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BRIEF COMMUNICATION

Further expansion of the mutational spectrum of spondylo-meta-epiphyseal dysplasia with abnormal calcification

Gizem Ürel-Demir[1] · Pelin Ozlem Simsek-Kiper[1] · Özlem Akgün-Doğan[1] · Rahşan Göçmen[2] · Zheng Wang[3,4] · Naomichi Matsumoto[5] · Noriko Miyake[5] · Gülen Eda Utine[1] · Gen Nishimura[6] · Shiro Ikegawa[3] · Koray Boduroglu[1]

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Abstract

Spondylo-meta-epiphyseal dysplasia, short limb-abnormal calcification type, is a rare autosomal recessive disorder of the skeleton characterized by disproportionate short stature with narrow chest and dysmorphic facial features. The skeletal manifestations include platyspondyly, short flared ribs, short tubular bones with abnormal metaphyses and epiphyses, severe brachydactyly, and premature stippled calcifications in the cartilage. The abnormal calcifications are so distinctive as to point to the definitive diagnosis. However, they may be too subtle to attract diagnostic attention in infancy. Homozygous variants in DDR2 cause this disorder. We report on a 5-year-old girl with the classic phenotype of SMED, SL-AC in whom a novel homozygous nonsense mutation in DDR2 was detected using exome sequencing.

Introduction

Spondylo-meta-epiphyseal dysplasia, short limb-abnormal calcification type (SMED, SLAC) (MIM 271665), is a rare autosomal recessive genetic disorder of the skeleton characterized by disproportionate short stature with short limbs, narrow chest and typical facial features [1, 2]. Platyspondyly with wide intervertebral spaces, short flared ribs, short tubular bones with abnormal metaphyses and epiphyses, severe brachydactyly in hands and feet, and premature stippled calcifications in the cartilage are among the main radiological findings [1–5]. Homozygous mutations in the discoidin domain receptor-2 (*DDR2)* gene (MIM 191311) are responsible for this disorder [6]. To date 28 patients with SMED, SL-AC have been reported [1–12]. Here we report on a 5-year-old girl with the classic phenotype of SMED, SL- AC in whom a novel homozygous nonsense mutation in *DDR2* was found using exome sequencing (ES). This report further expands the mutational spectrum of SMED, SL-AC.

Clınıcal report

The patient is the second live-born child of parents who are first-degree cousins. The pregnancy was complicated by polyhydramnios and an emergency caesarean section was required due to fetal distress at gestational age 36 weeks. Birthweight was 2400 g (−1.9 SD) but length and occipito-frontal circumference were not recorded. The patient had respiratory distress due to inadequate chest expansion and pulmonary hypoplasia requiring mechanical ventilation. She was discharged from the hospital at the age of 10 days without any respiratory support. The family history was remarkable for three children who did not survive infancy. These children died suddenly and were also diagnosed with pulmonary hypoplasia.

Physical examination at the age of 4 months revealed body length 54 cm (−3.3 SD), weight 4900 g (−2.1 SD) and

✉ Gizem Ürel-Demir
gizemurel@gmail.com

1 Department of Pediatric Genetics, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

2 Department of Radiology, Hacettepe University, Ankara, Turkey

3 Laboratory for Bone and Joint Diseases, RIKEN Center for Integrative Medical Sciences, Tokyo 108-8639, Japan

4 McKusick-Zhang Center for Genetic Medicine and State Key Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, , Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100005, People's Republic of China

