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Spondylocarpotarsal synostosis: long-term follow-up of a case due to *FLNB* mutations

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To the Editor:

Spondylocarpotarsal synostosis (SCT) syndrome (OMIM #272460), also known as congenital synspondylism, is a rare genetic disorder characterized by fusions of vertebral bodies, carpal and tarsal bones. The vertebral anomalies are responsible for congenital scoliosis and disproportionate short stature due to a short trunk. The syndrome was first recognized by Jones et al. [1973] and it was soon suggested to be inherited with an autosomal recessive pattern [Langer and Moe, 1975]. Indeed, it was recently found that SCT is due to homozygosity or compound heterozygosity for nonsense mutations in the Filamin B (*FLNB*) gene encoding for a multifunctional cytoplasmatic protein involved in skeletal development [Krakow et al., 2004]. Heterozygous mutations of *FLNB* gene, hypothesized to produce a dominant negative function, cause a spectrum of skeletal dysplasias including Larsen syndrome (OMIM #150250), atelosteogenesis type I (OMIM #108720), atelosteogenesis type III (OMIM #108721) and Boomerang dysplasia (OMIM #112310) [Krakow et al., 2004].

To date approximately 20 cases of SCT have been reported in the literature, but only few of them have been characterized at the molecular level [Krakow et al., 2004]. We report an additional patient with SCT due to a novel nonsense mutation in the *FLNB* gene and her follow-up over a period of more than 10 years. Our patient is remarkable for the presence of platybasia with basilar impression, narrowing of the foramen magnum, and growth hormone (GH) deficiency.

The patient was the third child of an Italian consanguineous couple. Parents were first cousins with mild short stature (father's height was 164 cm, SDS -1.6, and mother's height 150 cm, SDS -2). A previous child of this couple died at about 40 days of life with spina bifida. Her older sister was healthy. Her younger brother presented with short stature (adult height: cm 157, SDS - 2.6) with normal spine and hand x-rays and transient GH deficiency

as shown by abnormal GH response at the age of 16 years (GH peak of 3.5 ng/ml following clonidine stimulation; GH peak of 8.1 ng/ml following GHRH stimulation), and normal GH response after stimulation test at the age of 19 years.

The patient was born by spontaneous vaginal delivery after 38 weeks of uncomplicated gestation. Her birth weight was 3300 g (75th–90th centile) and her perinatal history was unremarkable. At age 3 years she was first evaluated for short stature with delayed growth velocity. Signs of scoliosis were evident at this first evaluation. At the age of 10 years she exhibited short stature (height: 114.4 cm; SDS -3.6), short trunk (sitting height: 61.8 cm), retardation of growth velocity (3.2 cm/years; SDS -2.5), and delayed bone age (bone age of 7 years and 10/12, according to the Greulich and Pyle method [Greulich and Pyle, 1959]). Endocrine evaluation of her short stature showed low IGF-I levels (108 ng/ml, SDS -2.5) and GH stimulation showed a GH peak of 2.9 ng/ml after clonidine and of 5.0 ng/ml following arginine stimulation. She was therefore started on GH treatment (33 µg/kg/day) which was continued for 4.5 years. Despite GH therapy at the age of 14.5 years her height was 137.6 cm (SDS -3.9) and her sitting height 76 cm. At a subsequent measurement at the age of 15.5 years her height was cm 139.5 (SDS -3.8) and no clinical and radiological evidence of worsening of the scoliosis with GH treatment was noted. Her pubertal development was normal with menarche at the age of 13 years. She exhibited normal intelligence and at the age of 14.5 years she was attending high school.

Pertinent physical findings included nondysmorphic facial features, short trunk with asymmetrically winged scapulae and scoliosis, dental enamel hypoplasia and failure of eruption of permanent teeth. Her abdomen was protuberant secondary to lordosis, but without organomegaly. An ophtalmologic exam revealed slight myopia and she had a normal hearing evaluation. Results of chromosome analysis showed 46, XX.

Radiographic evaluation showed severe scoliosis and multiple vetrebral fusions involving the thoracic and dorsal segments (Fig 1A) and absence of the posterior elements of the vertebrae from T10-T11. The pelvis X-rays showed coxa vara. Capitate-hamate coalition and short IV metacarpal were noted in the left hand (Fig 1B). There were no signs of bone fusion on foot radiographs. Computerized tomography (CT) scan of the head and cervical spine showed C1–C2 fusion and stenosis of the foramen magnum. Magnetic resonance imaging (MRI) of the hypothalamo-pituitary area did not show any abnormality. However, it showed platybasia, and basilar impression with shortening and flattening of the clivus (Figs 2A and B) but no signs of medullary compression at the cervicomedullary junction.

