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Letter to the Editor

SETBP1 mutations in two Thai patients with Schinzel–Giedion syndrome

To the Editor:

Schinzel–Giedion syndrome (SGS; MIM #269 150) is an autosomal-dominant disorder characterized by profound developmental delay, severe growth failure, characteristic facial features, multiple congenital anomalies including skeletal, cardiac, genitourinary and renal malformations, as well as an increased prevalence of neoplasia (1).

The gene responsible for SGS had been unidentified by traditional disease-gene identification approaches. Until very recently, using exome sequencing, Hoischen et al. successfully identified heterozygous *de novo* mutations in *SETBP1* as genetic defects causing SGS (2). Of the 13 patients with SGS, 12 were found to have *SETBP1* mutations. All were Caucasian (2).

We identified two unrelated Thai patients who were referred to our Genetics Clinic at King Chulalongkorn Memorial Hospital at 1 month of age because of growth failure, developmental delay and multiple anomalies. Both were sporadic cases with no history of consanguinity in their families. Case 1 was a son of a G2 P1 26-year-old mother and a 29-year-old father. The patient's elder sister was healthy. The pregnancy was complicated by maternal diabetes mellitus, adequately controlled by diet modification. He was born at term with a birth weight of 2650 g (third centile). The Apgar scores were 6 and 7 at 1 and 5 min, respectively. At age 1 month, he weighed 2800 g (<third centile) with head circumference (HC) of 36 cm (50th centile). Anterior fontanelle was 5 × 5 cm. He had coarse face, frontal bossing, prominent eyes, infraorbital grooves, midface retraction, upturned nose, low-set large pinnae with prominent ear lobes, macroglossia, micrognathia, stiff elbows, camptodactyly, micropenis, hypospadias, right indirect inguinal hernia, and spasticity (Fig. 1a,c). Radiographs showed wide occipital synchondrosis (Fig. S1), radioulnar synostosis and scoliosis (Fig. 1e). Thyroid function test showed free T4 (FT4) of 0.68 pg/dl (normal 0.8–1.8), T4 4.26 μg/dl (normal 6–12), thyroid-stimulating hormone (TSH) 1.29 μU/ml (normal 0.3–4.1). Levothyroxine was given as the age of 1 month, which brought his FT4 and TSH levels back to normal. Karyotype was 46,XY. Computed tomography (**CT**) of the brain revealed ventriculomegaly. Renal ultrasound showed hydronephrosis bilaterally. Bronchoscopy revealed a very short epiglottis, vocal cord paralysis, and laryngomalacia. Visual evoke response was normal. Auditory brainstem response showed bilateral sensorineural hearing loss with a threshold of 50 and 70 dB on the left and right sides, respectively. He had recurrent pneumonia requiring tracheostomy intubation at age 2 months. A gastrostomy tube was placed at 4 months of age. He later developed intractable seizure. He had no neurodevelopment and passed away at the age of 6 years and 2 months.

Case 2 was a son of a G1 P0 19-year-old mother and 18-year-old father. The pregnancy was uneventful. He was born at term by vaginal delivery with a birth weight of 3440 g (50th centile). The Apgar scores were 9 and 10 at 1 and 5 min, respectively. At the age of 1 month, his HC was 35 cm (25th centile) with anterior fontanelle 4 × 4 cm. He had prominent forehead, infraorbital grooves, midface retraction, prominent upturned nose, short philtrum, micropenis and hypertonia (Fig. 1b,d). Radiographs showed wide occipital synchondrosis (Fig. S2), short first metacarpal bones (Fig. 1f). Thyroid function test showed FT4 of 0.76 pg/dl (normal 0.8–1.8), TSH 1.77 μU/ml (normal 0.3–4.1). Karyotype was 46,XY. CT of the brain showed ventriculomegaly. Echocardiogram was normal. Renal ultrasound showed bilateral hydronephrosis. His head grew abnormally slow, with HC of 35.5 cm (10th centile) at 2 months of age. He developed intractable seizure at the age of 3 months, and his last follow-up was at the age of 11 months.

