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Available online 4 December 2020

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https://doi.org/10.1016/j.rec.2020.11.002
1885-5857/
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Shprintzen-Goldberg syndrome and aortic dilatation: apropos of 2 new cases

Síndrome de Shprintzen-Goldberg y dilatación aórtica: a propósito de dos nuevos casos

To the Editor,

Shprintzen-Goldberg syndrome (SGS) is a connective tissue disorder that must be included in the differential diagnosis of aortic syndromes such as Marfan syndrome (MS) and Loeys-Dietz syndrome (LDS). SGS is caused by pathogenic variants in the *SKI* gene, which is involved in the transforming growth factor beta (TGF-beta) signaling pathway.[1,2] Fewer than 100 patients have been reported with confirmed SGS. The phenotype includes craniofacial dysmorphism (such as dolichocephaly/scaphocephaly, a prominent forehead, proptosis, hypertelorism, auricular anomalies, and microretrognathia), skeletal, skin, and eye abnormalities, valvular heart diseases, aortic root dilatation, neurological defects, behavioral disorders, and various degrees of cognitive deficit.[3–5]

We report 2 unrelated patients and discuss our diagnostic and therapeutic approach with special reference to the aortic surgery indication.

The first patient was diagnosed at 12 years of age with MS based on clinical criteria (systemic score ≥ 7). His parents were not

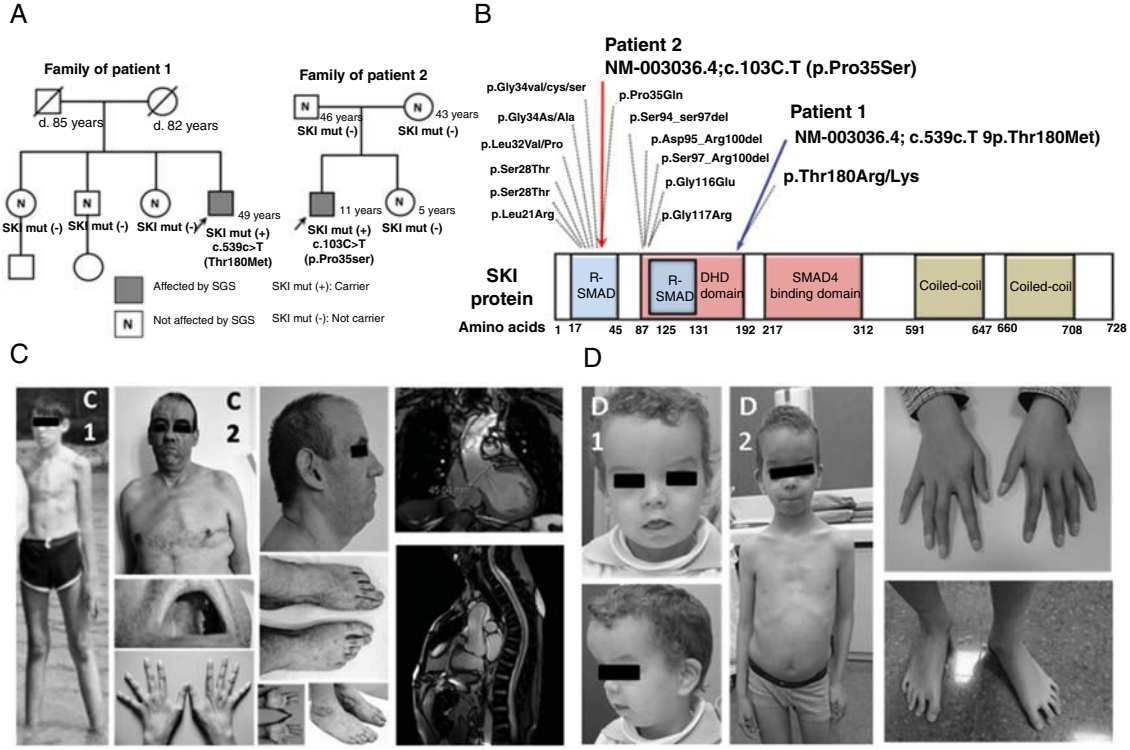

Figure 1. Clinical and genetic study of the probands and their families. A: pedigrees of the families and the genetic study results. B: variants described in the *SKI* gene at the protein level. C: phenotypes of patient 1 at 12 and 45 years of age (C1 and C2); cardiovascular magnetic resonance imaging of the patient (aortic root diameter, 45 mm). D: phenotypes of patient 2 at 4 and 9 years of age (D1 and D2); photographs taken with prior informed consent. SGS, Shprintzen-Goldberg syndrome.

