# Homozygous *TBCE* Gene Mutation c.155-166del in a Libyan Patient with Sanjad-Sakati Syndrome: Same Gene Mutation Responsible in All Arab Ethnic Patients

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## Abstract

Sanjad-Sakati syndrome (SSS) (Online Mendelian Inheritance in Man 241410) is a rare autosomal recessive disorder also known as hypoparathyroidism-retardation-dysmorphism syndrome. It is characterized by congenital hypoparathyroidism, growth retardation, typical facial features, and variable developmental delay. SSS is caused due to mutations of the tubulin-specific chaperone E (*TBCE*) gene. In this article, we reported the first Libyan child of first parental consanguinity with SSS and whole exome sequencing results identified the homozygous missense variant c.155–166del and it encodes p.(Ser52-Gly55del) (chr1:235564867) located in the *TBCE gene*, chromosome 1q42.3. In addition, the patient was also diagnosed with congenital hypothyroidism and presented with acquired bilateral cataract in the first year of life. Most likely, all Arab patients with SSS syndrome have the same *TBCE* gene mutation.

**Keywords**

- Sanjad-Sakati syndrome
- hypoparathyroidism-retardation-dysmorphism syndrome
- congenital hypothyroidism
- cataract

## Introduction

Sanjad-Sakati syndrome (SSS) also known as hypoparathyroidism-retardation-dysmorphism (HDR) syndrome is an autosomal recessive disorder first described in 1988 by Sanjad.[1] SSS is caused by a mutation in the tubulin cofactor E (TBCE) gene, the locus for which is located in chromosome 1q42–43. SSS has been listed in Online Mendelian Inheritance in Man no. 241410.

## Background

HDR consists of hypoparathyroidism leading to sever hypocalcemic seizures, intrauterine and postnatal growth retardation, typical facial features, and variable cognitive impairment associated with developmental delay.[2–4] The prevalence is not well established.

The TBCE gene encodes a molecular chaperone protein that is required for joining of two different subunits, α-tubulin and β-tubulin. These subunits are involved in the assembly of tubulin cytoskeleton protein responsible for cellular trafficking, signal transduction, and cell migration.[4] Most of the reported patients are from the Arabian Peninsula.[5] In addition, the other cases documented with SSS are Arabic in origin from Tunisia, Morocco and from the Ahvaz region of Iran that all presented the same *TBCE* gene mutation.[6,7] All these SSS cases are homozygous for the same 12-base pair (bp; 155–166) deletion.

## Clinical Manifestation

All children with SSS have prominent craniofacial features including microcephaly, deep-set eyes, depressed nasal

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bridge, thin upper lip, low-set ears, large floppy ear lobule, micrognathia, small hands and feet, and delayed dentition. All of these features result from significant prenatal and postnatal growth retardation.[4,8] The disorder is characterized by congenital hypoparathyroidism leading to early onset hypocalcemic seizures. In addition, ocular anomalies, such as nanophthalmos, retinal vascular tortuosity, and corneal opacification, were documented in literature.[9,10] Laboratory finding in SSS in all patients showed low levels of calcium in the setting of low parathyroid hormone (PTH) levels as well as high phosphorus level, low levels of magnesium, and high alkaline phosphatase (ALP) with low vitamin D level. Aminzadeh et al[8] described that the major biochemical levels are serum calcium ranged from 5 to 7 mg/dL (reference range: 8.5–11 mg/dL), phosphorus ranged from 6.4 to 13 mg/dL (reference range: 4–6.5 mg/dL), and high ALP (1350 U/L). Furthermore, low vitamin D 4.2 ng/mL (reference range: 30–50 ng/mL) and PTH values < 0.4 to 7.5 (reference range: 15–65 pg/mL) have also been seen in previous cases.

## Diagnosis

Serum calcium, phosphorus, PTH level, and serum ALP are important diagnostic tests. Furthermore, complete blood count and the serum electrolytes of patients must be measured. Brain imaging CT scan and magnetic resonance imaging (MRI) may reveal basal ganglia calcifications secondary to hyperphosphatemia. In addition, the genetic analysis for *TBCE* gene mutation is important. Main treatment is oral calcium and 1-alphahydroxycholecalciferol.

## Management

Management of hypocalcemia can be considered in two broad categories: symptomatic hypocalcemia and asymptomatic hypocalcemia. The treatment of patients suffering from SSS is challenging and involves a multidisciplinary approach. The primary management in patient with symptoms of acute hypocalcemia involves intravenous (IV) bolus of elemental calcium/kg, administered over 30 minutes with close monitoring of pulse rate and QT interval. Once serum calcium reaches a range >7.5 mg/dL, stop IV calcium and start oral calcium. For children and adolescents, dosage is 30 to 75 mg of elemental calcium/kg/day in four divided doses. As the calcitriol (active vitamin D) has a rapid onset of action, it can be a useful adjunct in the management of acute hypocalcemia, and is frequently used as the initial vitamin therapy.[11]

## Prognosis

SSS is an incurable condition, and management is mostly limited to palliative measures.[4] Functional hyposplenism leads to recurrent infections, especially involving the respiratory system. However, rare cases have survived up to the age of 18 years.[12] Complications related to disorders of calcium–phosphate metabolisms, such as intracranial calcification and corneal opacification have been documented in literature.[4]

**Fig. 1** Facial phenotype.

## Case Presentation

A female child was born to Libyan first-degree consanguineous parents by spontaneous vaginal delivery. The child has three older brothers, all healthy and developmentally typical. She was delivered at 36 weeks of gestational with a birth weight of 2,150 g (< 3rd percentile); birth length and birth occipitofrontal circumference were not documented. She showed facial dysmorphic features with deep-set small eyes, depressed nasal bridge, thin upper lip, micrognathia, and hypotonia (►**Fig. 1**).

