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CASE REPORT

Treatment of a case of severe insulin resistance as a result of a *PIK3R1* mutation with a sodium–glucose cotransporter 2 inhibitor

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Keywords
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ABSTRACT

A Japanese woman aged in her late 30s with severe insulin resistance and bodily features including a triangular face, prominent forehead, small chin, large and low-set ears, and ocular depression was investigated. A similar phenotype was not observed in other family members with the exception of her son, suggesting that the condition was caused by a de novo mutation that was transmitted from mother to son. Exome analysis showed the presence in the proband and her son of a c.1945C>T mutation in *PIK3R1*, a common mutation associated with SHORT (short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Rieger anomaly, and teething delay) syndrome. Administration of a sodium–glucose cotransporter 2 inhibitor lowered the proband's hemoglobin A_{1c} level and allowed a reduction in her insulin dose without treatment-related adverse events including ketoacidosis, exaggerated loss of body mass or hypoglycemia. Sodium–glucose cotransporter 2 inhibitors might thus offer an additional option for the treatment of genetic syndromes of severe insulin resistance.

INTRODUCTION

Mutations in genes related to insulin action, including those encoding the insulin receptor, a regulatory subunit of phosphatidylinositol 3-kinase (p85α), and Akt2, cause genetic syndromes of severe insulin resistance.[1–5] Mutations in the gene for p85α (*PIK3R1*) give rise to severe insulin resistance and characteristic bodily manifestations, including short stature, joint hyperextensibility, deformity of the anterior eye chamber, atrophy of the iris stroma (Rieger anomaly) and a recognizable facial gestalt (triangular face, prominent forehead, small chin and ocular depression).[3–7] SHORT syndrome is characterized by short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Rieger anomaly, and teething delay, and mutations of *PIK3R1* were first identified in individuals with this condition in 2013.[3–5] More than 30 families with this syndrome and mutations of *PIK3R1*, all of which (with one African exception) are Caucasian, have been reported to date.[3–7]

Here, we report the first case of SHORT syndrome caused by a mutation of *PIK3R1* in a Japanese person. We also report the investigative administration of a sodium–glucose cotransporter 2 (SGLT-2) inhibitor in this case.

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CASE REPORT

The study was approved by the ethics committee of Kobe University Graduate School of Medicine (approval no. 160099), and the proband provided written consent to publish data for her case and that of her son. The proband, a Japanese woman aged in her late 30s, was born with a birthweight of 1,800 g at 36 weeks-of-gestation, and had started insulin for diabetes at the age of 21 years. Her clinical manifestations in her early 20s were reported previously.[8] Despite the absence of an apparent cause of her insulin resistance, she had previously administered >200 U of insulin per day, suggestive of a genetic etiology. Her height was 143 cm, bodyweight 38 kg and body mass index 18.6 kg/m^2. Her visceral and subcutaneous fat areas assessed by abdominal magnetic resonance imaging were 57 and 95 cm^2, respectively, which were comparable with those observed in non-obese, young, normoglycemic individuals.[9] She had a triangular face, prominent forehead, small chin, large and low-set ears, and ocular depression (Figure 1), but not hyperextensibility of the joints or Rieger anomaly. Her son, whose birthweight

Figure 1 | Photos of the (a,c,d) proband and (b,e,f) her son at (a) age 7 months, (b) 4 months, (c,d) late 30s and (e,f) 3 years.

was 1,794 g at 34 weeks-of-gestation, had a small chin, large and low-set ears, hirsutism, and ocular depression (Figure 1). His serum insulin levels were suggestive of the presence of insulin resistance (Table S1). Given the absence of insulin-resistant diabetes or similar bodily characteristics in family members other than her son (Figure 2), we hypothesized that the proband's condition was caused by a de novo mutation that was transmitted to her son. Exome analysis of the proband, her parents and her son showed that she harbored 45,762 variants with allele frequencies of <0.0001 relative to data in the Exome Aggregation Consortium. A total of 219 of these variants were heterozygous and not present in her parents, 38 of the 219 variants were transmitted to her son and five of the 38 variants altered the amino acid sequence of the encoded proteins. One of the latter variants was c.1945C>T in *PIK3R1* (Figure 2), which had previously been identified in individuals with SHORT syndrome.[3–6]

