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CASE REPORT

# Novel *PIK3R1* mutation of SHORT syndrome: A case report with a 6-month follow up

Xiaofei Yin[1,2,3,4], Jidong Liu[1,2,3,4], Ruiying Feng[1,2,3,4], Mingyue Xu[1,2,3,4], Jinbo Liu[1,2,3,4]*

[1]Department of Endocrinology, Cheeloo College of Medicine, Qilu Hospital, Shandong University, Jinan, China, [2]Institute of Endocrine and Metabolic Diseases, Shandong University, Jinan, China, [3]Key Laboratory of Endocrine and Metabolic Diseases, Shandong Province Medicine & Health, Jinan, China, and [4]Jinan Clinical Research Center for Endocrine and Metabolic Diseases, Jinan, China

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***Correspondence**
Jinbo Liu
Tel.: +86-185-6008-5019
Fax: +86-531-8216-9323
E-mail address:
jinboliu@sdu.edu.cn

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## ABSTRACT

SHORT syndrome (short stature, hyperextensibility, ocular depression [deeply set eyes], Rieger anomaly and teething delay) is very rare, with a few cases reported in the literature. We report a case of SHORT syndrome with a novel *PIK3R1* mutation (c.2008delT) and complicated with severe insulin resistance. Although no treatment guidelines are available to relieve insulin resistance in SHORT syndrome, our treatment plans, including lifestyle intervention combined with metformin and pioglitazone, were carried out for this patient. After the intervention, insulin resistance and hyperinsulinemia in this patient were significantly decreased during a 6-month follow up, which showed the effect of our therapeutic strategies.

## INTRODUCTION

SHORT syndrome is an autosomal dominant genetic disorder and an acronym for several of the most striking clinical features of the original reported cases: short stature, hyperextensibility, ocular depression (deeply set eyes), Rieger anomaly and teething delay. However, it is now recognized that these five characteristics are neither indispensable for the diagnosis of SHORT syndrome nor necessarily the most common characteristics of SHORT syndrome.

SHORT syndrome is very rare, with a few cases reported in the literature, and mutations of the *PIK3R1* gene are seen in approximately 90% of patients. The *PIK3R1* gene encodes the phosphatidylinositol 3-kinase (PI3K) regulatory subunit p85α, which can bind to PI3K catalytic subunit p110α, and then the active PI3K/protein kinase B/mammalian target of rapamycin pathway, which plays an important role in chemical signal transduction within cells, including cell growth, protein synthesis and insulin resistance[1-4].

Here, we identified a novel *PIK3R1* mutation (c.2008delT) in a patient, which then established the diagnosis of SHORT syndrome. The patient was complicated with severe insulin resistance. Treatment plans, including lifestyle intervention combined with metformin and pioglitazone, were carried out. After a 6-month follow up, the insulin resistance was evaluated again. Written, informed consent from this patient was obtained, and the present study was approved by the ethics committee of Qilu Hospital of Shandong University.

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## CASE REPORT

The patient was a boy aged 11 years and 2 months, with chief complaints of blackened skin color on the neck over the past 10 years. Physical examination was characterized by height of 160 cm, weight of 64 kg and body mass index of 25.0 kg/m$^2$. Acanthosis nigricans was found on the neck, armpit, groin and other skin folds. Clinical features of SHORT syndrome, including hyperextensibility, ocular depression, Rieger anomaly and teething delay, did not appear in the patient. Fasting plasma insulin and glucose were tested, and homeostasis model assessment of insulin resistance was 14.5 (Table 1). The 75-g oral glucose tolerance test (OGTT) showed that the patient had normal glucose tolerance, but hyperinsulinemia (Figure 1). These clinical manifestations suggested that the patient might be diagnosed with type A insulin resistance syndrome. Whole exome sequencing was carried out, with a mutation of the *PIK3R1* gene (c.2008delT, p.C670Vfs*3) identified (Figure 2). This mutation was a frameshift mutation, which caused the premature termination of protein synthesis (Figure 3a). Homology models of the wild-type *PIK3R1* and c.2008delT mutant *PIK3R1* are presented in Figure 3b. Unfortunately, the patient was adopted, and we failed to obtain the family history of the