5 Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan

6 Department of Radiology, , Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

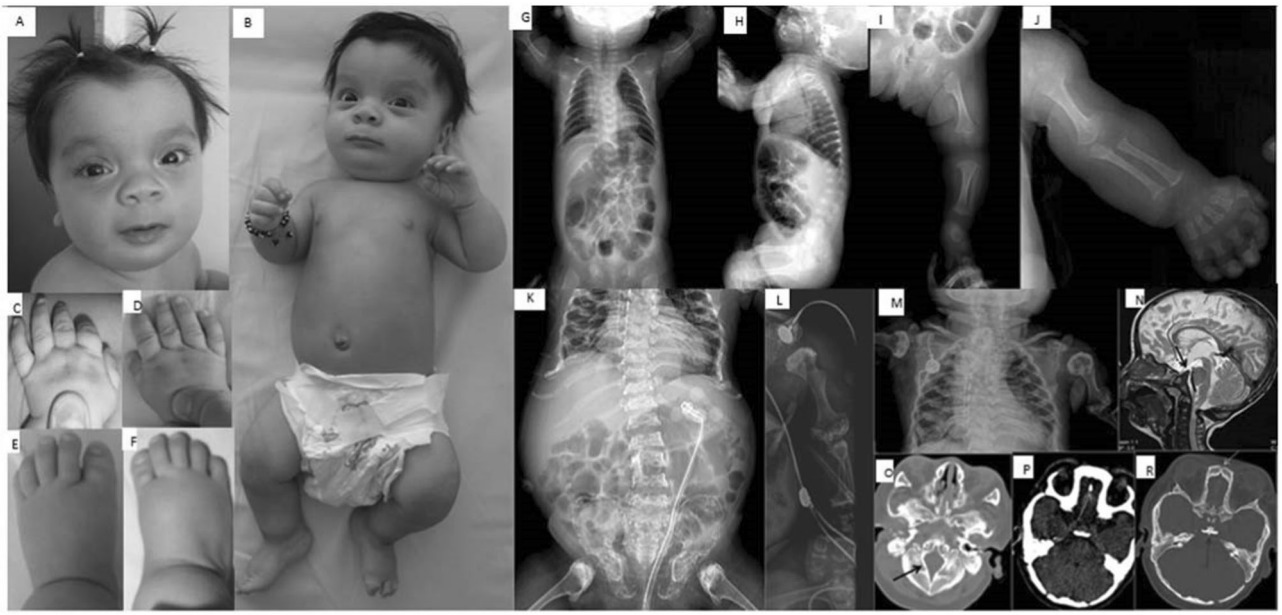

Fig. 1 Clinical picture of the patient at 4 months (**a**) and 6 months of age (**b–f**). Please note: Prominent forehead, medially sparse eyebrows, hypertelorism, a short nose with a depressed nasal bridge and anteverted nostrils, a long philtrum with thin upper lip, retromicrognathia (**a**, **b**), narrow chest, short limbs (**b**) and brachydactyly (**c–f**). Abdomen and limb radiograms at 4 months of age (**g–j**). Note small chest, and small pelvis (**g**), platyspondyly with mildly anterior wedging (**h**), retarded ossification (**ı**, **j**), broad, short metacarpal bones and phalanges (**j**), mild broad and frayed metaphyses and suggestive punctate calcifications (**ı**, **j**). Radiographic findings at 4 years of age (**k–r**). Note progressive skeletal findings. Abdomen radiogram shows small pelvis with abnormal ossification, and platyspondyly with irregular endplates. Marked irregular ossification and broad and frayed metaphyses and epiphyses of the femur, humerus, radius, and ulna (**k–m**). Note irregular calcification of scapulae and pelvis. Cranial magnetic resonance imaging (**n**) and computed tomography (**o**) reveals stenosis of the cranio-cervical junction from foramen magnum (**o**; arrows) to T1 vertebrae resulting in compressive myelopathy (**n**), odontoid hypoplasia (**n**), calcification of falx cerebri (**p**), and small sella turcica with prominent dorsum sella (**n**; black arrow **r**; white arrow), hypertelorism (**o**), open metopic sutur (**r**; short arrow)

occipito-frontal circumference 40 cm (mean). A prominent forehead, wide anterior fontanelle, sparse eyebrows, hypertelorism, a short nose with a depressed nasal bridge and anteverted nostrils, a long philtrum with thin upper lip, and retromicrognathia were noted. In addition she had a narrow chest, umbilical hernia, short limbs and brachydactyly (Fig. 1). A clinical diagnosis of SMED, SL-AC was made on clinical and radiological grounds. (Table 1) The patient was diagnosed with a facial nerve paralysis at 1 year of age without any evidence of a viral infection. During the follow-up, she had repeated episodes of pneumonia requiring recurrent hospitalizations. During one of her hospitalizations she was unable to maintain adequate ventilation related to rigidity and inadequate expansion of the chest wall due to short ribs and costochondral calcifications. She required additional respiratory support and a tracheostomy was performed. She was discharged home on mechanical ventilation because of chronic pulmonary insufficiency due to a narrow thorax and poor oxygenation. She was under follow-up until her last admission at the age of 5 years with fever and diarrhea for several days. At admission, she was found to be in cardiorespiratory decompansation due to severe shock and despite intensive treatment did not survive.

