case report

The Bedouin mutation c.155-166del of the TBCE gene in a patient with Sanjad-Sakati syndrome of Moroccan origin

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Sanjad-Sakati syndrome (SSS) or hypoparathyroidism-retardation-dysmorphism syndrome (HDR) is a rare autosomal recessive disorder. It is characterized by the association of congenital hypothyroidism, growth retardation, psychomotor retardation, epilepsy, dysmorphic features (microcephaly, facial, eye, and dental anomalies), and abnormalities of the extremities. The prevalence of SSS is unknown. Reported patients are were almost exclusively from the Arabian Peninsula. They are were all homozygous for the ancestral mutation c.155- 166del of the TBCE gene, also known as "the Bedouin mutation." We report on the first clinical and molecular description of a Moroccan patient with Sanjad-Sakati syndrome. He is was a carrier for the Bedouin mutation, not surprising, knowing that part of the Moroccan population has Arabian origin. This diagnosis allowed us to provide an appropriate management to the patient, to make a genetic counseling to his family, and to enrich genetic data on the Moroccan population.

Sanjad-Sakati syndrome (SSS) also known as hypoparathyroidism-retardation-dysmorphism syndrome (HDR) is an autosomal recessive disorder first described in 1988 by Sanjad et al.[1] SSS consists of hypoparathyroidism leading to hypocalcemic tetany and/or seizures, intrauterine and postnatal growth retardation, typical facial features, and variable mental retardation.[2,3] The incidence of SSS is unclear. Reported patients are almost exclusively from the Arabian Peninsula: Saudi, Qatari, Israeli Arabs, Kuwaiti, Omani, and Jordanian.[4] SSS is due to mutations of the tubulin-specific chaperone E (TBCE) gene at 1q42.3.[5] It encodes a chaperone protein involved in the assembly of tubulin cytoskeleton protein responsible for cellular trafficking, signal transduction, and cell migration.[6] All the Arab patients reported to date are homozygous for the same 12 base pair (bp) (155-166) deletion, also called "Bedouin" mutation, within the TBCE gene.[4,6] This mutation leads to the loss of 4 amino acids (p.del52-55) in the TBCE protein. Hereby, we report the first Moroccan patient with SSS carrying the Arab deletion of the TBCE gene.

CASE

A female baby born to Moroccan consanguineous parents (first degree) was admitted at birth to the neonatal intensive care unit of Children's Rabat Hospital Morocco. The infant was the first liveborn to a 34-year-old mother and 41-year-old father with a non-contributive familial history. The pregnancy was not medically followed, and it was without reported complications. The fetus was delivered by a cesarean section because of post-maturity and severe intra-uterine growth retardation. The Apgar score was (9/10) good. Birth weight and length were 2100 g and 42 cm, respectively (both <3rd percentile), and the head circumference was 31 cm (50th percentile). She showed facial dysmorphic features with deep-set small eyes, depressed nasal bridge with a beaked nose, long philtrum, thin upper lip, micrognathia, large floppy ear lobes, and axial hypotonia (**Figure 1**).

At Day 2, she presented generalized seizures. The results of laboratory examinations were: calcium: 38 mg/L (normal: 85-95 mg/L), phosphate: 78 mg/L (normal: 23-47 mg/L), alkaline phosphatase: 52UI/L

(normal: 40-150 UI/L), magnesium: 18 mg/L (normal: 16-26 mg/L), PTH 1 pg/L (n=10-554). Mother's serum calcium levels were normal. Cervical, transfontanellar, abdominal, and cardiac ultrasonography were normal. She responded well to calcium infusion. She was also started on oral calcium and alphacalcidol. Calcium was stopped in a few days, and she maintained her serum calcium on alphacalcidol only. Based on these findings, we suspected congenital hypoparathyroidism, and in the absence of cardiac or skeletal malformations, the diagnosis of SSS was considered. Informed consent was obtained from the proband's parents prior to implementing the genetic study reported here. Peripheral blood was collected from the proband and her parents. We looked for the recurrent 12 bp deletion in the exon 3 between 155 and 166 of the TBCE gene by polymerase chain reaction sequencing. The patient was homozygote for the mutation (**Figure 2**). As expected, the parents were heterozygote carriers. Despite an intensive care, the patient died in 3 months due to the complications of her hypoparathyroidism.

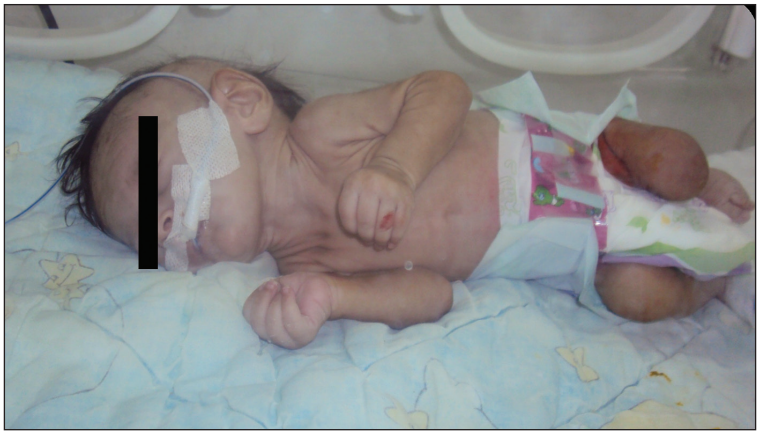

Figure 1. Patient with dysmorphic face and axial hypotonia.

