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Original research

Shprintzen-Goldberg syndrome: follow-up of the cardiovascular features in an international cohort of 29 patients with SGS

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ABSTRACT

Background Shprintzen-Goldberg syndrome (SGS) shares skeletal features with Marfan syndrome (MFS), but differs in its craniofacial and neurodevelopmental features. Cardiovascular features have been specifically investigated in few of the 57 known patients with SGS described in the literature, making it difficult to determine their prevalence and characteristics.

Methods We reviewed the medical records of an international cohort of 29 patients, with a particular focus on cardiovascular features. Data were compared with those of MFS.

Results The sex ratio was 1.9 and median age was 23 years (range: 4–54). 13 patients (44.8%) had mitral regurgitation (MR), 11 (37.9%) had a thoracic aortic aneurysm (TAA) and 9 (31.1%) had aortic regurgitation (AR). No cases of aortic dissection were reported. None had beta-blockers as a primary prevention of aortic events. The Kaplan-Meier method revealed a 30 years risk of 47%, 33% and 22% for occurrence of MR, TAA and AR, respectively. A statistically significant association was found between variants in the Dachshund Homology Domain and the risk of aortic aneurysm (11/20 vs 0/9, p=0.036).

Conclusion Patients with SGS also significantly have cardiovascular manifestations, encouraging the implementation of a follow-up and preventive cardiovascular treatment identical to that of MFS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Among the systemic connective tissue disorders underpinned by the transforming growth factor beta signalling pathway, Shprintzen-Goldberg syndrome (SGS) appears to be much rarer than Marfan syndrome (MFS) and is mainly known for its skeletal, craniofacial or neurodevelopmental features. Although an integral part of the differential diagnosis of MFS, few studies have focused on describing the cardiovascular involvement of SGS.

WHAT THIS STUDY ADDS

⇒ In a cohort of 29 patients with SGS, we showed that almost half of patients (44.8%) had mitral regurgitation and more than one-third of patients (37.9%) had thoracic aortic aneurysm. We also found a statistically significant association between the presence of a Dachshund Homology Domain variant and the occurrence of aortic aneurysm (p=0.036).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings therefore support rigorous cardiovascular monitoring of these patients with SGS, in line with current recommendations for MFS.

INTRODUCTION

Among the syndromes involving the transforming growth factor beta (TGF-β) signalling pathway, Shprintzen-Goldberg syndrome (SGS) is a rarer systemic connective tissue disorder than Marfan syndrome (MFS).[1 2] Considered as one of its differential diagnoses, both syndromes share common skeletal features. However, SGS is characterised by distinctive craniofacial features and neurodevelopmental features such as motor and cognitive delays, or mild-to-moderate intellectual disability.

Even though the clinical features of this syndrome were well described for more than 40 years,[3 4] its molecular basis was not discovered until 2012,[5 6] with a majority of missense variants in hotspot regions in the exon 1 of the *SKI* (*Sloan Kettering Institute*) gene on the chromosome 1, mostly occurring de novo. To date, 24 different pathogenic variants have been described in the literature, in 57 published SGS-affected individuals.[5–13] 49 patients shared 21 different missense variants, and 8 patients shared 3 different in-frame deletions. Missense variants occurred either in the R-SMAD binding domain (SMAD-receptor binding domain, molecular domain for interaction with SMADs, group of related intracellular proteins critical for transmitting to the nucleus signals from the transforming growth factor-β (TGFβ) superfamily - 34 patients; amino acids (aa) 20–35) or in the Dachshund Homology Domain (DHD) (15 patients; aa 112–117) and on the 180th amino acid. All of the in-frame deletions occurred on the DHD domain (eight patients; aa 94–100).

The consequences of these variants on the TGF-β signalling pathway are well-known in the literature.[14] Cardiovascular features are at the forefront in MFS and should not be overlooked in MFS-like diseases such as SGS. Thoracic aortic aneurysm (TAA) and mitral valve prolapse (MVP), the two main cardiovascular features of MFS, have been reported in about one-third of the 57 individuals with *SKI* variants, with some patients having to undergo surgery because of a voluminous TAA.[5 6 15] To our knowledge, the literature does not contain any case report of aortic dissection in individuals with *SKI* variants. Some have hypothesised that aortic complications are less frequent and less severe in SGS than in MFS, while others suggest that the lower median age of patients with SGS requires a longer follow-up to determine precisely their prevalence and characteristics in this population. Some reports also suggest that the cardiovascular involvement in SGS could extend to the peripheral arteries, with arterial tortuosity and peripheral artery aneurysms, but warranting further descriptions. To date, these cardiovascular features had been specifically investigated in few of the 57 individuals with *SKI* variants.[5 6 15]

In this study, we reviewed the medical records of an international cohort of 29 previously published or unpublished patients in order to further describe the cardiovascular manifestations of SGS and to improve our knowledge in order to optimise the cardiovascular follow-up and treatment.