**Table 1** | Laboratory results of the patient

| Factor | Before treatment | 6 months after treatment | Reference range |
|---|---|---|---|
| Height (cm) | 160 | 165 | – |
| Weight (kg) | 64 | 64.1 | – |
| BMI (kg/m$^2$) | 25.00 | 23.54 | – |
| FBG (mg/dL) | 73 | 77 | 70–110 |
| Total cholesterol (mg/dL) | 139 | 130 | 108–232 |
| HDL-c (mg/dL) | 70 | 56 | 31–77 |
| LDL-c (mg/dL) | 56 | 53 | 39–130 |
| Triglyceride (mg/dL) | 44 | 54 | 27–151 |
| Insulin (mU/L) | 80.02 | 21.79 | 3–25 |
| C-peptide (ng/mL) | 3.29 | 1.37 | 0.81–3.85 |
| HbA1c (mmol/mol) | 41 | 34 | 20–42 |
| Calcium (mEq/mL) | 2.56 | 2.44 | 2.11–2.52 |
| phosphorous (mEq/mL) | 1.94 | 1.55 | 0.6–1.6 |
| HOMA-IR | 14.47 | 4.14 | 0.5–1.4 |

BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-c, low-density lipoprotein cholesterol.

patient. The other major insulin resistance-related genes were also checked in this patient. No mutation was identified in the insulin gene. One additional insulin receptor missense mutation (c.2666G>A) was detected. However, this substitution was predicted as 'tolerated' by sift and 'benign' by polyphen-2, respectively (Table S1). Additionally, echocardiography found no pulmonary stenosis or other congenital heart disease. Hearing tests suggested mild hearing impairment in the left ear. Ophthalmological examination showed no dysplasia, but indicated decreased vision and increased intraocular pressure in the right eye. Dual-energy X-ray absorptiometry for the assessment of body composition was carried out. The patient's body fat percentage, visceral fat area and lean/height$^2$ were 28.5%, 47.3 cm$^2$ and 14.5, respectively. Therefore, the patient was finally diagnosed with SHORT syndrome.

This patient was complicated with severe insulin resistance, and lifestyle interventions as an initial management were carried out. Meanwhile, metformin (1,000 mg/day) and pioglitazone (30 mg/day) were prescribed. After 6-month follow up, his body mass index, glycated hemoglobin and homeostasis model assessment of insulin resistance were 23.54 kg/m$^2$, 5.3% and 4.1, respectively (Table 1). OGTT was carried out again, and showed a significant decrease of hyperinsulinemia (Figure 1).

## DISCUSSION

In the present study, we identified a novel *PIK3R1* mutation in a patient with SHORT syndrome. This patient was complicated with severe insulin resistance, and lifestyle intervention