Molecular analysis of the *FLNB* gene showed that the patient was homozygous for the mutation c.5548G>T predicted to create a translational termination codon (p.G1850X). Each parent and the younger brother were all found to be a heterozygous for this mutation. The molecular analysis of our patient has been report in more detailed elsewhere [Farrington-Rock et al., 2007].

SCT is recognized by the presence of fusion of multiple vertebral bodies in the cervical, thoracic and lumbar spine (block vertebrae), fusion of the posterior elements of the neural arch, and synostoses, most commonly lunate-triquetrum coalition, in at least one of the extremity [Al Kaissi et al., 2005]. SCT is distinguished from other conditions with spine involvement such as spondylocostal dysplasia (OMIM #277300) and cerebrofaciothoracic dysplasia (OMIM #213980) by the lack of rib anomalies and the presence of carpo-tarsal fusions. Additional features variably present in SCT patients include cleft palate, enamel hypoplasia, tooth fusion and agenesis [Breitling et al., 2006], limited joint mobility, and sensorineuronal or mixed hearing loss [Coelho et al., 1998]. Recent reports have also added epiphyseal dysplasia [Honeywell et al., 2002] and cervical spine instability [Seaver and

Boyd, 2000] as possible associated features of the disorder. It is unclear whether a distinct pattern of craniofacial anomalies is part of this condition [Coelho et al., 1998; Seaver and Boyd, 2000; Honeywell et al., 2002; Al Kaissi et al., 2005] and the patient we described did not present with craniofacial dysmorphic features.

Consistent with most of the previously reported cases, our patient had normal intelligence and she never exhibited any seizures. The absence of brain involvement is thought to clearly distinguish patients with *FLNB* mutations from patients with Filamin A (*FLNA*) mutations, although the two genes have a similar pattern of expression in the brain and they are hypothesized to interact with each other [Takafuta et al., 1998; Sheen et al., 2001; Sheen et al., 2002].

Our case is remarkable for the presence of platybasia, basilar impression, and stenosis of the foramen magnum. Given the important health implications of these findings, prompt investigation for cervicomedullary abnormalities are warranted. In addition to the characteristic vertebral fusion, our patient was also found to have absence of the posterior elements of the vertebrae from T10–T11. It is not clear if this abnormality of vertebral development may be related to disturbances of Filamin B function.

Another significant finding in our patient was GH deficiency diagnosed on the basis of reduced growth velocity, delayed bone age, reduced serum IGF-I levels, and decreased GH serum levels following two independent stimulation tests. However, GH therapy did not result in a significant height improvement and this may be due to the severe spinal deformities. The occurrence of GH deficiency in our patient with SCT syndrome may be purely coincidental. However, the expression of *FLNB* in brain [Sheen et al., 2002] may lead to some speculation on its putative involvement in pituitary dysfunction. Interestingly, GH deficiency was previously reported in cerebrofaciothoracic syndrome, a condition characterized by malformations of the ribs and vertebrae sharing some similarities with those seen in SCT [Kanaka-Gantenbein et al., 2004].

Mutations in the *FLNB* gene have been so far reported in a total of six patients from six unrelated families with SCT [Krakow et al., 2004; Farrington-Rock et al., 2007]. In all cases the mutations were either nonsense or frameshift mutations that predicted premature translation terminations. Our patient born to a consanguineous couple was also found to harbor a homozygous nonsense mutation. The parents of the proband were both found to carry the mutation and showed short stature. The younger brother of the proband also exhibited short stature and transient growth deficiency.

Detailed analysis of the phenotype from further SCT cases will clarify whether pituitary dysfunction is indeed a feature of this condition and whether *FLNB* haploinsufficiency may be a predisposition factor for short stature. Studies from the mouse knock-out model of the human SCT [Farrington-Rock et al., 2007] may also be instrumental in clarifying the role of Filamin B during skeletogenesis and pituitary development.