MATERIAL AND METHODS

Patient recruitment

This study was initiated by the FAVA-Multi (French rare diseases Healthcare Network : rare multisystemic vascular diseases) and AnDDI-Rares (French rare diseases Healthcare Network : rare developmental defect and rare intellectual disability) networks in France, in order to obtain a better description of the cardiovascular involvement of patients with SGS patients with a confirmed pathogenic or likely pathogenic *SKI* variant, alive or dead. In collaboration with the Marfan Reference Centre for Rare Diseases at the Bichat Hospital in Paris, we created a data collection sheet, gathering each patient's manifestations, with a focus on cardiovascular features. This document was sent to the collaborators of our previous studies.[6 15] Thanks to a collaboration call through the ERN ITHACA (European Reference Network for Developmental Anomalies and Intellectual Disability) network, we included two new patients from Spain and the Netherlands. The cardiologist filled in the data collection sheet with the last visit data. All data were collected anonymously from patient's care and did not require additional investigations.

Data collection

The data collection sheet was composed of four parts (available on request): Part 1 provided general information (gender, age, genotype, family history of SGS, death and cause of death if applicable); Part 2 collected most of the extracardiac clinical features known in the SGS (neurodevelopmental, craniofacial, skeletal, ocular, cutaneous and miscellaneous features); Part 3 focused on the cardiovascular symptoms, including ECG as well as valvular and aortic involvement; Part 4 investigated the cardiovascular risk factors (tobacco consumption, dyslipidaemia, diabetes or arterial hypertension).

We investigated the presence of mitral or aortic valvular disease and the presence of an aortic aneurysm. Mitral valve disease (MVD) was defined as the presence of MVP and/or mitral regurgitation (MR). Aortic valve disease (AVD) was defined as the presence of bicuspid aortic valve (BAV) and/or aortic regurgitation (AR).

In the case of aortic dilatation, aortic diameters were requested at the time of the diagnosis of the aneurysm and at the highest value over time, for the following parts of the aorta: the four segments of the ascending aorta, the descending thoracic aorta and the abdominal aorta. For children (<18 years), Z-scores of the ascending aorta were calculated according to the *2010 Paris AJC* (Am J Cardiol) nomogram[16]; a Z-score greater than or equal to +3 SD was considered to confirm the presence of an aneurysm. For adults, Z-scores of the ascending aorta were calculated according to the *2014 Campens* nomogram[17]; a Z-score greater than or equal to +2 SD was considered to confirm the presence of an aneurysm. Concerning the descending thoracic aorta and abdominal aorta, Z-scores were calculated according to the *Detroit* nomogram for the corresponding parts called 'distal arch' and 'aorta at diaphragm', respectively. *2010 Paris AJC* and *Detroit* nomograms were available through the software 'Echo Z-score calculators' (available at https://www.rchsd.org/zscore/). *2014 Campens* nomogram was available on https://www.rchsd.org/zscore/.

We also asked about the cardiovascular treatment in order to evaluate the medical practices, and especially the use of beta-blockers in the prevention of TAA.

Statistical analysis

The main statistical analysis was a descriptive analysis of the proportion of patients with each of the cardiovascular signs studied. Qualitative data were expressed as percentages; quantitative data were expressed as medians (min; max).

The χ^2 test was used to analyse the association between the main cardiovascular events (MR, AR and TAA) and patient characteristics such as gender, age or the protein domain affected by the variant (DHD or R-SMAD domain).

We also analysed the cumulative probability of occurrence of MR, AR and TAA over time using the Kaplan-Meier survival curve method.

A time-to-event analysis technique was used to estimate a reliable cumulative probability of observing each event. The baseline date (time zero) was the date of birth and the time to event diagnosis was defined as the interval between the date of birth and the date of the manifestation of the event. The Kaplan-Meier method was used to estimate the cumulative probabilities of clinical manifestations. SAS software V.9.2 and Stata software V.8 were used for all statistical analyses. P values <0.05 were considered significant.

