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Clinical Report

Shprintzen – Goldberg syndrome without intellectual disability: A clinical report and review of literature

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ABSTRACT

Shprintzen-Goldberg syndrome is a rare systemic connective tissue disorder caused by heterozygous mutations in the Sloan-Kettering Institute (SKI) gene. The clinical presentation is reminiscent of Marfan and Loeys-Dietz syndromes, making differential diagnosis challenging. Shprintzen-Goldberg syndrome's distinctive features are craniosynostosis and learning disabilities. The pathophysiology of these three conditions is similar as they all result in the deregulation of the *transforming growth factor beta* (TGF-β) signaling pathway and thus an altered expression of TGF-β responsive genes.

We report a family of two patients: one with initial suspicion of hypermobile Ehlers-Danlos syndrome and the second with suspicion of Marfan syndrome, as the Marfan systemic score was positive and no craniosynostosis or learning disabilities were described. They were diagnosed with Shprintzen-Goldberg syndrome after a heterozygous probably pathogenic variant in the second mutational hotspot of *SKI* Dachshund homology domain was identified.

We reviewed the genotype-phenotype correlation among the three mutational hotspots in *SKI*: the amino acids 20 to 35 of the receptor-regulated small mothers against decapentaplegic domain (group 1, n = 32), amino acids 94 to 117 of Dachshund homology domain (group 2, n = 12), and threonine 180 of Dachshund homology domain (group 3, n = 11 including our patients).

As the main differential diagnoses of Shprintzen-Goldberg syndrome are Marfan and Loeys-Dietz syndromes, we completed the comparison already made by *Loeys and Dietz. (2008)* of Shprintzen-Goldberg syndrome clinical features among the different mutational hotspots with Marfan syndrome and the different types of Loeys-Dietz syndrome.

In addition to the already described absence of learning disabilities in Shprintzen-Goldberg patients with a pathogenic variant in the threonine 180 of Dachshund homology domain, facial features also appeared to be less severe. The clinical overlap with Marfan and Loeys-Dietz patients requires genetic testing in order to establish an accurate molecular diagnosis at the variant level, and to adapt genetic counseling and clinical management.

1. Introduction

Shprintzen-Goldberg syndrome (SGS) is a rare systemic connective tissue disorder. The exact prevalence is currently unknown. To date, fifty-three patients have been described in the literature (Arnaud et al., 2020; Au et al., 2014; Carmignac et al., 2012; Doyle et al., 2012; O'Dougherty et al., 2019; Saito et al., 2017; Schepers et al., 2015; Zhang et al., 2019).

The clinical presentation is reminiscent of Marfan or Loeys-Dietz syndrome (LDS) (Dietz, 2001; Milewicz et al., 2021; Gouda et al., 2022). Patients with SGS may additionally present delayed motor and cognitive milestones, mild-to-moderate intellectual disability, and craniosynostosis. Clinical overlap between these three disorders can be explained by a shared physiopathology (Takeda et al., 2018; Tecalco-Cruz et al., 2018; Gori et al., 2021).

SGS is caused by heterozygous pathogenic variants in the Sloan-Kettering Institute gene (*SKI*). The mode of inheritance is autosomal dominant. *SKI* is an avian sarcoma viral oncogene homolog located in

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the chromosomal region 1p36.33. This gene consists of seven exons. It encodes the nuclear protein SKI which consists of 728 amino acids. SKI is composed of several domains playing different roles, in particular: the receptor-regulated small mothers against decapentaplegic (R-SMAD) binding domain and the Dachshund homology domain (DHD) transcription regulatory domain. There were three mutational hotspots described within the SKI gene: one in the amino acids 20 to 35 of R-SMAD domain and two within the DHD. SKI acts as a repressor of the *transforming growth factor beta* (TGF-β) signaling pathway (Greally et al., 2006).

