



Case Report

The first SHORT syndrome in a Taiwanese boy: A case report and review of the literature

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ABSTRACT

SHORT syndrome is a rare, multisystem disease named with the acronym arising from short stature, hyperextensibility of joints, ocular depression, Rieger anomaly, and teething delay. Metabolic anomalies such as insulin resistance and diabetes are also present. This disease is related to heterozygous variants in the *PIK3R1* and is inherited in an autosomal-dominant manner. In this case report, we present a Taiwanese boy with SHORT syndrome who had growth retardation and dysmorphic features, including a triangular face, prominent forehead, and small chin. We performed anthropometric and laboratory measurements and imaging examinations. We noted no insulin resistance or diabetes. We performed whole exome and Sanger sequencing and confirmed the underlying genetic variant, detecting a heterozygous variant of *PIK3R1* (NM_181523.3) (c.1945C > T). In a family survey, his parents indicated no similar clinical symptoms and no gene variant. This case is the first SHORT syndrome in Taiwan. Specific facial dysmorphisms of this case help us confirm the diagnosis with timely genetic testing and then we can provide appropriate management and proper care.

1. Introduction

SHORT syndrome is a rare, autosomal-dominant disease characterized by short stature, hyperextensibility of joints, ocular depression, Rieger anomaly, and teething delay [1]. The acronym SHORT was first used by Gorlin et al. (1975) [2]. Mild intrauterine growth restriction (IUGR), partial lipodystrophy, delayed bone age, hernias, and progeroid appearance could be found in SHORT syndrome [3,4]. Most patients with the disease have normal intelligence [4].

There are very few patients of SHORT syndrome in the world. No more than 50 cases have been reported currently [5]. SHORT syndrome is caused by multiple different variants of the *PIK3R1* gene, which is located in 5q13.1 and encodes phosphatidylinositol 3-kinase regulatory

subunit alpha. The variant of the *PIK3R1* would interfere the PI3K/AKT/mTOR pathway and influence cellular proliferation and growth. According to previous studies, the variants of the *PIK3R1* are the primary cause of SHORT syndrome [5–9].

Eleven variants of the *PIK3R1* are associated with this disease. Variants (*PIK3R1*, NM_181523.3) of c.1929_1933delTGGCA [11], c.1945C > T [7,13,], c.1615_1617delATT [10,13,], c.1465G > A [10], c.1906_1907insC [8], c.1971T>G [10], c.1956dupT [12], c.1943dupT [10], and c.1892G > A [10] are related to insulin resistance and lipodystrophy. We could find Rieger anomaly in patients with variants (*PIK3R1*, NM_181523.3) of c.1906_1907insC [8], c.1971T > G [9], and c.1945C > T [7,13,]. A patient with a *de novo* c.1960C > T variant (*PIK3R1*, NM_181523.3) could easily develop thyroid disease later in life [14].

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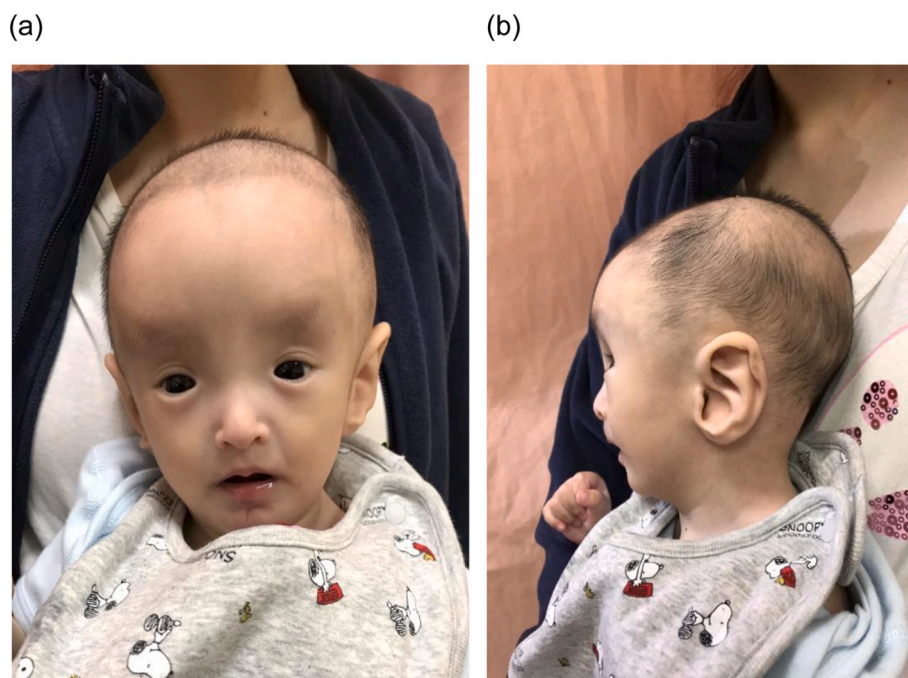