RESULTS

Population characteristics

We received the medical records of 29 patients from four European countries, USA and Australia (online supplemental table 1). Of the 29 patients, 19 were male (65.5%) and 10 were female (34.5%), carrying 13 different *SKI* pathogenic variants. 19 cases were sporadic and 10 cases were familial cases distributed in three families. The median age at last physical examination was 23 years (4; 54). Three patients of the cohort were dead. 20 patients carried a variant in the DHD domain (69%) and 9 patients carried a variant in the R-SMAD binding domain (31%). Two new missense variants were reported in the DHD domain: the c.349G>A (p.Gly117Ser) and the c.350G>C (p.Gly117Ala). The reference transcript of the *SKI* gene can be found in the previous publication by Carmignac *et al*.[6] As most of this work was based on observations already published, the extracardiac features are not detailed here, and are listed in the online supplemental table 2.

Cardiovascular manifestations of SGS

In our cohort, 19 patients (65.5%) had at least one of the following cardiovascular features: MVD, AVD, TAA, peripheral artery disease (PAD) or congenital heart disease (CHD) (online supplemental tables 1and 3). Thus, 15 patients (51.7%) had at least one valvular disease, distributed as follows: 7 patients had both MVD and AVD (24.1%); 6 patients had isolated MVD (20.7%) and 2 patients had isolated AVD (6.9%).

MVD was reported in 13 patients (44.8%): all were affected by MR and 9 patients had MR due to MVP (69%). We found no case of MVP without MR. The median age at diagnosis of MR was 17.5 years (3; 45). The median severity of MR was 1/4 (1/4; 4/4). Four patients underwent mitral valve surgery (13.8%). Patient 22, a male in the 10–15 years age range, developed infective endocarditis on the mitral valve leading to a 3/4 MR with MVP and requiring surgical management through a valve-sparing technique. Patient 26, a male in the 30–35 years age range, had developed MR due to MVP from the age of 24, progressing to the maximum severity of 4/4 and requiring mechanical valve replacement at the age of 31. The same applies to patient 29, a male in the 50–55 years age range, who presented with 3/4 MR at the age of 40. Patient 17, a male in the 45–50 years age range, must be described separately because his cardiovascular features are not secondary to SGS. He had ischaemic heart disease in the context of multiple cardiovascular risk factors. This ischaemic heart disease was responsible for an alteration in left ventricular ejection fraction (LVEF) to 30% and ischaemic MR grade 2/4. He underwent annuloplasty.

AVD was reported in 9 patients (31.1%): 8 patients had AR with a normal tricuspid aortic valve (27.6%) and 1 patient had BAV without AR (3.5%). Of the 8 patients, 5 (62.5%) had an aneurysm on the sinuses of Valsalva. The median age at diagnosis of AR was 40 years (range 3–51). The median severity of AR was 1/4 (1/4; 3/4). Four patients benefited from aortic valve surgery (13.8%): one patient underwent Bentall surgery and three patients underwent Tirone David surgery.

TAA was reported in 11 patients (37.9%), involving the ascending aorta in all cases and the descending thoracic aorta in 2 patients (6.9%). In seven patients (63.6%), the aneurysm was confined to the sinuses of Valsalva; in three patients (27.3%), the aneurysm was confined to the tubular part of the aorta. Finally, in one patient (9.1%), the aneurysm involved both the sinuses of Valsalva and the tubular part of the ascending aorta. The median age at diagnosis of ascending TAA was 28 years (range 15–46). The median age at diagnosis of descending TAA was 34.5 years (range 31–38 years). We found no cases of abdominal aortic aneurysm or aortic dissection in our cohort. Four patients underwent aortic surgery (13.8%). Patient 1, a male in the 50–55 years age range, was lost to follow-up until the age of 46 years when he resumed medical follow-up after an aneurysm of the left popliteal artery had ruptured spontaneously. After an emergency embolisation, he was diagnosed with AR and an ascending TAA (59 mm at the sinuses of Valsalva, ie, Z-score+5.5; 58 mm on the tubular aorta, ie, Z-score+6), for which he required surgery using the Bentall technique. Patient 3, a male in the 35–40 years age range, was diagnosed with a TAA at the age of 31 years, involving both the ascending and descending thoracic aorta (50 mm, ie, Z-score+4.8 on the sinuses of Valsalva; 37 mm, ie, a Z-score of+5.1 on the descending part). At the age of 37, he underwent a Tirone David procedure to treat the ascending TAA. Patient 16, a male in the 45–50 years age range, was diagnosed 3 years earlier with an ascending TAA confined to the sinuses of Valsalva (48 mm, Z-score+3.5) and was rapidly treated that same year with Tirone David surgery. Patient 23, a male in the 20–25 years age range, was diagnosed at the age of 15 with an ascending TAA. He underwent Tirone David surgery in the same year, as he had mild AR from infancy.