Table 1
Phenotypes of patients 1 and 2 and of carriers of variants affecting amino acids Thr180 and Pro35

	Patient 1	Carriers of variants in AA p.Thr180[a] (n = 9)[5]	Patient 2	Carriers of variants in AA p.Pro35[b] (n = 6)[2–4]
Age at diagnosis	45 y	Average, 15.8 (range, 2-47) y	4 y	Average, 17.5 (range, 6-46) y
Age at last follow-up	49 y	Average, 21.8 (range, 3-49) y	11 y	ND
SKI gene variants	c.539C > T, p.Thr180Met	p.Thr180Met (5), p.Thr180Lys (3), p.Thr180Arg (1)	c.103C > T, p.Pro35Ser	p.Pro35Ser (5), p.Pro35Gln (1)
Inheritance	Sporadic (without paternal samples)	7 de novo 2 sporadic (without paternal samples)	De novo	6 de novo
Craniosynostosis	Brachycephaly	0/7, 2 ND	Scaphocephaly	6/6
Ocular proptosis	Yes	4/8, 1 ND	Yes	6/6
Hypertelorism	Yes	6/8, 1 ND	Yes	6/6
Visual acuity abnormalities	No	9 ND	Myopia and astigmatism	1/6
High-arched palate	Yes	8/8, 1 ND	Yes	4/4, 2 ND
Ear abnormalities	Large outer ears	1/7, 2 ND	High-set ears	1/1, 5 ND
Malar hypoplasia	Yes	5/8, 1 ND	Yes	6/6
Micrognathia or retrognathia	Yes	5/9	Yes	6/6
Prolapse/mitral valve regurgitation	No	4/9	Mitral valve regurgitation	3/6
Aortic dilatation	Aortic root dilatation (45 mm)	6/9	No (24-mm aortic root)	1/6
Arterial tortuosity	No	0/4, 5 ND	No	1/6 (p.Pro35Gln carrier): vertebrobasilar and internal carotid
Thoracic deformity	Pectus carinatum	8/9	Pectus excavatum	3/3, 3 ND
Arachnodactyly	Yes	8/9	Yes	6/6
Tall stature (for age)	Yes	ND	Yes	ND
Dolichostenomelia	Yes	6/9	Yes	6 ND
Osteopenia	Yes	9 ND	No	6 ND
Scoliosis or kyphosis	Severe kyphoscoliosis	4/8, 1 ND	No	4/5, 1 ND
Joint laxity	Yes	8/9	No	3/3, 3 ND
Joint contractures	No	4/8, 1 ND	Yes, camptodactyly	5/5, 1 ND
Foot deformity	Yes (bilateral corrected)	9/9	Yes	6 ND
Acetabular protrusion	No	4/5, 4 ND	Pelvic tilt due to right femoral dysmetria	6 ND
Flat feet	Yes	9/9	No	6 ND
Skin abnormalities	Stretch marks, oily skin with nevus comedonicus	3/9	Translucent skin	3/5 inguinal hernia, 1 ND
Venous abnormalities	Varicose veins in the LLs	9 ND	No	6 ND
Hypotonia	Yes	2/9	No	1/1, 5 ND
Other neuromuscular abnormalities	No	9 ND	Psychomotor retardation	No
Brain abnormalities	ND	9 ND	Dysplasia of the corpus callosum and hippocampus	6 ND
Dural ectasia	No	9 ND	No	1/1, 5 ND
Cognitive deficit	No	0/8, 1 ND	Mild	6/6
Learning problems	No	3/8, 1 ND	Yes	6 ND
Speech disorder	Yes	9 ND	Yes	6 ND
Behavioral disorders	ND	9 ND	ADHD	6 ND
Cancer	No	9 ND	Hepatoblastoma	6 ND
Other anomalies	No	ND	Right hemibody hypertrophy	ND