TGF-β plays a major pleiotropic role. It regulates many physiological processes in development and tissue homeostasis. Canonical TGF beta pathway starts with TGF-β binding to its transmembrane receptors I (TGFBR1) and II (TGFBR2). This leads to the phosphorylation of downstream small mothers against decapentaplegic II (SMAD2) and III (SMAD3), which then form the activated receptor-regulated SMAD (R-SMAD). The activated R-SMAD binds to SMAD4. The R-SMAD/SMAD4 complex enters the cell nucleus and enables the expression of more than five hundred genes involved in the normal development and maintenance of various organs, including the vascular system and cartilage.

SKI interacts with SMAD2, SMAD3 and SMAD4 and negatively regulates the TGF-β signaling pathway by preventing the formation of the R-SMAD/SMAD4 complex and its nuclear translocation. The TGF-β/SMAD pathway and the co-regulator SKI regulate each other through several positive and negative feedback loops. These cross-regulatory processes control the magnitude and duration of TGF-β signals. *SKI* is ubiquitously expressed and is generally active during development, playing an important role in morphogenesis and homeostasis of the aorta (Takeda et al., 2018; Tecalco-Cruz et al., 2018).

Therefore, any alteration in these regulatory mechanisms can lead to the development of disease (Fig. 1). Deregulation of TGF-β signaling pathway causes aortic aneurysms formation in patients with SGS, as it occurs in Marfan syndrome and LDS. However, the impact on the TGF-β signaling remains controversial (Takeda et al., 2018; Tecalco-Cruz et al., 2018; MacFarlane et al., 2019; Gori et al., 2021).

In patients with SGS, SKI is less degraded and interacts more with SMAD4. Heterozygous pathogenic variants within *SKI* result in increased inhibition of the TGF-β signaling pathway and thus milder expression of TGF-β responsive genes (Gori et al., 2021).

Marfan syndrome is caused by heterozygous pathogenic variants within the fibrillin-1 (FBN1) gene. The fibrillin-1 is a glycoprotein essential for the formation of connective tissue elastic fibers, which also regulates the bioavailability of TGF-β. Pathogenic variants in *FBN1* not only lead to structural weakness of the connective tissue, but also to a release of TGF-β into the extracellular matrix, causing deregulation of the TGF-β signaling pathway (Takeda et al., 2018; Tecalco-Cruz et al., 2018; Gori et al., 2021).

LDS consists of six subtypes, ranging from the most severe to the least severe. Type I and II are caused by heterozygous pathogenic variants within *TGFBR1* and *TGFBR2* respectively. Type VI and III are associated with heterozygous pathogenic variants within *SMAD2* and *SMAD3* respectively (Granadillo et al., 2018; Cannaerts et al., 2019). Types IV and V are caused by heterozygous pathogenic variants within the genes of TGFB2 and TGFB3 ligands respectively (Takeda et al., 2018; Tecalco-Cruz et al., 2018).

2. Objectives & methods

We report a family of two patients with SGS and compare their phenotypes to the fifty-three patients previously described in the