PAD was less commonly reported in our patients but not specifically looked for by clinicians. It concerned two patients (Patient 1 and Patient 29; 6.9%) who displayed peripheral artery involvement, often in multiple arterial sites (cerebral, carotid, subclavian, mesenteric and lower limb arteries). Patient 1 has been treated by an emergency embolisation. Patient 29 developed mitral infective endocarditis and died before his peripheral arterial disease could be treated.

Finally, Patient 25 was the only one to carry a CHD associated with her SGS as she had a partial anomalous pulmonary venous drainage of the left upper pulmonary veins to the right atrium.

LVEF data were available in 20 patients. Of these, Patient 29 was the only patient who had an impaired LVEF below 50% in the context of SGS, as he had an LVEF of 38% because of a dilated cardiomyopathy secondary to progressive severe MR. The second patient with impaired LVEF was patient 17 with ischaemic heart disease. The other 18 patients all had a normal LVEF, that is, LVEF values ≥50%.

Other cardiovascular features and risk factors

We investigated the following cardiovascular symptoms: faints, syncope, palpitations and dyspnoea. Most patients were asymptomatic; three patients had at least one of the physical and/or functional symptoms (10.3%) (online supplemental table 4). Six patients had ECG abnormalities (20.7%). However, most of these ECG abnormalities were known not to cause symptoms on their own. They were as follows: right bundle branch block, left anterior hemiblock, first-degree atrioventricular block, left ventricular electrical hypertrophy and ventricular extrasystoles. Only ventricular extrasystoles could cause symptoms and explain the palpitations experienced by Patient 29.

Patient 26 presented with dyspnoea, which may have been secondary to increased pulmonary pressures due to a post-capillary pulmonary arterial hypertension mechanism as he developed progressive 4/4 MR. Finally, Patient 29 presented with faints and dyspnoea because of a dilated cardiomyopathy secondary to a progressive severe MR evolving over the years, which was responsible for ventricular extrasystoles leading to palpitations. He died of infective endocarditis.

We investigated the following cardiovascular risk factors: arterial hypertension, diabetes, dyslipidaemia and smoking. Two patients (6.9%) had risk factors. Patient 6, a male in the 20–25 years age range, had juvenile diabetes since the age of 13, currently treated with insulin. Patient 17 had arterial hypertension, dyslipidaemia and was a smoker.

Cardiovascular preventive treatment

Beta-blockers are the only medication that has been proven to be effective to prevent aortic aneurysm and aortic dissection, unlike ACE inhibitors (Angiotensin-converting enzyme inihibitors) and ARB (Angiotensin 2 receptor blockers) (table 1 and online supplemental file 4).[16 17] We investigated the prescription of beta-blockers in our cohort (type, posology, indication). Of the 29 patients in our cohort, 9 patients (31%) were receiving beta-blockers either as monotherapy or in combination with another therapeutic class. Four patients received beta-blockers as secondary preventive treatment following the diagnosis of a TAA and four other patients were treated for MR or AR. One patient, Patient 17 was receiving beta-blockers as secondary prevention for ischaemic heart disease.

Table 1 Indication and posology for beta-blockers in our cohort

	Age range (years)	Treatment and posology	Indication
Patient 1	50–55	Bisoprolol 2.5 mg/day	Secondary prevention of aneurysm
Patient 3	35–40	Bisoprolol 5 mg/day	Secondary prevention of aneurysm
Patient 8	25–30	Bisoprolol 10 mg/day	Secondary prevention of aneurysm
Patient 9	30–35	Atenolol 50 mg/day	Treatment of mitral and aortic regurgitations
Patient 12	15–20	Unknown beta-blocker	Secondary prevention of aneurysm
Patient 17	45–50	Bisoprolol 2.5 mg/day	Secondary prevention of ischaemic heart disease
Patient 23	20–25	Atenolol 0.7 mg/kg/day (40 mg)	Treatment of mitral and aortic regurgitations
Patient 26	30–35	Carvedilol 12.5 mg/day	Treatment of mitral regurgitation
Patient 29	50–55	Metoprolol (unknown posology)	Treatment of mitral regurgitation

Cause of death

Three patients were dead in our cohort: Patient 25, Patient 27 and Patient 29.

