature. GH dosage was increased from 0.23 to 0.36 mg/kg/week, but statural response to GH therapy remained poor. Her blood HbA1c level, though it remained 5.5–6.0% in childhood, began to elevate with puberty and increased to 9.2% at 10 6/12 years of age, despite the discontinuation of GH therapy at 9 11/12 years of age. Laboratory studies indicated antibody-negative IRDM. She was treated with metformin and canagliflozin (a sodium glucose co-transporter 2 (SGLT2) inhibitor), which ameliorated overt diurnal hyperglycemia and mild nocturnal hypoglycemia and reduced her blood HbA1c around 7%. Whole exome sequencing revealed a *de novo* heterozygous pathogenic variant (c.1945C>T:p.(Arg649Trp)) in *PIK3R1* known as the sole causative gene for SHORT syndrome. Subsequent literature review for patients with molecularly confirmed SHORT syndrome revealed the development of IRDM in 10 of 15 GH-untreated patients aged ≥12 years but in none of three GH-treated and six GH-untreated patients aged ≤10 years. These findings imply a critical role of pubertal development and/or advanced age rather than GH therapy in the development of IRDM, and a usefulness of SGLT2 inhibitor in the treatment of IRDM.

Key words: SHORT syndrome, Insulin resistant diabetes mellitus, Pubertal development, GH therapy, Sodium glucose co-transporter 2 inhibitor

SHORT SYNDROME is a rare developmental disorder named by the acronym of salient clinical features, *i.e.*, short stature (S), hyperextensibility of joints or inguinal hernia (H), ocular depression (O), Rieger anomaly (R), and teething delay (T) [1]. This syndrome is also frequently associated with intrauterine growth retardation, characteristic face, sensorineural hearing loss, lipodystrophy, and insulin resistance, and occasionally accompanied by recurrent infections [1, 2]. Since SHORT syndrome is caused by heterozygous loss-of-function variants of *PIK3R1* involved in multiple signal transductions including GH receptor (GHR) signaling, insulin-like growth factor 1 receptor (IGF1R) signaling, and insulin receptor (INSR) signaling as well as immune-related signalings [1-5], this would primarily explain the development of such clinical features in SHORT syndrome. Importantly, GH therapy has been regarded as a contraindication in this syndrome, because GH has the potential to promote the development of insulin resistant diabetes mellitus (IRDM) [3, 6, 7].

Here, we report a girl with molecularly confirmed SHORT syndrome who received GH therapy for a long term and developed IRDM with puberty. The results, in conjunction with the literature review for IRDM in SHORT syndrome, imply that pubertal development and/or advanced age, rather than GH therapy, is the major risk factor for the occurrence of IRDM. Furthermore, this study suggests the usefulness of a sodium glucose co-transporter 2 (SGLT2) inhibitor in the treatment of IRDM.

Case Presentation

This Brazilian girl was delivered by Caesarean section at 35 weeks of gestation, because of fetal growth arrest and oligohydramnios. The parents were

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non-consanguineous and clinically normal, with the paternal height of 171 cm (+0.1 SD) and the maternal height of 150 cm (–1.5 SD). At birth, her length was 41.5 cm (–1.8 SD), her weight 1.51 kg (–2.6 SD), and her occipitofrontal circumference (OFC) 29.3 cm (–1.7 SD). Feeding difficulty was observed in infancy. She had severe hearing difficulty, and received cochlear implant surgery at two years of age. (Note: the body growth of this patient and her parents were assessed by the sex- and gestational age- or postnatal age-matched growth references for Japanese subjects [http://jspe.umin.jp/medical/taikaku.html], because (1) growth references for Brazilian children are available only for height and weight, but not for OFC, from seven to 17 years [8], and there are no gestational age-matched neonatal growth data in the WHO Child Growth Standards [https://www.who.int/childgrowth/standards/en/]).