On day 2, she admitted to the neonatal intensive care unit (NICU) because of uncontrolled seizures. Laboratory investigations showed low serum calcium (4.6 mg/dL), magnesium 0.6 mg/dL (reference interval, 1.7–2.2 mg/dL), and phosphorus 8 mg/dL (reference interval, 3.4–4.5 mg/dL). PTH was 4.2 pg/L (reference interval, 10–554) and vitamin D level was 17.3 (reference normal > 35). Liver transaminases (AST 92 UI/L [reference, < 40], ALT 41UI/L [reference, normal < 45]). ALP level result was not documented at admission time but in the follow-up visit after discharge her ALP was 480 UI/L. Furthermore, echocardiography and transfontanellar ultrasonography were normal. She was discharged from the hospital on oral calcium and alfacalcidol (1-alpha hydroxycholecalciferol). The patient was readmitted in NICU at the age of 1 month and at the age of 2 months due to episodes of generalized convulsion with low serum calcium level in both admissions 2 and 4.6, respectively, with a history of blood transfusion in second admission due to severe anemia (her hemoglobin was 7 g/dL). In addition, due to persistence of jaundice, thyroid function test that was done that showed a thyroid-stimulating hormone level of 65 µUI/mL, free T4 of 7.4 pmol/mL (reference range:

 

**Table 1** Patient DNA sequencing

| Gene (isoform) | OMIM (mode of inheritance) | Variant | Zygosity | Classification |
|---|---|---|---|---|
| TBCE (NM_003193.5) | 241410 (AR) | c.155–166del p.(Ser52-Gly55del) chr1:235564867 | Homozygous | Pathogenic |

12–22). She was diagnosed as a case of congenital hypothyroidism and started on replacement therapy with levothyroxine. In addition, at the age of 6 months, she presented with bilateral cataract and had lensectomy, the first one at the age of 7 months for left eye and at 9 months of age for the right eye. MRI of brain was normal. During hospital admission at the age of 11 months with low calcium level, she was already on replacement treatment with oral calcium, alfacalcidol, and levothyroxine. Based on clinical features and medical history, dysmorphic features, and failure to thrive with laboratory documentation of congenital hypoparathyroidism in the absence of cardiac or skeletal malformations, the diagnosis of SSS was suspected. Informed consent was obtained from the proband's parents prior to sending patient's blood sample for genetic study. Peripheral blood was collected from the proband and it was sent to Bioscientia Genetic Laboratory, Germany. The results showed homozygous recurrent 12-bp deletion in the exon 3 between 155 and 166 of the *TBCE* gene (►**Table 1**).

## Discussion

To our knowledge, this is the first genetically proven case of SSS in Libya. SSS or HDR syndrome is a rare autosomal recessive condition described in the populations from the Saudi, Jordan, Tunisia, Oman, Kuwait, and Ahvaz (southwest of Iran). Clinical and biochemical findings were consistent with the diagnosis of SSS characterized by typical facial features, hypocalcemia, congenital hypoparathyroidism, and severe growth retardation, which are similar to reported SSS cases.[6] In addition, the patient was diagnosed with congenital hypothyroidism and developed acquired bilateral cataract, which is a rare presentation in SSS. Eye abnormality is a clinical feature of Kenny-Caffey syndrome (KCS) with congenital hypoparathyroidism and similar SSS facial dysmorphism. SSS and KCS syndrome genetic subtypes are currently recognized. Type 1 KCS and SSS syndromes are allelic with homozygous mutations in the *TBCE* gene,[13,14] but KCS syndrome is different by the presence of osteosclerosis, medullary stenosis of long bones, and normal intelligence.

The previous reports cases of SSS were confirmed due to the 12-bp (155-166del) deletion in exon 3 of the *TBCE* gene[15] (►**Table 2**). In addition, all Arab patients from different Arabic countries including those patients from Ahvaz region of Iran with SSS showed homozygosity for this *TBCE* gene mutation.

## Conclusion

Congenital hypoparathyroidism since birth, in association with intrauterine growth retardation in babies with craniofacial dysmorphic feature, should raise suspicion for SSS. The detection of *TBCE* gene mutation and presenting clinical manifestation of this rare disease in Arabic patients makes the diagnosis and treatment much easier, which will help to prevent the critical complication. Furthermore, it is helpful in differentiation of this SSS from other similar syndromes, particularly in the Arab origin population.

**Table 2** A review of genetic data of Sanjad-Sakati syndrome cases of Arabic origin

| Number of cases | Origin of the data | TBCE gene mutations | References |
|---|---|---|---|
| 1 | Tunisia | c.155–166 deletion | 6 |
| 1 | Morocco | c.155–166 deletion | 7 |
| 8 | Jordan | c.155–166 deletion | 10 |
| 6 | Middle East | c.155–166 deletion | 13 |
| 21 | Kuwait | c.155–166 deletion | 16 |
| 1 | Oman | c.155–166 deletion | 17 |
| 29 | Ahvaz, southwest of Iran | c.155–166 deletion | 8 |
| 1 | Libya | c.155–166 deletion | This study |

## Limitation

Our case report was associated with a lack of genetic analysis for the other family members because this type of genetic analysis is available only outside of Libya.

### Patient Consent

Written informed consent was obtained from patient's family for publication.

### Funding

None.

### Conflict of Interest

None declared.

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