The observation of a very short epiglottis and vocal cord paralysis in Case 1 and a possible hypothyroidism in both cases has never been previously reported in this syndrome. Although levothyroxine brought FT4 and TSH levels of

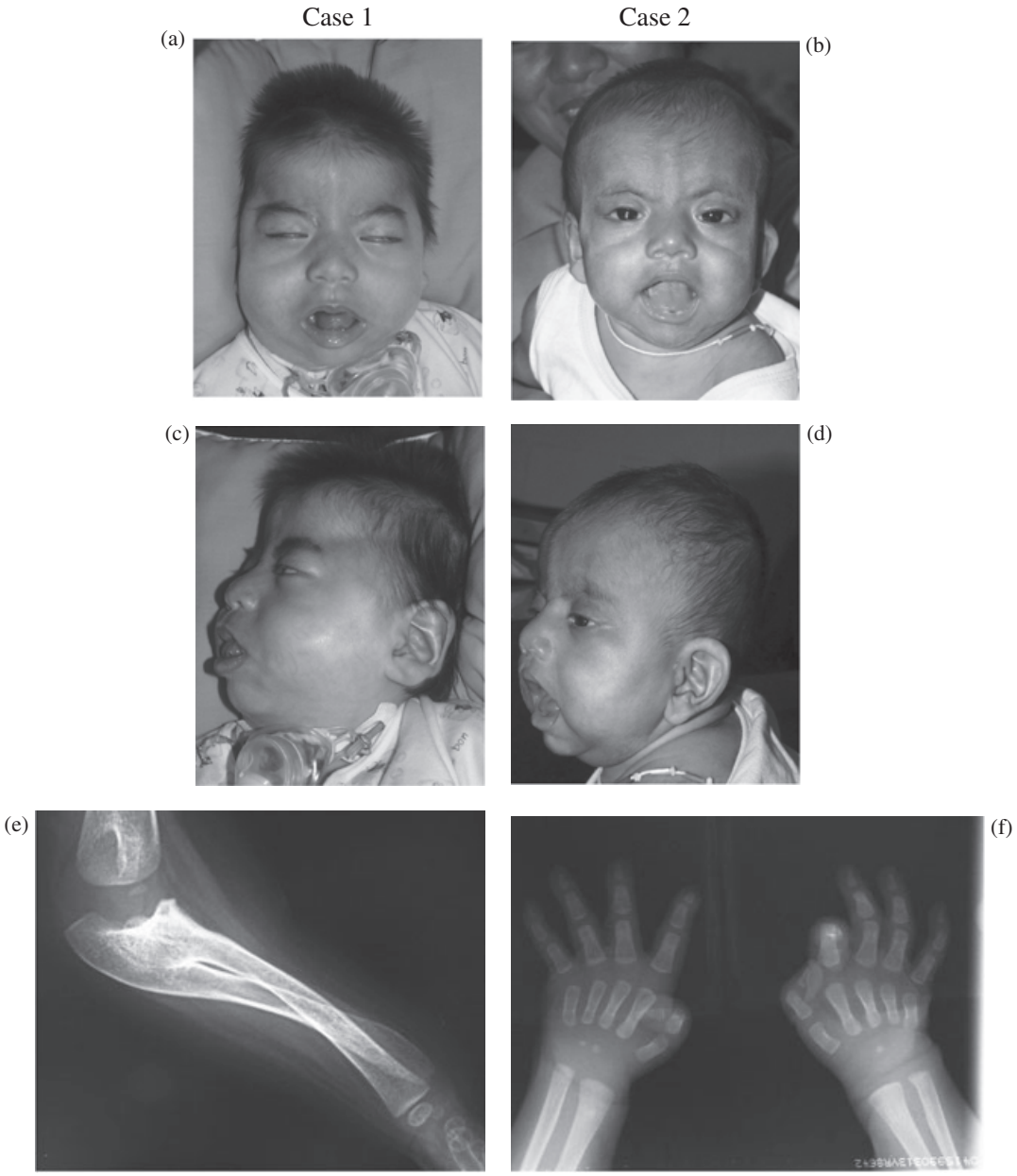

Fig. 1. Clinical and radiographical features. The left panel for Case 1 (**a, c, e**) and right panel for Case 2 (**b, d, f**). Faces anteriorly (**a** and **b**) show prominent forehead, bitemporal narrowing, shallow orbits, midface retraction and a protruding tongue. Faces laterally (**c** and **d**) show prominent ear lobes. Radiograph of the left elbow of Case 1 shows radioulnar synostosis (**e**) and that of hands of Case 2 shows short first metacarpals and hypoplastic distal phalanges bilaterally (**f**).