At 4 6/12 years of age, she was seen because of persistent postnatal growth failure. Her height was 88.1 cm (–3.7 SD), her weight 10.9 kg (–2.5 SD), and her OFC 47.2 cm (–1.9 SD). Physical examination revealed triangular face with borderline prominent forehead, depressed eyes, micrognathia, low-set and posteriorly rotated ears, and irregular teeth (Fig. 1A), together with bilateral short 5th fingers. Thus, in conjunction with oligohydramnios, feeding difficulty, and hearing impairment, she was suspected as having Silver-Russell syndrome (SRS) or some SRS-related disorder [6, 9], although she lacked relative macrocephaly at birth and hemihypoplasia. Endocrine and roentgenographic studies for short stature showed no abnormal findings. Her mental development was apparently normal.

She was placed on GH therapy for children who were born small for gestational age and manifested persistent short stature (Fig. 1B). GH dosage was increased from 0.23 mg/kg/week to 0.36 mg/kg/week, but statural response to GH therapy remained poor. Rather, since bone age advanced faster than her chronological age, her height for bone age was decreased from ~ –1.5 SD to below –3 SD. During the GH treatment, serum IGF-I values remained around +1 SD for her age (Fig. 1C). At 9 5/12 years of age, she exhibited breast development (Tanner stage 2). With pubertal development, her blood HbA1c level, though it remained 5.5–6.0% in childhood, gradually increased to 7.0% at 10 1/12 years of age, despite discontinuation of GH therapy at 9 11/12 years of age (Fig. 1D). An oral glucose tolerance test (O-GTT) at that time indicated glucose intolerance and markedly high serum insulin values (Fig. 1E). The blood HbA1c level further increased to 9.2% at 10 6/12 years of age (Fig. 1D), and continuous glucose monitoring (CGM) for two days performed at that time revealed overt hyperglycemia in the daytime and mild hypoglycemia in the nighttime (Fig. 1F). An insulin receptor antibody was negative. She was diagnosed with IRDM, and was treated with metformin (500→1,000 mg/day) and canagliflozin (an SGLT2 inhibitor) (33→75 mg/day). The therapy successfully reduced the blood HbA1c level around 7%, despite further pubertal progression (Fig. 1D). At 11 10/12 years of age, while an O-GTT still revealed a diabetic pattern of blood glucose levels with markedly high serum insulin values (Fig. 1E), CGM for two days showed fairly stable glucose levels without severe daytime hyperglycemia and mild nighttime hypoglycemia (Fig. 1F). On the last examination at 12 1/12 years of age, she enjoyed her school life without a hyperglycemic or hypoglycemic episode.

After the identification of a pathogenic *PIK3R1* variant, detailed clinical assessment was carried out, revealing four of the five salient features of SHORT syndrome, as well as multiple features frequently reported in SHORT syndrome (Table 1). Rieger anomaly was excluded by ophthalmologic examination, and she had no episode of recurrent infections.

Molecular Studies

To reveal an underlying (epi)genetic factor, we performed molecular studies using leukocyte gDNA samples of the patient and the parents. This study was approved by the Institutional Review Board Committee at Hamamatsu University School of Medicine (91-002), and performed after obtaining written informed consent. We first examined SRS-related underlying factors. The methods utilized in this study were as described previously [14]. Array comparative genomic hybridization using a catalog human array (1 × 1M format, ID G4447A) (Agilent Technologies, CA, USA) showed neither pathogenic nor significance-unknown copy-number variant. Pyrosequencing-based methylation analysis indicated no abnormal methylation pattern for SRS-related differentially methylated regions (DMRs) including *H19/IGF2*:IG-DMR and *KCNQ1OT1*:TSS-DMR on chromosome 11, *MEST*:alt-TSS-DMR and *PEG10*:TSS-DMR on chromosome 7, *MEG3/DLK1*:IG-DMR and *MEG3*:TSS-DMR on chromosome 14, *GNAS A/B*:TSS-DMR on chromosome 20, and *ZNF597*:DMR on chromosome 16.