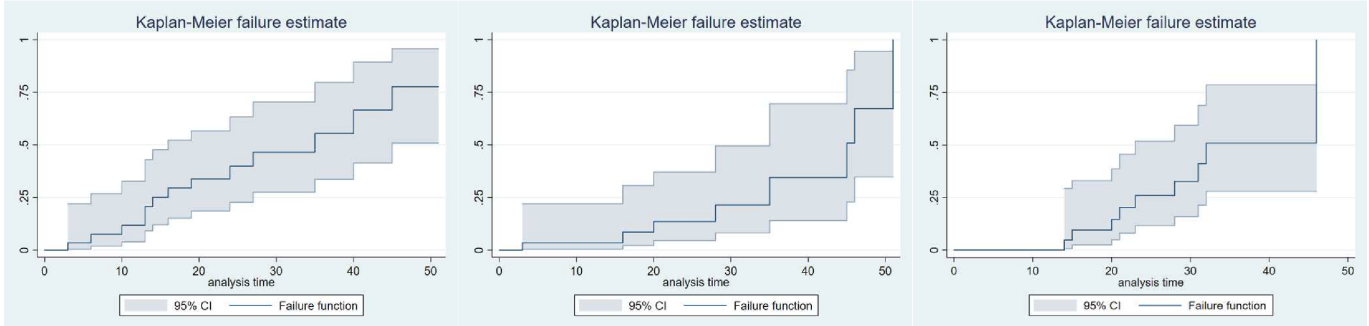
Patient 25, a female in the 25–30 years age range, displayed most of the clinical extracardiac features of SGS. She had a de novo pathogenic variant in the R-SMAD hotspot: c.101G>T (p.Gly34Val), as there was no family history of SGS. She suffered a syncope during the meal, and first aid measures were ineffective. The coroner identified a known marked MVP with calcification of the mitral annulus, which led to left atrial dilatation. MVP and MR had been diagnosed when she was 3 years old. Tricuspid and aortic valves also showed marked dysplasia. Finally, she displayed partial anomalous pulmonary venous drainage of the left upper pulmonary veins to the right atrium. There was neither aortic aneurysm nor aortic dissection. It was presumed that death was caused by the mitral valvulopathy, leading to ventricular arrhythmia as MVP is well known to cause ventricular arrhythmia, especially in an untreated patient.

Patient 27, a female in the 5–10 years age range, carried a pathogenic variant in the R-SMAD hotspot: c.100G>A (p.Gly34Ser). She mostly displayed neurodevelopmental and craniofacial findings of SGS. She had a family history of SGS as her older brother, a male in the 10–15 years age range, had SGS (Patient 28). Patient 27 did not display any cardiovascular physical nor functional symptoms; no cardiovascular treatment had been initiated. She died of a midgut volvulus, complicated by bowel perforation and necrosis.

Patient 29, a male in the 50–55 years age range, developed mitral infective endocarditis on a mechanical valve 15 years after valve replacement, and died of acute pulmonary oedema secondary to acute heart failure.

Association of gender with MR, AR or TAA and cumulative probability of each cardiovascular feature over time

We found no statistically significant association between gender and MR, AR or TAA (p respectively 0.29, 0.13 and 0.062) (figure 1). Survival analysis using the Kaplan-Meier curve showed that the cumulative probability of developing MR at 30 years



A: Kaplan Meier curves for cumulative probability of MR over time

B: Kaplan Meier curves for cumulative probability of AR over time

C: Kaplan Meier curves for cumulative probability of TAA over time

Figure 1 Kaplan-Meier curves for survival analysis of main cardiovascular events. AR, aortic regurgitation; MR, mitral regurgitation; TAA, thoracic aortic aneurysm.A: Kaplan Meier curves for cumulative probability of MR over time. The cumulative probability of developing MR at 30 years was 47% (95% CI: 28-70%). The median follow-up was 20 years. B: Kaplan Meier curves for cumulative probability of AR over time. The cumulative probability of developing AR at 30 years was 22% (95% CI: 8-50%). The median follow-up was 23 years. C: Kaplan Meier curves for cumulative probability of TAA over time. The cumulative probability of developing a TAA at the age of 30 years to be 33% (95% CI: 16-59%). The median follow-up was 21 years.