Molecular analysis

The study protocol was approved by the ethical committee of RIKEN and participating institutions. The informed consent was obtained from the parents. Peripheral blood was collected from the patient and her parents. Genomic DNA was extracted from blood using QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA). ES was performed for the proband as previously described [13, 14]. We obtained 3.07 Gb sequences, which were mapped to human RefSeq19 by the method described previously [13, 14]. Of all the coding regions, 96.1% were covered with a depth of at least 10 reads. After the initial filtering, 5431 sequence variants were identified in the proband, among which 2169 were homozygous. A homozygous nonsense variant, c.1465 C > T (p. R489*) in exon 13 of *DDR2* (NM_001014796) was detected and confirmed by Sanger sequencing (Fig. 2). This variant was located on chr1:162740263 in hg19 in a ~9.3 Mb homozygous stretch It was not present in HGMD and the 1000 Genome database. In gnomAD, only one allele was observed in the African population with the allele frequency of 0.00003229. The parents were heterozygous for the variant.

Table 1 Clinical and radiographic features of the patient compared to those of the previously reported patients

	Literature (1–12)	Present case
Clinical features		
Short limbs	28/28	+
Short broad hands	28/28	+
Short broad fingers	15/28	+
Thoracic hypoplasia	22/28	+
Pectus excavatum	12/28	−
Respiratory problems	15/28	+
Hypertelorism	25/28	+
Short flat nose	26/28	+
Wide nostrils	21/28	+
Long philtrum	21/28	+
Short neck	10/28	+
Neck hyperextension	5/28	−
Peculiar voice	6/28	+
Delayed motor development	18/28	+
Developmental delay	4/28	+
Hypotonia	13/28	+
Radiological features		
Short and broad long bones	28/28	+
Short and broad round bones	28/28	+
Abnormal metaphyses & epiphyses	28/28	+
Rib abnormalities	28/28	+
Chondral calcification	15/28	+
Platyspondyly	28/28	+
C1–C2 instability	13/28	−
Scoliosis	7/28	+
Odontoid hypoplasia	4/28	+
Falx cerebri calcifications	2/28	+
Foramen magnum stenosis	6/28	+

Discussion

SMED, SL-AC was first described in 1993 by Borochowitz et al. in three unrelated patients with small stature, short limbs and short hands, typical facial and radiographic features and a characteristic narrow chest [1]. Then in 1993 Langer et al., reported eight additional patients with similar findings [2]. The finding of abnormal premature calcification in cartilaginous structures was suggested to be distinctive and therefore the term, SMED, short limb-abnormal calcification type was suggested for this disorder [2]. The facial features include a relatively large head, broad face, prominent forehead, short nose with a flat bridge and wide nostrils, hypertelorism, long philtrum and retro/micrognathia [1–5]. Radiological features include short lower and upper limbs with wide metaphyses and flattened, fragmented epiphyses, severe brachydactyly, flattened vertebral bodies with wide disc spaces, short ribs and calcifications involving epiphyses, chondral and soft tissues [1–3]. The facial and radiographic findings of our patient were very suggestive of SMED, SL-AC. The level and amount of abnormal calcification shows variation in SMED, SL-AC [2, 3]. Al-Gazali et al. observed that the severity between two siblings with excessive calcification involving epiphyses, costochondral junctions, thyroid and hyoid cartilage varied [3]. Although these siblings presented with significant widespread calcification around 4 and 8 years of age, a patient with only calcification of the hallux at 5 years of age has been reported by Smithson et al [5]. The punctate calcifications were noted by the age of 4 months in our patient. The genetic etiology of SMED, SL-AC was revealed in 2009 by using a homozygosity mapping approach in three unrelated patients in whom an identical homozygous 2.4-Mb region on chromosome 1q23 including *DDR2* was identified [6]. DDR2 was considered a good candidate because it is a tyrosine kinase cell-surface receptor which plays a crucial role in type X collagen regulation and bone growth. Furthermore, the skeletal phenotype of ddr2 knockout mice is similar to SMED, SL-AC [6, 15, 16]. To date 7 mutations in 28 SMED, SL-AC patients from 22 families have been reported. ES revealed a novel homozygous nonsense *DDR2* mutation in our patient. Theoretically, in this case DNA sequencing of *DDR2* is sufficient for the diagnosis. However, ES provides a powerful and cost-effective tool for both clinically and genetically heterogeneous disorders, and enables faster molecular diagnosis. Early diagnosis is critical and this fact mandates screening of neurologic complications including atlantoaxial instability in order to provide the option of surgical decompression in a timely manner [2, 3, 11]. Respiratory failure in association with rigidity and inadequate expansion of the chest wall due to the presence of narrow thorax, short ribs and costochondral calcifications is a major cause of mortality in SMED, SL-AC [4]. The present patient had recurrent episodes of pneumonia requiring several hospitalizations and in one of the admissions, tracheostomy was performed. In addition significant foramen magnum stenosis leading to spinal cord compression between C1-C3 was detected however; no intervention could be performed because of the necessity of frequent hospitalizations due to pulmonary infections. Facial paralysis without evidence of viral illness may occur as a complication in the course of the disease as was seen in our patient [8].