We next performed whole exome sequencing (WES), using SureSelect Human All Exon V6 (Agilent Technologies). Captured libraries were sequenced using NextSeq 500 (Illumina, San Diego, CA, USA) with 150 bp paired-end reads. Exome data processing, variant calling, and variant annotation were carried out as described previously [15], with Human GRCh37 (UCSC Genome Browser; http://genome.ucsc.edu/) as the reference genome. Consequently, we revealed a *de novo* heterozygous

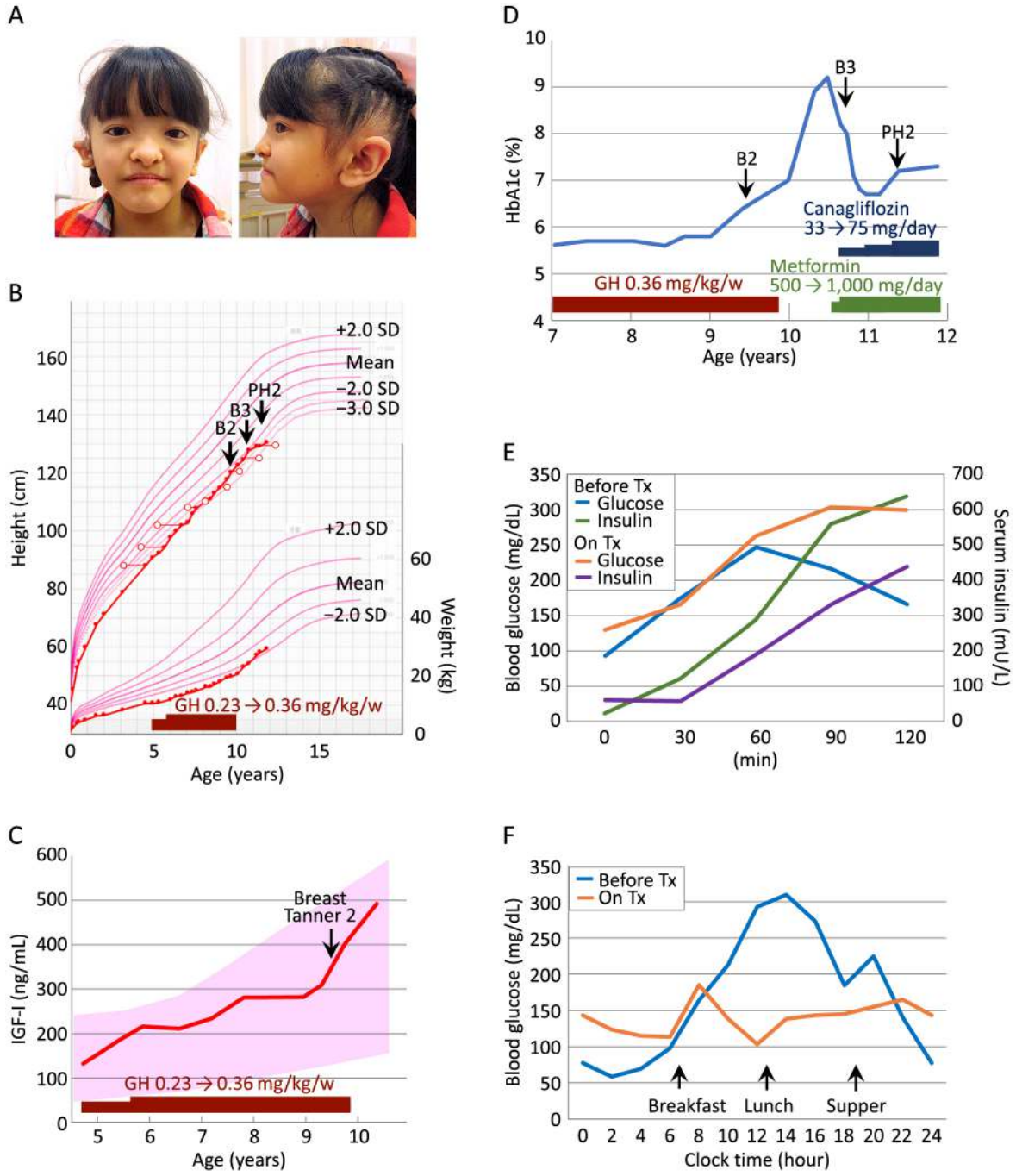

Fig. 1 Clinical findings of this patient

A. Facial pictures at 10 years of age.

B. Growth chart plotted on the standard growth curves of Japanese girls.

C. Serum IGF-I values during GH treatment. Pink background indicates the reference range of serum IGF-I in Japanese girls.

D. Change in blood HbA1c value and therapeutic interventions.

E. The results of oral glucose tolerance tests before (at 10 1/12 years of age) and during (at 11 10/12 years of age) metformin and canagliflozin treatment.