was 47% (95% CI: 28% to 70%). The median follow-up for this cardiovascular event was 20 years (range 3–51). The cumulative probability of developing AR at 30 years was 22% (95% CI: 8% to 50%). The median follow-up was 23 years (range 3–51). The cumulative probability of developing a TAA at the age of 30 years was 33% (95% CI: 16% to 59%). The median follow-up was 21 years (range 4–46).

Genotype-phenotype correlation

The χ^2 test revealed a statistically significant association between the protein domain and the occurrence of aneurysm (table 2). Indeed, 11/20 patients with variants in the DHD domain have aortic aneurysm against 0/9 patients with variants outside the DHD domain (11/20 vs 0/9, p=0.036).

In addition, of the 11 patients with aortic aneurysm and a DHD domain variant, 5 (45.5%) have a variant on Thr180. Thus, as mentioned by Arnaud *et al* in 2020, it appears that Thr180 is a preferential mutation cluster and is more common in patients with aortic aneurysm compared with other mutation clusters in the DHD domain.

However, regarding the occurrence of MR and AR, we did not find a statistically significant association with the protein domain affected by the patient's variant (respectively, p=0.24 and p=0.14).

DISCUSSION

Our study is the first to focus on the cardiovascular features of a relatively large cohort of patients with SGS. Long considered to be a syndrome with a low aortic risk compared with MFS, we hypothesised that the young median age of published patients could explain this low risk. Indeed, patients with SGS often have greater skeletal and morphological signs than patients with MFS, and therefore an earlier median age at diagnosis and at report. Therefore, we carried out a follow-up of previously published patients, and collected new patients in order to better describe the cardiovascular risks of SGS. The median age of patients with SGS in our study was 23 years, as compared with 16 years in the previous literature. Cardiovascular features of SGS in our cohort essentially consist of mitral regurgitation and thoracic aortic aneurysm. AR is less common, but still affects more than a quarter of patients. The results can be compared with a large international study reporting cardiovascular events in patients with MFS and a pathogenic or probably pathogenic *FBN1* variant, with a median age of 22 years.[18 19] Our study shows that the cardiovascular features of patients with SGS are of the same spectrum as those described in MFS.

MR is the most frequent cardiovascular feature (44.8% of patients) often secondary to MVP (69% of MR), and Kaplan-Meier analysis estimated a 47% cumulative risk before 30 years old (95% CI: 28% to 70%). Most of MR were of mild-to-moderate severity, but the median age of our cohort remains quite young. Observation of the oldest adult patients showed that progressive evolution to the most severe stages could occur, justifying surgery in 13% of patients. In *FBN1* patients, the probability of presenting with MR and MVP at 30 years of age was 24% (95% CI: 21% to 28%) and 43% (95% CI: 40% to 47%), respectively. Surgery for MR at 30 years was uncommon, performed in 3% of patients (95% CI: 2% to 5%).

TAA is also a frequent feature in SGS. When it occurs, it mostly localises at the sinuses of Valsalva. This cardiovascular feature generally occurs later in life than MR, with a 33% risk of aortic aneurysm at 30 years old (95% CI: 16% to 59%). In MFS, the probability of aortic aneurysm at 30 years was 57% in males (95% CI: 52% to 63%) and 50% in females (95% CI: 45% to 55%).[19] Our study showed a statistically significant association between the *SKI* hotspot affected by the variant and the risk of aortic aneurysm, in favour of the DHD domain, which was exclusively represented in patients with aortic aneurysms (p=0.036). However, it was too small to demonstrate any association between gender and the occurrence of TAA (p=0,62). Four patients (13.8%) had aortic surgery because of TAA but none had aortic dissection. The absence of aortic dissection is probably explained by the young age of our patients. In MFS, 9% of males (95% CI: 7% to 13%) and 5% of females (95% CI: 3% to 8%) had aortic dissection at 30 years, and 12% of males (95% CI: 9% to 16%) versus 7% of females (95% CI: 4% to 11%) had aortic surgery at 30 years.[19]

Finally, AR was less frequent. Among the eight patients with AR, five patients had an ascending TAA located in the sinuses of Valsalva, explaining the annulo-ectasising mechanism of aortic valve regurgitation following dilatation of the annulus by the aortic aneurysm. For three other patients, AR still occurred even without aortic aneurysm. In our cohort, one patient had a clear diagnosis of BAV, which can also explain AR.