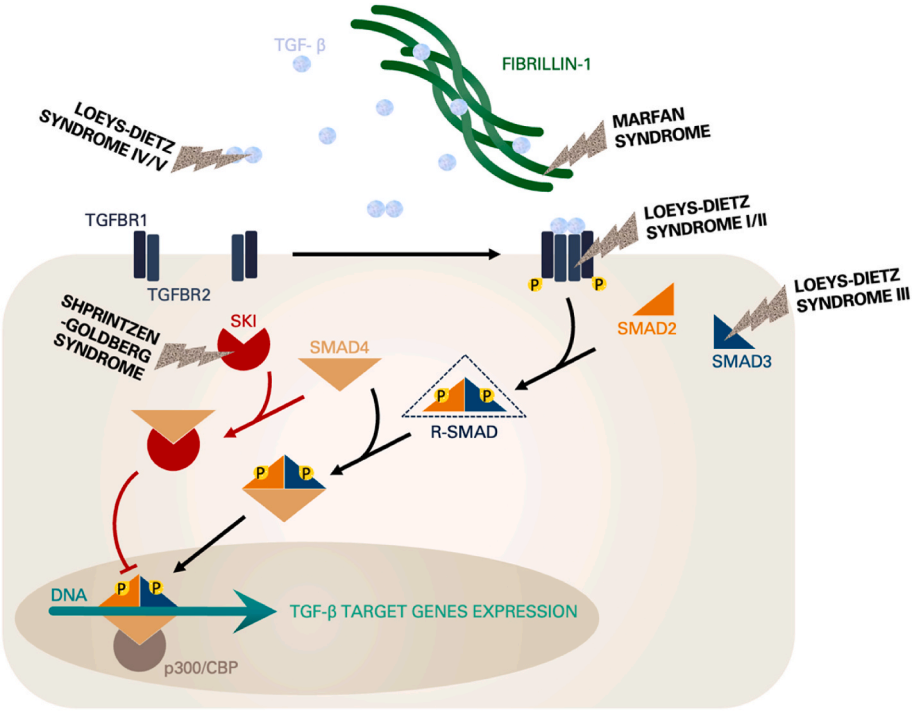

Fig. 1. Simplified shared physiopathology of SGS differential diagnoses
Fibrillin-1 regulates the bioavailability of the transforming growth factor beta (TGF-β). Canonical TGF-β signaling occurs when a TGF-β dimer binds to transforming growth factor beta receptor II (TGFBR2), which then recruits and phosphorylates transforming growth factor beta receptor I (TGFBR1). TGFBR1 phosphorylates downstream the small mothers against decapentaplegic II (SMAD2) and III (SMAD3), which then form the activated regulated-receptor SMAD (R-SMAD). R-SMAD can then bind to the small mothers against decapentaplegic IV (SMAD4). The R-SMAD/SMAD4 complex can enter the cell nucleus. With the help of various co-activators, such as p300/CREB-binding protein (p300/CBP), and various transcription factors, the R-SMAD/SMAD4 complex enables the expression of TGF-β target genes. SKI protein interacts with SMAD2, SMAD3 and SMAD4 and negatively regulates the TGF-β signaling pathway, by preventing the formation of the R-SMAD/SMAD4 complex and its nuclear translocation and competing with p300/CBP for SMAD binding. Alterations in TGF-β/SMAD pathway and its regulation, underlie SGS, Marfan syndrome and LDS.

literature (Arnaud et al., 2020; Au et al., 2014; Carmignac et al., 2012; Doyle et al., 2012; O'Dougherty et al., 2019; Saito et al., 2017; Schepers et al., 2015; Zhang et al., 2019). We divided the patients into three groups, according to the location of the *SKI* pathogenic variant in the three mutational hotspots and compared them to search for a genotype-phenotype correlation. Group 1 is composed of 32 patients with a pathogenic variant in amino acids 20 to 35 of R-SMAD domain (Au et al., 2014; Carmignac et al., 2012; Doyle et al., 2012; O'Dougherty et al., 2019; Saito et al., 2017; Schepers et al., 2015), group 2 is composed of 12 patients with a pathogenic variant in amino acids 94 to 117 of DHD (Au et al., 2014; Carmignac et al., 2012; Doyle et al., 2012; Schepers et al., 2015; Zhang et al., 2019) and group 3 is composed of 11 patients, including our two new patients, with a pathogenic variant in the threonine 180 of DHD (Arnaud et al., 2020). We compared the three groups using a Chi-Square Test or a Fisher's Exact Test (where indicated) with R Core Team software (2022 version) (R Core Team, 2022).

Loeys and Dietz (2008) already compared the clinical presentation of the different types of LDS with the clinical features of Marfan syndrome and SGS. We completed the comparison with the clinical features of SGS by mutational hotspots. The sixth LDS type was not included due to the limited number of patients reported in the literature (Granadillo et al., 2018; Cannaerts et al., 2019).