ADHD, attention deficit hyperactivity disorder; LLs, lower limbs; ND, not determined.
[a] p.Thr180Arg, p.Thr180Lys, and p.Thr180Met.
[b] p.Pro35Gln and p.Pro35Gln.

consanguineous and none of his parents or siblings had the same phenotype. At 45 years old, aortic root dilatation (45 mm) was detected (figure 1) and its prophylactic surgical replacement was planned, given the suspected MS. The patient was referred to the inherited cardiovascular disease unit for study. A genetic study was performed using next-generation sequencing (NGS) (35 genes, including *FBN1*), which identified the p.Thr180Met variant in the *SKI* gene. In addition to the marfanoid habitus, the patient exhibited a characteristic craniofacial dysmorphism, without intellectual disability (table 1). None of his siblings had the variant and, although the parents were not studied, they died at advanced ages. The most likely explanation is that the variant in question is de novo. The patient was diagnosed with SGS and a wait-and-see approach was adopted. After 4 years, no events have occurred and the aortic diameter is stable.

The p.Thr180Met variant has been reported in 5 sporadic cases of SGS and is classified as pathogenic.[5] Two other variants have been described in 4 patients with SGS that affect the same amino acid. In total, 9 affected carriers have been reported; 6 were found to have aortic dilatation at between 15 and 47 years of age: only 1 of these patients was treated with surgery, at 47 years old, after the dilatation reached a diameter of 59 mm. The cognitive deficit appears to be mild or absent in these carriers.

The second patient underwent a genetic study at 4 months old due to craniofacial dysmorphism and prenatally diagnosed ventriculomegaly. Umbilical hernia and hemihypertrophy were evident and hepatoblastoma was identified on ultrasound. Beckwith-Wiedemann and otopalatodigital syndromes were ruled out via molecular analysis. When the patient was 4 years old, marfanoid habitus was observed, as well as skeletal anomalies and a learning disorder, and SGS was suspected (figure 1). A genetic study of the *SKI* gene undertaken using Sanger sequencing identified the p.Pro35Ser variant. The patient is currently 11 years old and does not have aortic dilatation (a 24-mm aortic root).

The p.Pro35Ser variant has been reported to be pathogenic in 5 sporadic cases of SGS. Another variant has been described in 1 patient with SGS (table 1) that affects the same amino acid. In total, 6 affected carriers have been reported at between 6 and 46 years old, and only 1 carrier of another variant (p.Pro35Gln) required surgical intervention at 16 years old due to aortic root dilatation (Z-score = 7.01; the aortic diameter was not reported).[2–4]

SGS displays a complex phenotype requiring its differential diagnosis with MS and LDS. In these syndromes, the surgical indication for aortic dilatation is clearly established. However, there are no clear recommendations for SGS. To date, no SGS patients have been reported to have died from aortic dissection. Close follow-up of the aortic diameter is recommended if risk factors are not present. Prophylactic surgery can be indicated according to some expert recommendations (in the 50-55-mm range or with a rate of progression > 5 mm/y[6]). Given the lack of large studies of this disease due to its very low prevalence, the reporting is required of more clinical cases.

The clinical application of gene panels via NGS to the study of aortic syndromes facilitates the analysis of these overlapping diseases that have been linked to adverse cardiovascular events, which can be less severe or very severe and/or multiple and require more aggressive clinical and surgical approaches.

CONFLICTS OF INTEREST

L. Monserrat is a shareholder in the genetic company Health in Code. The other authors have no conflicts of interest to report.

Acknowledgments

We particularly thank the patients and their families for sharing their clinical information and images for this article. We also thank Dr Carme Vila Obradors (of the primary care team of Sant Quirze del Vallès) for her commitment to children with rare diseases.

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Available online 18 January 2021

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https://doi.org/10.1016/j.rec.2020.11.006
1885-5857/
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