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REFERENCES

- Al Kaissi A, Ghachem MB, Nassib N, Ben Chehida F, Kozlowski K. Spondylotarsal synostosis syndrome (with a posterior midline unsegmented bar). *Skeletal Radiol.* 2005; 34:364–366. [PubMed: 15891931]

- Breitling M, Lemire EG, Rabin M. Spondyllocarpotarsal synostosis syndrome: MRI evaluation of vertebral and disk malformation. *Pediatr Radiol*. 2006; 36:866–869. [PubMed: 16761119]
- Coelho KE, Ramos ES, Felix TM, Martelli L, de Pina-Neto JM, Niikawa N. Three new cases of spondyllocarpotarsal synostosis syndrome: clinical and radiographic studies. *Am J Med Genet*. 1998; 77:12–15. [PubMed: 9557886]
- Farrington-Rock C, Kirilova V, Dillard-Telm L, Borowsky AD, Chalk S, Rock MJ, Cohn DH, Krakow D. Disruption of the *Flnb* gene in mice phenocopies the human disease spondyllocarpotarsal synostosis syndrome. *Hum Mol Genet*. 2007
- Greulich, W.; Pyle, SI. Radiographic atlas of skeletal development of the hand and wrist. Stanford, CA.: Stanford University Press; 1959.
- Honeywell C, Langer L, Allanson J. Spondyllocarpotarsal synostosis with epiphyseal dysplasia. *Am J Med Genet*. 2002; 109:318–322. [PubMed: 11992487]
- Jones, KL.; Guthrie, RD.; Smith, DW. Case report 8. Syndrome Identification: 10–11. 1973.
- Kanaka-Gantenbein C, Fryssira H, Chrousos G, Mastorakos G. Growth hormone deficiency in a case of cerebrofaciothoracic syndrome in one of two affected siblings. *Am J Med Genet A*. 2004; 129:330. [PubMed: 15326640]
- Krakow D, Robertson SP, King LM, Morgan T, Sebold ET, Bertolotto C, Wachsmann-Hogiu S, Acuna D, Shapiro SS, Takafuta T, Aftimos S, Kim CA, Firth H, Steiner CE, Cormier-Daire V, Superti-Furga A, Bonafe L, Graham JM Jr, Grix A, Bacino CA, Allanson J, Bialer MG, Lachman RS, Rimoin DL, Cohn DH. Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. *Nat Genet*. 2004; 36:405–410. [PubMed: 14991055]
- Langer LOJ, Moe JH. A recessive form of congenital scoliosis different from spondyllothoracic dysplasia. *BD:OAS*. 1975; XI:83–86.
- Seaver LH, Boyd E. Spondyllocarpotarsal synostosis syndrome and cervical instability. *Am J Med Genet*. 2000; 91:340–344. [PubMed: 10766994]
- Sheen VL, Dixon PH, Fox JW, Hong SE, Kinton L, Sisodiya SM, Duncan JS, Francois Dubeau, Scheffer IE, Schachter SC, Wilner A, Henchy R, Crino P, Kamuro K, DiMario F, Berg M, Kuzniecky R, Cole AJ, Bromfield E, Biber M, Schomer D, Wheless J, Silver K, Mochida GH, Berkovic SF, Andermann F, Andermann E, Dobyns WB, Wood NW, Walsh CA. Mutations in the X-linked filamin 1 gene cause periventricular nodular heterotopia in males as well as in females. *Hum Mol Genet*. 2001; 10:1775–1783. [PubMed: 11532987]
- Sheen VL, Feng Y, Graham D, Takafuta T, Shapiro SS, Walsh CA. Filamin A and Filamin B are co-expressed within neurons during periods of neuronal migration and can physically interact. *Hum Mol Genet*. 2002; 11:2845–2854. [PubMed: 12393796]
- Takafuta T, Wu G, Murphy GF, Shapiro SS. Human beta-filamin is a new protein that interacts with the cytoplasmic tail of glycoprotein Ibalph. *J Biol Chem*. 1998; 273:17531–17538. [PubMed: 9651345]

Figure 1.

A. Radiograph of the spine showed scoliosis, fusion of the thoracic vertebrae. **B.** Radiograph of the right hand showed capitate-hamate fusion and delayed bone age.

Figure 2.

A and B. Brain and spine MRI showing platybasia, deformity of the pons and medulla due to basilar impression, C1–C2 fusion, and foramen magnum stenosis.