Fig. 1. (a) Facial dysmorphism of triangular face, high anterior hairline, prominent forehead, eyebrows broad and sparse, telecanthus, thin alae nasi, retrognathia and micrognathia with a dimple (b) large ears with overfolding of the superior part of the antihelix and deficiency of the earlobe. (long axis of left ear: 7.2 cm, right ear: 7.4 cm).

Furthermore, we should realize that the sample size of known patients is simply too small to make strong generalizations based on the data available. And we should need for longitudinal data over the lifespan.

The clinical criteria for the diagnosis and treatment of SHORT syndrome are undetermined. Further research is required because this disease affects multiple systems and the health of patients and their descendants. In this article, we present a case of a Taiwanese boy with complicated clinical manifestations. SHORT syndrome was finally diagnosed from a variant in the *PIK3R1*. We also review the literature on SHORT syndrome to help clarify the picture of this disease.

2. Case presentation

A 5-month-old male patient presented with IUGR and failure to thrive. The patient was referred from another hospital to our genetic outpatient department because the patient was suspected of having Silver–Russell syndrome or a related condition. His body length was 58 cm (<3rd percentile, Z-score: -3.74), his head circumference was 38.7 cm (<3rd percentile, Z-score: -3.20), and his body weight was 3.8 kg (<3rd percentile, Z-score: -5.87). His birth history showed gestational age at 39 weeks, his birth body weight was 2140 g (<3rd percentile, Z-score: -2.84) and small for his gestational age, his head circumference was 32.5 cm (3rd–15th percentile, Z-score: -1.54), his body length was 45 cm (<3rd percentile, Z-score: -2.58), and the patient was born by Cesarean section because of malpresentation. His non-fasting glucose level when birth was in normal range (glucose: 62 mg/dl, normal range: 40–120 mg/dl). Taiwanese newborn screening program for neonatal hypothyroidism had no specific finding (Thyrotropin: 8.2 μ U/ml, normal range: < 10 μ U/ml).

The patient appeared to have triangular face with a high anterior hairline, in addition to the prominent forehead. Furthermore, the eyebrows appeared to be particularly broad and sparse. The palpebral fissures also appeared relatively short, with the possibility of telecanthus. The ears also appeared relatively large, compared to the head overall (long axis of left ear: 7.2 cm, right ear: 7.4 cm). There was overfolding of the superior part of the antihelix and deficiency of the earlobe. Triangular face with thin alae nasi was also noted. There also appeared to be

Table 1
Typical features of SHORT syndrome in this patient.

Declaration of Competing Interest	Declaration of Competing Interest	Declaration of Competing Interest
SHORT acronym signs	S (short stature) < -2 SD	+
	Hyperextensibility of joints/ inguinal Hernia	–
	O (ocular depression)	+
	R (Rieger abnormality)	–
	T (Teething delay)	–
Facial dysmorphism	Triangular face	+
	Prominent forehead	+
	Hypoplastic or thin alae nasi	+
	Mild mid-face hypoplasia	+
	Small chin or micrognathia	+
	Thin lip and downturned mouth	+
	Large, low-set ears	+
	Progeroid face	+
Other signs	Anterior chamber of eye abnormalities	–
	Lipoatrophy	+
	Thin, wrinkled skin, and visible veins	+
	Glaucoma	–
	Insulin resistance	–
	Diabetes	–
	Intellectual deficiency	–
	Speech delay	–

Abbreviations: –, absence of a feature; +, presence of a feature.

retrognathia and micrognathia with a dimple (Fig. 1a and b).