Case 1 back to normal, he still had no neurodevelopment. Whether treatment of hypothyroidism should be advised in patients with SGS requires further studies. Radiographically, both had previously reported findings including the short first metacarpals and scoliosis (3, 4). Of note, the radioulnar synostosis in Case 1 has never been previously described.

After informed consent was obtained, genomic DNA was isolated from peripheral blood, according to established protocols. Intronic primers were used to specifically amplify the exon 4 of *SETBP1*, as previously described (2). PCR products were directly sequenced.

PCR sequencing of both the cases revealed the same variant, c2608G>A (p.G870S) (Fig. 2a). The presence of the mutation was confirmed by restriction enzyme digestion using *Bbv*I (New England Biolabs, Berverly, MA). All the reactions were performed according to the manufacturer's recommendations. For parental DNA, only the mother of Case 1 was available. Using PCR

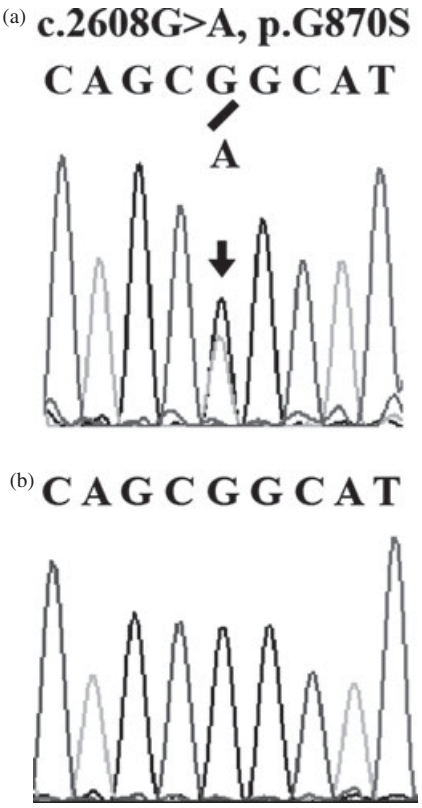

Fig. 2. Mutation analysis. Chromatograms demonstrate a nucleotide change detected in Case 1 (**a**) compared to his unaffected mother (**b**). A black arrow shows the c2608G>A mutation.

sequencing and restriction enzyme digestion, she was found to carry the wild-type allele (Fig. 2b). This method was also used to screen for the variant in 100 control chromosomes of Thai ethnicity. None of them was found to carry the mutation.

The c2608G>A (p.G870S) mutation was previously reported in one of the 12 patients with molecularly confirmed SGS (2). All the identified mutations involve only three amino acid residues of the *SKI* homologous region of the SETBP1. These affected residues are highly conserved throughout evolution. The p.G870S has been predicted to be possibly damaging and not tolerated by PolyPhen and SIFT, respectively. It might alter the SETBP1 protein structure causing abnormal regulation of the Ski dimerization (2). The finding of mutation cluster supports the hypothesis of a gain-of-function or dominant negative effect.

Here we describe two unrelated Thai patients with clinical manifestations fulfilling the proposed diagnostic criteria of SGS (1). We report on the first observation of a very short epiglottis, vocal cord paralysis, radioulnar synostosis and possible hypothyroidism in this syndrome. We also demonstrate that *SETBP1* is the gene responsible for SGS in Thai patients confirming the previous report of this gene associated with SGS in Caucasians. The mutations so far found in *SETBP1* were all heterozygous in the *SKI* homologous region, supporting the hypothesis of the gain-of-function or dominant negative effect.

Supporting Information

The following Supporting information is available for this article:

Fig. S1. Lateral view of a skull X-ray of Case 1 demonstrating the wide occipital synchondrosis.

Fig. S2. Lateral view of a skull X-ray of Case 2 demonstrating the wide occipital synchondrosis.

Additional Supporting information may be found in the online version of this article.

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