3. Clinical report

Our Caucasian patient was referred to the Genetics consultation at the age of twenty-eight by his dermatologist for a suspicion of a collagenopathy such as Ehlers-Danlos syndrome or Marfan syndrome. He was treated since childhood for severe atopic dermatitis. He had worsening symptoms since the age of seventeen, evolving by flare-ups. He was hospitalized six times in this context. Orthopedically, he presented multiple episodes of spontaneous subluxations of the distal and proximal interphalangeal joints, as well as the trapezius-metacarpal joints and knees. He had one episode of knee dislocation during adolescence. He regularly suffered from ankle sprains. He had an old rib fracture and dorsal-lumbar scoliosis. The patient had severe myopia. He also presented asthma, treated with budesonide. He had a social phobia. There was no history of recurrent epistaxis, gingivorrhagia or spontaneous hematomas. There was no evidence of inguinal or umbilical hernias. He never had a pneumothorax. There was no history of global developmental delay or intellectual disability.

At twenty-eight years of age, our patient was 186 cm (+0.84 SD) and weighed 85kg (+1.25 SD). There was no clinical evidence of craniosynostosis, dolichocephaly, hypo- or hypertelorism. Clinical examination revealed enophthalmos, deeply set eyes, downslanting palpebral fissures and malar hypoplasia. He had an asymmetric pectus carinatum and dorsolumbar scoliosis. He had joint hypermobility involving small and large joints, with a Beighton score of 7/9. He had no reduced elbows extension. The patient did not have dolichostenomelia. He had bilateral arachnodactyly. The distal and proximal interphalangeal joints were in continuous hyperextension. He had flat feet with severe deformities. The patient had numerous wide stretch marks. There was no scarring, nor any skin hyperelasticity. There were no varicose vein (Fig. 2).

X-rays of hands and feet showed arachnodactyly with increased metacarpal index, lateral trapezius-metacarpal subluxation and severe bilateral hallux valgus. Cardiac ultrasound showed a mild tricuspid insufficiency and a normal thoracic aorta diameter. The vascular work-up, including an ultrasound of the neck vessels and an ultrasound of the abdominal aorta, was normal.

Our patient had a twin sister presenting joint hypermobility. Their mother had been diagnosed with Ehlers-Danlos syndrome hypermobility type during childhood, in a context of joint hypermobility. She presented with knee dislocations in adolescence. She had an umbilical hernia and an episode of abdominal eventration. At sixty-two years of age, she was 172.5 cm (+1.01 SD) and weighed 95kg (+2.39 SD). There was no clinical evidence of craniosynostosis or dolichocephaly. The palpebral fissures were horizontal. There was no hypo- or hypertelorism and no eno- or exophthalmos. However, she had malar hypoplasia with a