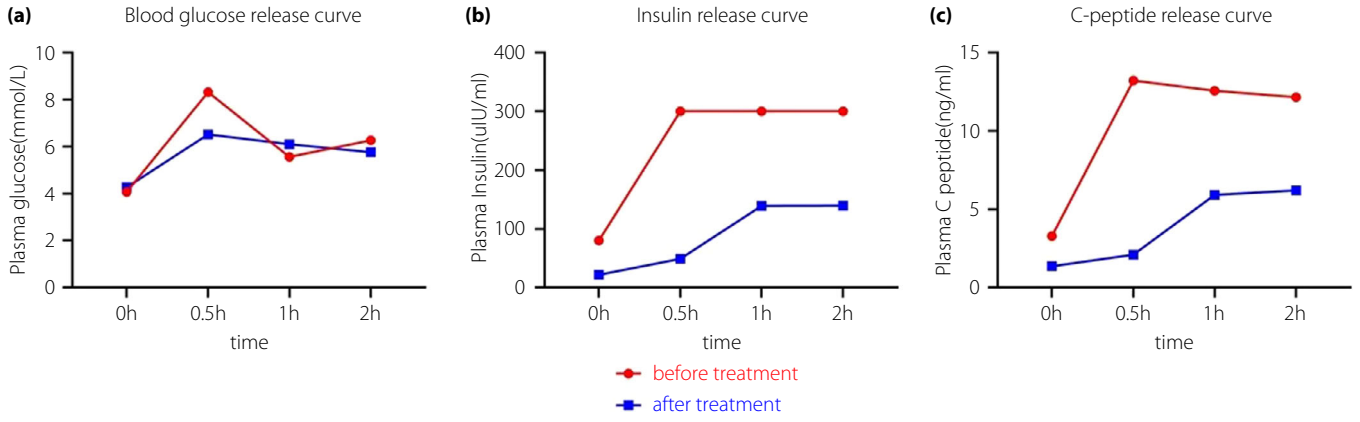


**Figure 1** | Results of a 75-g oral glucose tolerance test in the patient with SHORT (short stature, hyperextensibility, ocular depression [deeply set eyes], Rieger anomaly and teething delay) syndrome.

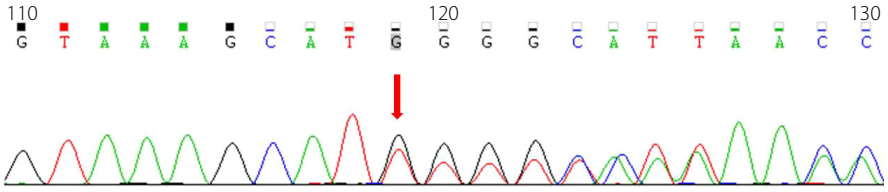


**Figure 2** | Sanger sequencing showed a heterozygous deletion mutation of the *PIK3R1* gene:c.2008delT (p.C670Vfs*3) in the patient.

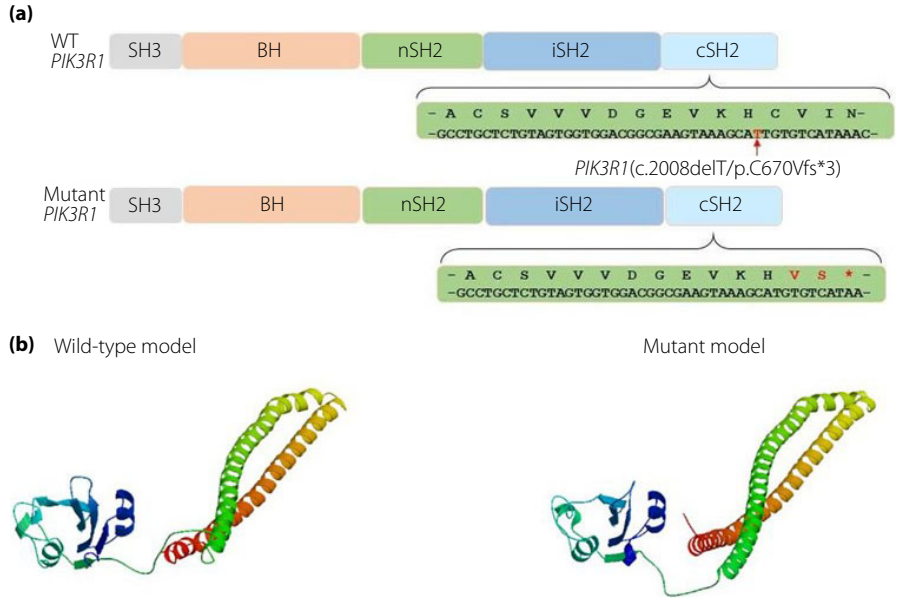


**Figure 3** | The *PIK3R1* variant identified in this patient.

combined with metformin and pioglitazone were carried out. After a 6-month follow up, insulin resistance was clearly relieved.

The diagnosis of SHORT syndrome is established in a proband with phenotypic and laboratory findings, and a heterozygous pathogenic variant in *PIK3R1* identified by molecular genetic testing. At the beginning, as there was a lack of the typical facial features of SHORT syndrome in the present patient, we took it for granted that this patient might have type A insulin resistance syndrome. After this patient was diagnosed with SHORT syndrome, some combination was evaluated. The 75-g OGTT showed severe insulin resistance in this patient with normal glucose tolerance. Sensorineural hearing loss is one of the clinical features of SHORT syndrome, and mild hearing impairment in the left ear was diagnosed in this patient. An ophthalmological examination suggested decreased vision and increased intraocular pressure in the right eye. Glaucoma, which has been reported in individuals with SHORT syndrome, is considered the result of poorly developed aqueous humor drainage structures of the anterior chamber of the eye.