Treatment

The proband administered >200 U of insulin daily during her late 20s. After the maximum daily dose of metformin was increased from 750 to 2,250 mg in May 2010 in Japan, she began high-dose metformin therapy. At the current presentation, she administered 2,250 mg of metformin and ~80 U of insulin daily (Figure 3). Her hemoglobin A_{1c} (HbA_{1c}) level did not fall below 7.0%, however. Given that SGLT-2 inhibitors lower blood glucose through a mechanism independent of insulin action, we hypothesized that such a drug might have a beneficial effect on the proband's glycemia. We initiated treatment with 5 mg of dapagliflozin per day. Within 3 months, her

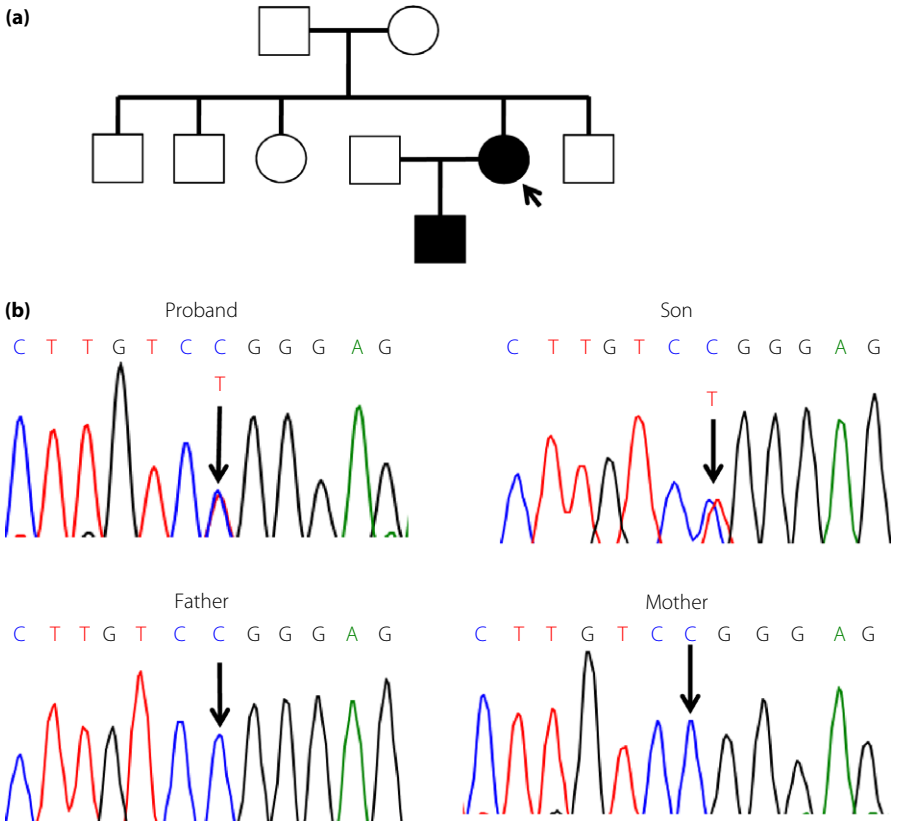

Figure 2 | (a) Family pedigree, with the arrow showing the proband, and (b) deoxyribonucleic acid sequencing electrophoretogram traces showing the position of the mutation in *PIK3R1*.

HbA_{1c} level had decreased from 7.5% to 6.5%, and her daily insulin dose had fallen to ~50 U (Figure 3). Five months after the initiation of dapagliflozin, she developed a common cold and subsequently manifested a transient elevation of her HbA_{1c} level. At 14 months, her HbA_{1c} level and daily insulin dose were 6.6% and 50 U, respectively. The proband's body mass declined by 2–3 kg during dapagliflozin treatment, an effect similar to that observed for this drug in the treatment of type 2 diabetes.

Serum levels of total ketone bodies were not increased during dapagliflozin therapy (Table S2), and hypoglycemia, urinary tract or genital infection, polyuria and thirst were not reported. The hematocrit before and 12 months after the initiation of treatment was 35.5 and 42.0%, respectively.