In conclusion, SMED, SL-AC should be considered in patients with consistent clinical and radiographic findings. Molecular diagnosis provides early confirmation of the clinical diagnosis and enables prevention and appropriate management of possible complications. In this case Sanger sequencing theoretically would have been enough for

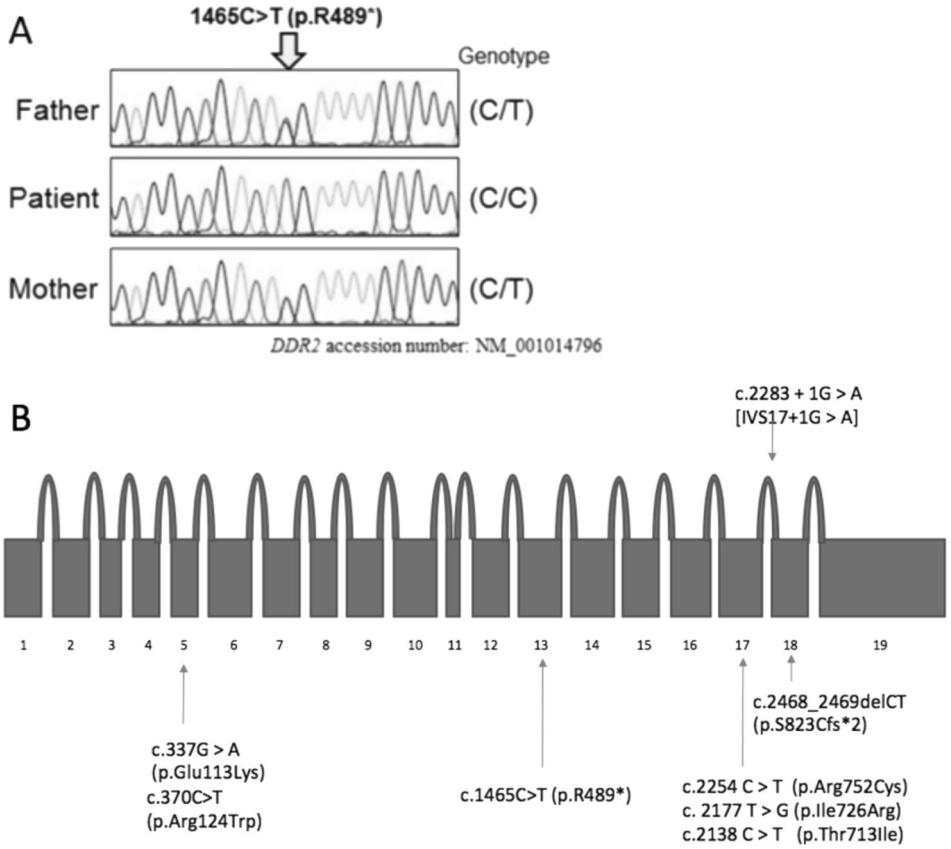

Fig. 2 *DDR2* mutation (homozygous) was found in the patient. c.1465 C > T (p.R489*) exon13 (NM_001014796) (**a**) Schematic representation of all known mutations in the *DDR2* gene (**b**)

diagnostics, but practically ES is quicker method to amplify a bigger gene.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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