DISCUSSION

Sanjad-Sakati syndrome (SSS) or hypoparathyroidism-retardation-dysmorphism syndrome (HDR) (OMIM #241410) is a rare autosomal recessive condition described in the populations of the Middle East, mainly Saudi and Kuwaiti.[2,3] It is characterized by the association of congenital hypothyroidism, growth retardation, psychomotor retardation, epilepsy, dysmorphic features (microcephaly, facial, eye, and dental anomalies), and abnormalities of the extremities.[2,3] Its prevalence is unknown. SSS is linked to mutations in the TBCE gene. Patients with SSS should have close monitoring for calcium profile and benefit from vitamin D treatment. The use of growth hormone may be helpful. All reported Middle Eastern patients carry the same founder deletion of 12 bp (c.155-166del).[4,6] The differential diagnosis of SSS may include Di-George syndrome, Kenny-Caffey syndrome, and familial hypoparathyroidism, but the absence of cardiac lesion, lymphopenia, or skeletal abnormalities may help to differentiate between SSS and other entities.[6] In the patient described here, we screened first for SSS because of the classic presentation, the typical facial features, and the lack of support for other entities.

The characterization of the Bedouin mutation c.155-166del in the proband whose both parents confirmed their Moroccan origin through at least 3 generations is related to the history of the settlement of Morocco. It is known that Berbers were the earliest known inhabitants of Morocco, but through the centuries, they have mixed with many other ethnic groups: the Phoenicians, Carthaginians, Romans (first century), Vandals (fifth century), and Byzantines (sixth century). Arabs arrived

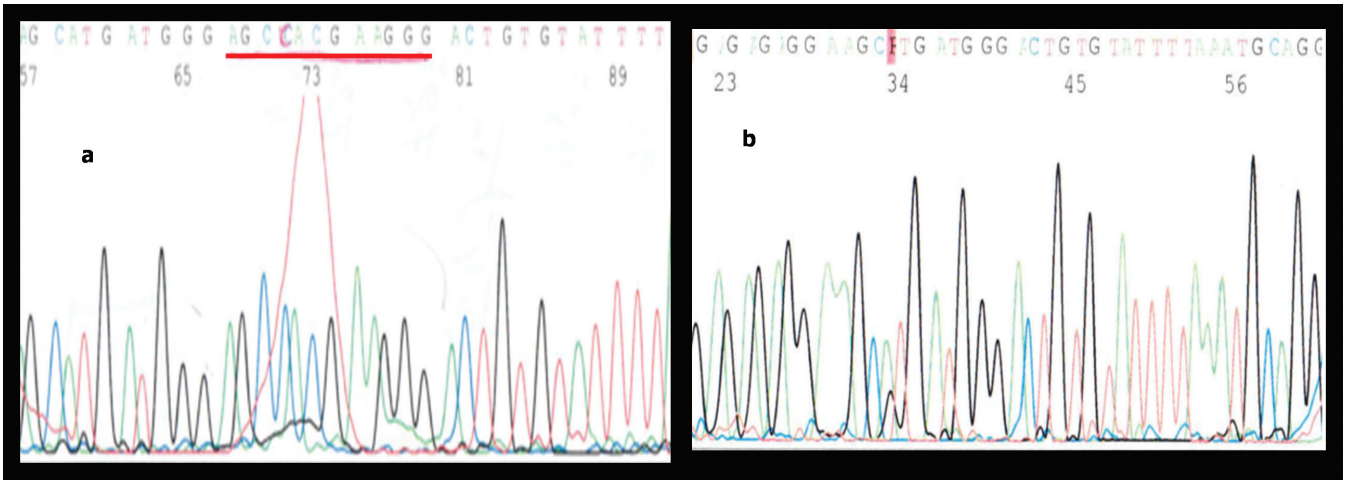

Figure 2. a) Electropherogram showing a normal sequence and the b) homozygous 12 bp deletion (155-166) of exon 3 on the TBCE gene.

to Morocco with the expansion of Islam to North-Africa in the seventh century. This migration explains the origin of some rare mutations and variants that are common to Arabian Peninsula and North-Africa populations. Besides an ethnic diversity, there is a high rate of consanguinity in Moroccans (15.25%).[7] It contributes to the increasing prevalence of recessive genetic disorders and congenital malformations. Parental consanguinity was recorded in the reported family.

In conclusion, we report on the first clinical and molecular description of a Moroccan patient with Sanjad-Sakati syndrome. This diagnosis allowed us to provide an appropriate management to the patient, to make a genetic counseling to his family, and to enrich genetic data on the Moroccan population.

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