*PIK3R1* is a well-known gene causing SHORT syndrome. So far, there have been 11 pathogenic variants of *PIK3R1* identified from affected individuals (Table 2)[1,2,5–8]. Whole exome sequencing of this patient identified a novel mutation of *PIK3R1* (c.2008delT, p.C670Vfs*3). This mutation is a frameshift mutation and has not been reported in the previous literature. This variation results in the change of the codon reading frame of the amino acid triplets encoding the protein and the premature termination of protein synthesis. The mutation has not been detected in the normal population database.

**Table 2** | *PI3KR1* pathogenic variants identified in SHORT syndrome

| DNA nucleotide change | Amino acid change | References |
|---|---|---|
| c.1615_1617del | p.Ile539del | 1 |
| c.1945C>T | p.Arg649Trp | 5 |
| c.1956dupT | p.Lys653* | 6 |
| c.1929_1933delTGGCA | p.Asp643Aspfs*8 | 7 |
| c.1465G>A | p.Glu489Lys | 1 |
| c.1943dupT | p.Arg649Profs*5 | 1 |
| c.1892G>A | p.Arg631Gln | 1 |
| c.1906_1907insC | p.Asn636Thrfs*18 | 2 |
| c.1971T>G | p.Tyr657* | 2 |
| c.1906_1907delAA | p.Asn636ProfsTer17 | 6 |
| c.1960C>T | p. Gln654* | 8 |
| c.2008delT | p.C670Vfs*3 | |

SHORT syndrome is also characterized by insulin resistance and diabetes mellitus, due to the immediate post-receptor defects in insulin signaling. Downstream effects appear to be mediated by lower levels of phosphorylation of proteins in the protein kinase B and mammalian target of rapamycin signaling pathways[1,2,5]. Knock-in mice that are heterozygous for the *PIK3R1*$^{Arg649Trp}$ mutation, which is the most common mutation observed in patients with SHORT syndrome, are associated with a reduced capacity of insulin to active PI3K in the liver, muscle and fat[4].

The patient was complicated with severe insulin resistance, but with normal glucose tolerance. There have been no widely accepted therapeutic plans for alleviating insulin resistance in patients with SHORT syndrome. Metformin inhibits hepatic glucose production and increases peripheral glucose uptake. Pioglitazone, as a peroxisome proliferator activated receptor γ

agonist, decreases insulin resistance in the liver and peripheral tissues. We speculated that these two groups of insulin sensitizers might be effective in SHORT syndrome. Thus, the combination of metformin (1,000 mg/day) and pioglitazone (30 mg/day) was prescribed for the present patient. After a 6-month follow up, body mass index, homeostasis model assessment of insulin resistance and hyperinsulinemia were significantly decreased. The present results suggested that lifestyle intervention combined with metformin and pioglitazone might serve as effective measures for insulin resistance in patients with SHORT syndrome.

One study showed that metformin could exacerbate insulin resistance in a patient with SHORT syndrome. After 4 days of metformin treatment (850 mg twice a day), repeated OGTT showed dramatic worsening of glucose tolerance[9]. Therefore, the present report was limited to the short-term follow up. Our study showed that the combination of metformin and pioglitazone exerted a therapeutic effect in this patient with SHORT syndrome. Further studies will be carried out to determine the effects of metformin and pioglitazone, respectively.

In conclusion, we identified a novel heterozygous mutation of the *PIK3R1* gene in a patient with SHORT syndrome. The patient presented severe insulin resistance without typical clinical signs of SHORT syndrome. Lifestyle intervention combined with metformin and pioglitazone as treatment plans were carried out for 6 months, insulin resistance in this patient was clearly relieved. Further studies with larger numbers of participants are necessary to confirm the therapeutic utility in SHORT syndrome.

## DISCLOSURE

The authors declare no conflict of interest.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Annotation and functional prediction of possibly pathogenic variants in the proband.

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