F. Circadian blood glucose patterns before (at 10 6/12 years of age) and during (at 11 10/12 years of age) metformin and canagliflozin treatment (average values of two days).

missense variant of *PIK3R1* (NM_181523.3:c.1945C>T:p.(Arg649Trp)) which was confirmed by Sanger sequencing (Fig. 2). This variant was completely absent from three representative public databases and in-house database, and was assessed as highly pathogenic by four different *in silico* predictions. According to the

Table 1 Clinical findings in patients with SHORT syndrome caused by *PIK3R1* pathogenic variants

	This patient	Reported patients	References
Sex	Female	Male:Female = 20:21	2, 10, 11, 13
Present age or age at description (year)	11 2/12	14 (0 ~ 79)	2–5, 10–13
<Main features of SHORT syndrome>			
Short stature (<–2 SD)	+	71.1% (27/38)[c]	2, 10, 11, 13
Hyperextensibility or hernia	+	32.2% (10/30)[c]	2, 10, 13
Ocular depression	+	100% (30/30)[c]	2, 10, 13
Rieger anomaly	–	42.9% (15/35)[c]	2, 10, 13
Teething delay	+	100% (21/21)[c]	2, 10
<Other findings frequently reported in SHORT syndrome>			
Intrauterine growth retardation[a]	+	73.5% (25/34)[c]	2, 10–13
Triangular face	+	100% (33/33)[c]	2, 10, 13
Prominent forehead	+	97.1% (33/34)[c]	2, 10, 13
Glaucoma	+	10.0% (1/10)[c]	5, 10, 12
Myopia	+	25.0% (2/8)[c]	5, 10
Hypoplastic ala nasi	+	96.8% (30/31)[c]	2, 10
Micrognathia	+	96.9% (31/32)[c]	2, 10, 13
Low-set ears	+	90.9% (30/33)[c]	2, 10, 13
Hearing loss	+	42.9% (3/7)[c]	5, 10
Thin, wrinkled skin	–	74.1% (20/27)[c]	2, 10
Delayed bone age	–	70.0% (7/10)[c]	3, 5, 10, 13
Developmental/speech delay	–	53.6% (15/28)[c]	2, 10
Lipodystrophy	+[b]	90.3% (28/31)[c]	2, 10, 13
Ovarian cysts	–	100% (4/4)[c]	3
Recurrent infections	–	33.3% (2/6)[c]	3

[a] Birth length and/or birth weight below –2 SD or 3rd percentile for gestational age.
[b] Lipodystrophy is clinically evident, although magnetic resonance imaging and computed tomography were not obtained because of the risk to damage the cochlear implant which is difficult to remove and to install.
[c] The denominators indicate the number of patients examined for the presence or absence of each feature, and the numerators represent the number of patients assessed to be positive for that feature.

ACMG Standards and Guidelines [16], this variant was evaluated as "pathogenic" (positive for PS1, PS2, PS3, PM1, PM2, PP2, PP3, and PP4). No other rare (minor allele frequency, ≤0.01) pathogenic or likely pathogenic variant was identified, under the assumption of Mendelian inheritance with complete penetrance by the trio analysis.

Discussion

We identified a pathogenic variant of *PIK3R1* in a girl who was initially suspected to have SRS or some SRS-related disorder. *PIK3R1* is the sole known causative gene for SHORT syndrome, and the p.(Arg649Trp) variant has been identified most frequently in SHORT syndrome [3-5, 10-13]. These findings indicate that this girl had molecularly confirmed SHORT syndrome, an SRS-related disorder [6].