DISCUSSION

We report the first Japanese case of severe insulin resistance caused by a mutation in *PIK3R1*. The sporadic insulin resistance syndrome was transmitted from the proband to her son, and exome analysis allowed us to identify the responsible mutation. In retrospect, the facial gestalt of the proband and her son was similar to that described for individuals with mutations in *PIK3R1*.[3–7] This case thus underscores the importance of recognition of facial gestalt in suspicion of this syndrome.

Despite the administration of a large amount of insulin and oral hypoglycemic agents, it is often difficult to achieve desirable glycemic control in individuals with genetic syndromes of severe insulin resistance.[1] SGLT-2 inhibitors might provide an alternative treatment option for such syndromes. Indeed, a case of lipodystrophic diabetes treated successfully with an SGLT-2 inhibitor was recently reported.[10] Although fat tissue was not severely decreased in the present case, SHORT syndrome is sometimes associated with lipodystrophy.[3–7] Metreleptin, which ameliorates various metabolic disorders of lipodystrophy,[11] might be a useful option for SHORT syndrome with lipodystrophy. Along with lean body composition, the secession or the reduction of insulin are risk factors for SGLT-2 inhibitor-related ketoacidosis.[12] It is important to evaluate whether insulin is adequately supplemented to prevent exaggerated catabolism during the treatment with SGLT-2 inhibitors. In the present case, an increase in the serum ketone bodies was not observed during treatment. Further studies are warranted to confirm the clinical benefits of SGLT-2 inhibitors for treatment of genetic syndromes of severe insulin resistance.

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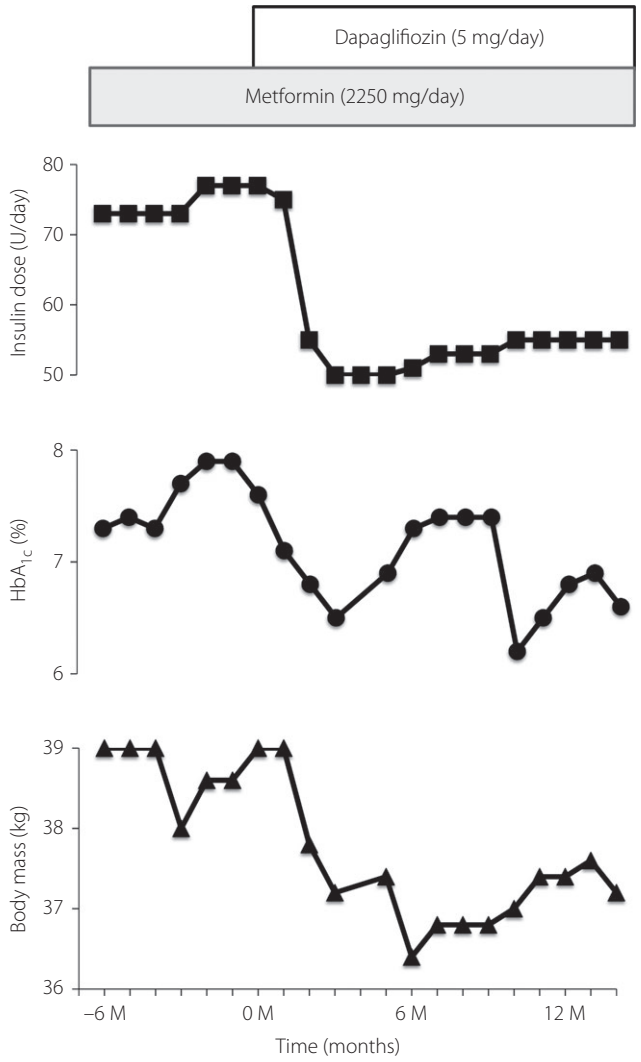

Figure 3 | Clinical course for treatment of the proband with dapagliflozin. HbA_{1c}, hemoglobin A_{1c}.

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DISCLOSURE

WO has received a research grant, and WO and YH have received lecture fees from Astra Zeneca. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Plasma glucose and serum insulin levels of the proband's son
Table S2 | Fasting serum levels of ketone bodies during treatment