Two patients of the cohort had peripheral artery aneurysms, and two patients had descending TAA, of which one displayed both features simultaneously. In MFS, non-dissecting distal aortic and peripheral artery aneurysms are infrequently described, in 1.2% of patients.[20] Systematic investigations in SGS should be proposed in order to determine the associated risk. If an arterial aneurysm is diagnosed, we recommend an annual ultrasound Doppler scan.

Cardiovascular features of SGS could be responsible for significant morbidity or mortality. Three of our 29 patients have died. Cardiovascular features appear to be the cause of death in two patients, mainly due to infectious complications (endocarditis) or rhythmic complications (ventricular arrhythmia) of valvular features.

These observations call for rigorous cardiovascular monitoring and preventive treatment of TAA in patients with SGS. As in MFS, echocardiography should be recommended once a year by a cardiologist to monitor the status of the ascending aorta and valves. We suggest that surveillance should begin at 6 years of age. This frequency will be adjusted according to any clinical or ultrasound abnormalities. The presence of echographic

Table 2 Distribution of the different cardiovascular manifestations according to the domain of *SKI* gene variants

	Patients with a DHD variant	Patients with a R-SMAD variant
Number of patients with cardiovascular feature	14 of 20	5 of 9
Median age (years)	21.5 (4–54)	27 (5–37)
Aortic bicuspid valve	1 of 20	0 of 9
Aortic regurgitation	8 of 20	0 of 9
Mitral valve prolapse	6 of 20	3 of 9
Mitral regurgitation	8 of 20	5 of 9
Thoracic ascending aortic aneurysm	11 of 20 5 of 11 at AA position Thr180 6 of 11 at other AA position	0 of 9
Thoracic descending aortic aneurysm	2 of 20	0 of 9
Peripheral arteries aneurysms	2 of 20	0 of 9

DHD, Dachshund Homology Domain; R-SMAD, Interacting domain with SMAD receptor.

abnormalities will guide the performance of additional procedures such as an ECG or Holter rhythm. The frequency of magnetic resonance angiography or CT angiography evaluation to image the entire arterial tree depends on clinical findings. Subacute bacterial endocarditis prophylaxis in those undergoing dental work or other procedures expected to contaminate the bloodstream with bacteria should be considered. Contact sports, competitive sports and isometric exercise should be avoided. Regarding primary preventive treatment, it has been shown in MFS that early treatment by beta-blockers was able to slow the growth rate for aortic aneurysm, leading to less cardiovascular events by reducing haemodynamic stress, even in the absence of aortic dilatation.[21 22] We can presume that the same recommendations should be followed in SGS in the presence of common physiopathology through the TGF-β pathway.

In conclusion, the cardiovascular manifestations of SGS appear to be fairly similar to those of MFS, encouraging the implementation of a follow-up and preventive treatment identical to that of MFS. The frequency of distal aortic and peripheral artery aneurysms remains to be clarified to determine whether targeted follow-up should also be implemented. It seems that patients with variants localised in the DHD domain have a higher aortic risk than patients with variants localised elsewhere, especially when the variant occurs at the Thr180 position. However, it is legitimate to maintain identical monitoring for all patients before confronting these results with other cohorts of patients with SGS. Further studies to accumulate data from more patients at older ages are essential to optimise follow-up of these patients.

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Contributors Y-MB, CB and LF conceived the study and developed the methodology. PA, GJ, DB, FR, GP, AV, FL, PM, JD, MM, CC, CBo, LG, SO, AB, SD-G, MB, EG, BD, GV, J-LA, LAA, ET, SJ, BCh, YD, BCa, BL, MV, LAM, MG, LA, MJB-M, ALS, ST, PG, CT-R, J-CE, SF-E, CBi and NH recruited patients and collected clinical and molecular data. CBi conducted the statistical analysis, and LF validated the interpretation of the results. Y-MB and LF drafted the first version of the manuscript, and all authors contributed to revisions and approved the final version. LF supervised the project and provided overall guidance. LF is the guarantor.

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