We also noted a grade 2 systolic murmur, freely movable extremities, except for a mild limit in the range of motion in the bilateral hip joints, and a right undescended testis. A heart echocardiogram showed mild pulmonary stenosis (pressure gradient, 22 mmHg) with post-stenotic dilatation of the main pulmonary artery and atrial septal defect II (0.430–0.505 cm). X-rays of the chest, pelvis, and thoracic–lumbar spine showed no specific findings. Table 1 shows the typical features of SHORT syndrome in this patient.

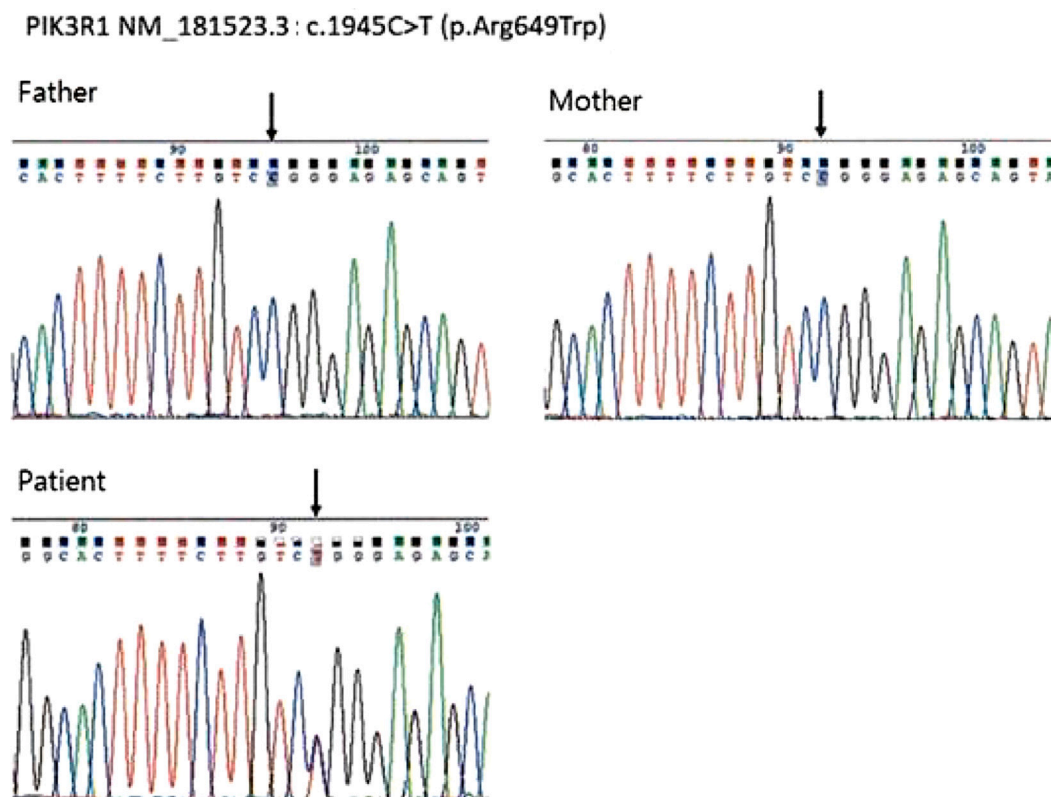


Fig. 2. Mutational profile of the patient and his parents by whole exome sequencing.

Table 2
Pathogenic *PIK3R1* (NM_181523.3) mutations and related phenotypes in SHORT syndrome.