This girl had IRDM. Notably, her IRDM, though it remained clinically unrecognizable in childhood despite GH therapy, developed with puberty and worsened despite the cessation of GH treatment. In this regard, several findings are noteworthy: (1) PIK3R1 is involved in the INSR signaling, and *PIK3R1* pathogenic variants including p.Arg649Trp compromise the PI3K-AKT signal transduction and glucose intake in skin fibroblasts derived from patients [3, 4]; (2) of 24 previously reported patients with molecularly confirmed SHORT syndrome, who were identified by a PubMed search up to April 2020 using SHORT syndrome and/or *PIK3R1* as the key word, the development of IRDM has been described in 10 of 15 GH-untreated patients aged 12–79 years but in none of three GH-treated patients aged 7–10 years and six GH-untreated patients aged 0–4 years (Table 2) [3-5, 10-13]; and (3) to our knowledge, while only a single boy with clinically diagnosed (not molecularly confirmed) SHORT syndrome developed IRDM after 25 months of GH therapy which was started at 11.5 years of age with a dosage of 0.5 U (~0.175 mg)/kg/week, his

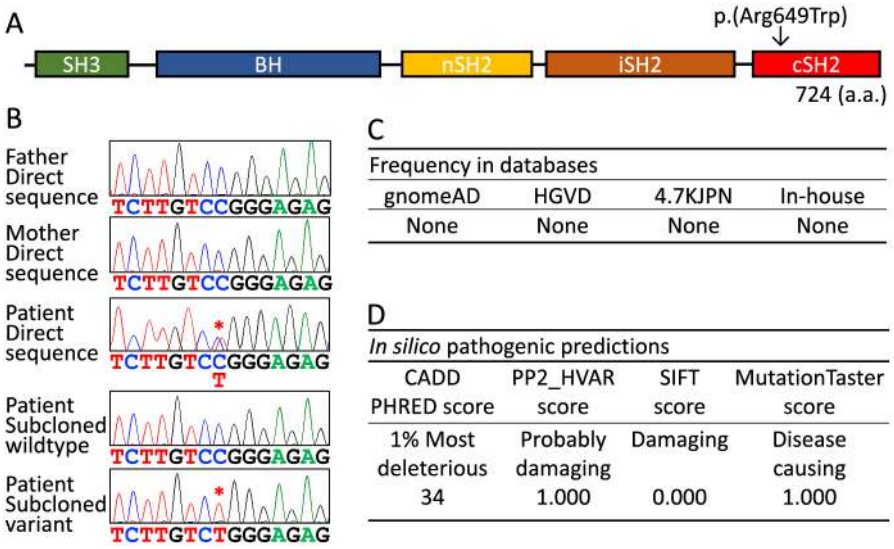

Fig. 2 *PI3KR1* variant identified in this patient

A. Structure of the PI3K protein and the position of the p.(Arg649Trp) variant. The PI3K protein contains SH3 (SRC homology 3 domain), BH (breakpoint cluster region homology), and three SH2 (SRC homology 2 domain) domains.

B. Electrochromatograms showing a *de novo* c.1945C>T substitution (marked with red asterisks). The primers utilized are: forward, 5'-GTCTGACTGGCTTGGTAGGG-3'; and reverse, 5'-AAATCTTTGCCCCCAAAACT-3'.

C. Absence of NM_181523.3:c.1945C>T:p.(Arg649Trp) in the public and in-house databases. (1) gnomAD (Genome Aggregation Database), http://gnomad.broadinstitute.org/; (2) HGVD (Human Genetic Variation Database), http://www.hgvd.genome.med.kyoto-u.ac.jp/; and (3) 4.7KJPN (Whole-genome sequences of 4,773 healthy Japanese individuals and construction of the highly accurate Japanese population reference panel), https://jmorp.megabank.tohoku.ac.jp/.

D. High pathogenicity of this variant. (1) CADD (Combined Annotation–Dependent Depletion), http://cadd.gs.washington.edu/ score; PHRED scores of >10–20 are regarded as deleterious, and those of >20 indicates the 1% most deleterious; (2) Polyphen-2 Hum Var, http://genetics.bwh.harvard.edu/pph2/; HumVar scores range from 0.000 (most probably benign) to 1.000 (most probably damaging); (3) SIFT (Sorting Intolerant From Tolerant), http://sift.jcvi.org/; scores of ≤0.05 and those >0.05 are assessed as damaging and tolerated, respectively; and (4) MutationTaster, http://www.mutationtaster.org/ (MutationTaster2, GRCh37/Ensembl 69); alterations are classified as disease causing or polymorphisms.

Table 2 Frequency of IRDM in 24 patients with molecularly confirmed SHORT syndrome

	Frequency	Reported age (year)	References
GH therapy (+)	0/3 (0.0%)	7–10	3, 5
GH therapy (–)	10/21 (47.6%)	0–79	3–5, 10–13
Infancy ~ childhood	0/6 (0.0%)	0–4	3, 5, 10, 13
Puberty ~ adulthood	10/15 (66.7%)[a]	12–79	3–5, 11–13

Tanner pubertal stage has not been reported in most patients.

[a] The age of IRDM onset has been described as 12, 13, 16, and 21 years in four patients and in adulthood in the remaining six patients.

pubertal stage has rapidly progressed from Tanner stage 1 to stage 4 during the 25 months [7]. These findings, in conjunction with the clinical course of this girl, suggest that *PIK3R1* pathogenic variants constitute an underlying factor for insulin resistance, and that pubertal development associated with physical and endocrinological changes [17] and/or advanced age indicative of a long-term exposure to insulin resistance, rather than GH treatment, is the major factor(s) facilitating the development of IRDM. Such a plausible diabetogenic effect of pubertal development and/or advanced age may also be operating in the occurrence of other types of DM, such as maturity onset diabetes of the young and 6q24-related DM, in puberty to adulthood [18, 19].

This study would provide useful information on the management of IRDM in SHORT syndrome. First, she had overt diurnal hyperglycemia and mild nocturnal hypoglycemia which would reflect postprandial hyperglycemia and fasting hypoglycemia. Since such a circadian blood glucose pattern has also been observed in

patients with heterozygous *INSR* pathogenic variants [20], it would be characteristic of heterozygous defects in the INSR signal transduction. Thus, small frequent diets and protein-rich evening meals may serve to ameliorate the severe circadian fluctuation of blood glucose in patients with *PIK3R1* pathogenic variants, as reported in those with *INSR* pathogenic variants [21]. Second, IRDM of this girl was fairly well controlled by metformin and canagliflozin (an SGLT2 inhibitor). In particular, an SGLT2 inhibitor may serve as an effective and easy-to-use drug because of the very low risk to cause hypoglycemia [22], although long-term effectiveness and safety remain to be clarified. Indeed, while the O-GTT data at 11 10/12 years of age indicates that the SGLT2 inhibitor is incapable of preventing the occurrence of overt hyperglycemia and resultant severe hyperinsulinemia after a certain amount of acute glucose load, the CGM data at that time would imply that the SGLT2 inhibitor mitigates not only overt diurnal hyperglycemia after ordinary food intake by reducing the renal threshold for glucose excretion and increasing the urine glucose excretion [22] but also mild nocturnal hypoglycemia probably because of the attenuated hyperinsulinemia in the absence of overt hyperglycemia. In this regard, Hamaguchi *et al.* [13] have also reported a beneficial effect of an SGLT2 inhibitor on IRDM in an adult female with molecularly confirmed SHORT syndrome.

Several findings are also worth pointing out in this study. First, she exhibited SRS-like features such as oligohydramnios, feeding difficulty, and hearing impairment [6, 9], in addition to growth failure and craniofacial features. In this regard, oligohydramnios may be due to placental hypoplasia as observed in SRS [9], because *PIK3R1* is expressed in the placenta (GeneCards: https://www.genecards.org). Second, despite *PIK3R1* being involved in immune-related signal transductions [1, 23], she had no episode of recurrent infections. This would not be surprising, because recurrent infections are rather infrequent in patients with SHORT syndrome (Table 1). Lastly, GH therapy apparently had no beneficial effect on growth. This would also be explained by the *PIK3R1* variant, because *PIK3R1* is known to mediates GHR and IGF1R signalings [24, 25]. In this context, serum IGF-I values remained around +1 SD during GH treatment in this girl. This would suggest that the *PIK3R1* variant has compromised IGF1R signaling more severely than GHR signaling.

In summary, clinical findings of this girl and those of previously reported patients with molecularly confirmed SHORT syndrome imply that pubertal development and/or advanced age rather than GH therapy is the major factor(s) facilitating the development of IRDM. However, it is recommended to avoid GH therapy in SHORT syndrome [3, 6], because of the potential to promote the development of DM and the poor statural response. Furthermore, this study suggests the usefulness of an SGLT2 inhibitor in the management of IRDM. Further studies will provide useful implications for the development and management of IRDM in SHORT syndrome.

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Disclosure

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