DNA nucleotide change	Protein amino acid change	Related phenotype	References
c.1465G > A	p.Glu489Lys	S, O, R, T, IR, partial lipoatrophy	[10]
c.1615_1617delATT	p.Ile539del	S, O, T, IR, partial lipoatrophy	[10,13]
c.1892G > A	p.Arg631Gln	S, IR, partial lipoatrophy	[10]
c.1906_1907delAA	p.Asn636ProfsTer17	S, R	[12]
c.1906_1907insC	p.Asn636Thrfs*18	S, R, T, IR, partial lipoatrophy	[8]
c.1929_1933delTGGCA	p.Asp643Aspfs*8	S, H, O, R, IR, partial lipoatrophy	[11]
c.1943dupT	p.Arg649Profs*5	S, O, partial lipoatrophy	[10]
c.1945C > T	p.Arg649Trp	S, O, R, T, lipoatrophy	[7,13]
c.1971 T > G	p.Tyr657Ter	S, H, O, T, partial lipoatrophy	[10]
c.1956dupT	p.Lys653	S, O, partial lipoatrophy	[12]
c.1960C > T	p.Gln654Ter	S, O, T, thyroid disease	[14]

Abbreviations: H, hyperextensibility of joints; IR, insulin resistance; O, ocular depression; R, Rieger anomaly; S, Short stature; T, teething delay.

According to the DNA analysis of the proband, the heterozygous genetic variant c.1945C > T in the *PIK3R1* gene (NM_181523.3) lead to a variant in p.Arg649Trp (NP_852664.1) (Fig. 2). This variant showed as pathogenic in the American College of Medical Genetics database. The genetic variant of c.1945C > T was *de novo*. No parents carried the variant.

3. Discussion

The name “SHORT syndrome” does not fully describe all possible phenotypes. Most patients are identified by genetic testing. To date, fewer than 50 cases have been reported in the literature. According to a previous meta-analysis of SHORT syndrome in 2016 [5], nearly 80% of patients have short stature, a small chin, and mid-face hypoplasia. More than 90% of patients have a small chin and low-set ears. Nearly all patients have ocular depression, teething delay, and a triangular face and deep-set eyes. Nevertheless, fewer than 50% of patients have the hyperextensibility of joints and Rieger sign. Our patient has a prominent forehead, deep-set eyes, mild mid-face hypoplasia, lipoatrophy, prominent and floppy ears, and a small and pointed chin with a dimple. His facial dysmorphism is in accordance with previously reported features of SHORT syndrome [6,13].

The variants of the *PIK3R1* (5q13.1) cause SHORT syndrome. This gene encodes phosphatidylinositol 3-kinase regulatory subunit p85 α , and this protein plays an important role in chemical signal transduction within cells, the control of cell growth and proliferation, protein synthesis, and the maturation of adipocytes [6]. This gene variant would affect the PI3K/AKT/mTOR pathway. Many research teams have reported that a variant in the *PIK3R1* is the primary cause of SHORT syndrome independently [7–10]. A total of 11 different variants in the *PIK3R1* have been reported to cause SHORT syndrome (Table 2). The c.1945C > T missense variant (*PIK3R1*, NM_181523.3) is the most common [7,13]. Other variants (*PIK3R1*, NM_181523.3), such as missense (c.1465G > A and c.1892G > A), deletion

(c.1615_1617delATT), truncation (c.1971T > G and c.1960C > T), and frame-shift insertions (c.1906_1907insC, c.1929_1933delTGGA, and c.1943dupT), have also been reported [7,8,10–14]. Our patient has the transition of C > T at position c.1945 of the *PIK3R1* (NM_181523.3) (NP_852664.1, c.1945C > T, p.Arg649Trp), which tends to be the hotspot variant site.

According to previous studies, the sequencing in *PIK3R1* is related to the phenotype of SHORT syndrome [1,8,9]. Typical facial anomalies appear in most of patients, including triangular shape, prominent forehead, small chin, and aged appearance [6–9]. Metabolic problems in patients are also related to certain genotypes. Variants (*PIK3R1*, NM_181523.3) of c.1929_1933delTGGA, c.1945C > T, c.1615_1617delATT, c.1465G > A, c.1943dupT, c.1906_1907insC, c.1971T > G, c.1971T > G and c.1892G > A are related to insulin resistance and lipodystrophy [7,8,10,11,12,13]. Patients with Rieger anomaly had variants (*PIK3R1*, NM_181523.3) of c.1906_1907insC, c.1465G>A, c.1906_1907delAA, c.1929_1933delTGGA, and c.1945C > T [7,10,11,12,13]. Thyroid disease has been observed in a patient with a c.1960C > T variant (*PIK3R1*, NM_181523.3) [14]. Our patient, who had c.1945C > T in the *PIK3R1* (NM_181523.3), had lipodystrophy. The insulin resistance does not occur until later childhood, at the earliest. We would not expect this feature to present in a 5-month-old infant. The Rieger anomaly or other anterior chamber defects are seen in about half of individuals and that there is no comment about an ophthalmological examination in our case description. To discover the possibility of insulin resistance and Rieger anomaly, we should follow up his condition closely.

Multisystem problems exist in SHORT syndrome. More than half of patients have short stature and diabetes. There are no clinical criteria for SHORT syndrome and a diagnosis does require the clinical features in addition to the identification of a likely pathogenic or pathogenic variant in *PIK3R1*. With regards to treatment, this is based on an individual's symptoms and surveillance measures have been suggested in Avila [5] and Genereviews [16]. It is reasonable to treat metabolic abnormalities over time. Mild IUGR with premature delivery is usually present. Different degrees of short stature have been noted for patients with SHORT syndrome throughout their childhood. According to Thauvin-Robinet et al., male patients with SHORT syndrome have an adult height of 155–163 cm, and female patients have an adult height of 143–160 cm [10]. In Verge et al.'s study [15], one patient had treatment with recombinant human growth hormone (rhGH) for 2 years. The patient's growth rate before rhGH treatment was 4.9 cm/year, and this rate increased to 11.3 cm/year during the first year of therapy and to 8.8 cm during the second year. However, after 25 months of rhGH therapy, this patient developed diabetes. Physicians should avoid using rhGH therapy in patients with SHORT syndrome because this therapy can induce hyperinsulinemia and aggravate the degree of insulin resistance and diabetes [10,15].

Even though our patient had no insulin resistance or diabetes, metabolic problems are important to monitor. Insulin and metformin have been used for patients with SHORT syndrome in previous studies. Nevertheless, insulin resistance and glucose tolerance have worsened in some patients with metformin treatment [13,17]. The cause of worsening of glucose tolerance after metformin treatment is still unknown. More studies on SHORT syndrome are required, as is long-term follow-up of patients. Age, number of involved organs and their function, and response to treatment can influence the prognosis of SHORT syndrome. Life expectancy is unaffected in most patients [4]. Genetic counseling should be conducted for patients with SHORT syndrome because this disease is inherited in the autosomal-dominant pattern and a 50% chance exists for transmission to the next generation.

4. Conclusion

We presented a *de novo* heterozygous variant in the *PIK3R1* (NM_181523.3) (c.1945C > T), the first variant in Taiwan. Our patient

had the most common clinical features of SHORT syndrome, including short stature, a triangular face and prominent forehead, and lipodystrophy. Due to the relatively mild clinical presentation without insulin resistance, it is important to identify the dysmorphic features of SHORT syndrome. These facial dysmorphism helped us confirm the diagnosis with timely genetic testing and then provide appropriate management and proper care.

Author contributions

C.-L.L. drafted the manuscript. S.-P.L. and H.-Y.L. participated in the patient's follow-up and helped draft the manuscript. C.-K.C. performed biochemical analyses and revised the manuscript. H.-C.C., R.-Y.T., Y.-T.L. and Y.-H.C. were responsible for patient screening and revised the manuscript. All of the authors have read and approved the final manuscript.

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Declaration of Competing Interest

The authors declared that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgmr.2021.100768>.

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