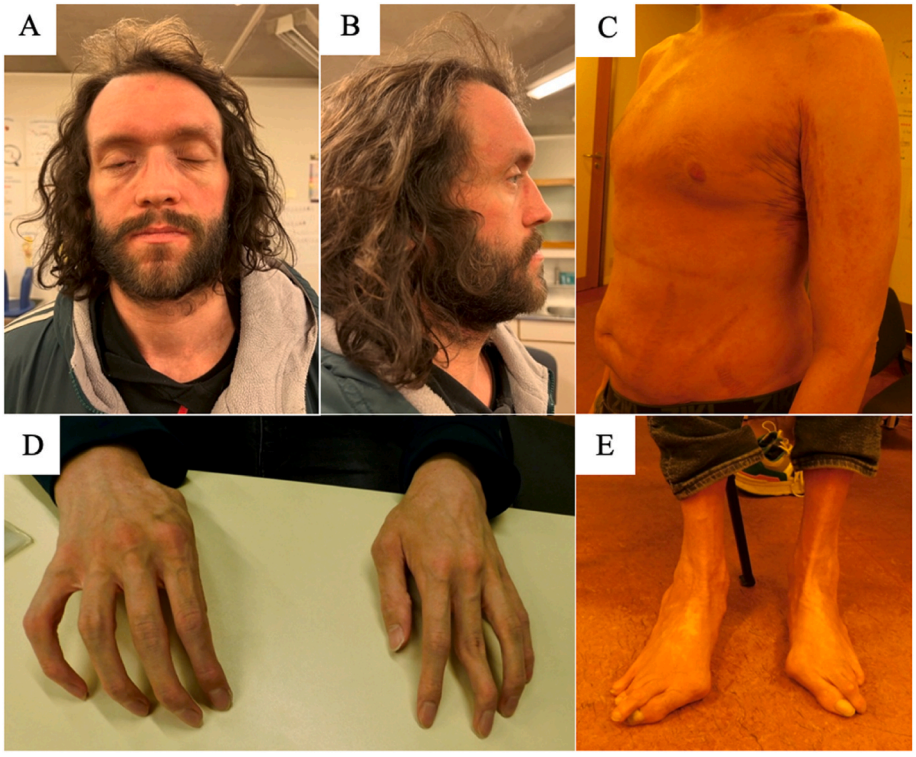

Fig. 2. Clinical features of our patient
A and B: enophthalmos, deeply set eyes and downslanting palpebral fissures, malar hypoplasia. C: numerous wide stretch marks and asymmetric pectus carinatum. D: bilateral arachnodactyly, proximal interphalangeal joint of the third digit in continuous hyperextension. E: flat feet with severe hallux valgus deformities.

normal chin. Orthopedically, she had dolichostenomelia with an arm-span-to-height *ratio* of 1,10. She had pectus excavatum and scoliosis in the context of lower limb dysmetria. She had a Beighton score of 6/9. She did not have hyperlaxity of the elbows and back. She also presented bilateral arachnodactyly with interphalangeal joints hyperextension. Her feet were flat with a bilateral sandal gap. Her skin was slightly elastic, with marked scars, not papyraceous. She had varicose veins in her lower limbs. She had no stretch marks or history of atopic dermatitis (Fig. 3). The rest of the family history was not contributory.

Since the index patient presented with clinical signs suggestive of Marfan syndrome (systemic Marfan score was 11/20: arachnodactyly (wrist and thumb sign, +3), pectus carinatum (+2), valgus deviation of the hindfoot (+2), scoliosis (+1), facial dysmorphia (+1), stretch marks (+1) and severe myopia (+1)), a whole exome sequencing filtered with a panel of 42 genes associated with thoracic aortic aneurysms and dissections was performed. This analysis did not reveal a pathogenic variant in *FBN1*. However, the *c.539C > T p.(Thr180Met)* variant (NM_003036.4), in the heterozygous state, in exon 1 of *SKI*, was identified. This variant is classified as probably pathogenic based on ACMG criteria, establishing the diagnosis of SGS. The presence of this variant was also confirmed in his mother. An annual cardiological follow-up has been set up for our patient and is currently unremarkable.

Following this result, a cardiac ultrasound was also performed in our patient's mother, showing a dilated aorta at sinus of valsalva at 41 mm (+2.69 SD), as well as a slightly sclerotic aortic valve and a mild mitral valve leak. This examination had never been recommended before as her diagnosis was considered to be Ehlers-Danlos syndrome (Malfait et al., 2017). Treatment with Losartan and annual cardiological follow-up were instituted. The vascular evaluation, including ultrasound of the neck vessels and ultrasound of the abdominal aorta, was normal.

Our patient's sister chose not to undergo familial variant testing. Annual cardiological follow-up was therefore recommended.

4. Results & discussion

We initially suspected a diagnosis of Marfan syndrome for our patient, as the Marfan systemic score was positive. He was later diagnosed with Shprintzen-Goldberg syndrome as a heterozygous probably pathogenic variant in the second mutational hotspot of *SKI* Dachshund homology domain was identified. This diagnosis was surprising, as no craniosynostosis or learning disabilities were described. Reviewing the literature, patients with a mutation in this hotspot of *SKI* seem to present a milder phenotype compared to other patients with SGS (Arnaud et al., 2020). We collected data available in the literature for a genotype-phenotype correlation based on the location of the variant within the different *SKI* hotspots (Arnaud et al., 2020; Au et al., 2014; Carmignac et al., 2012; Doyle et al., 2012; O'Dougherty et al., 2019; Saito et al., 2017; Schepers et al., 2015; Zhang et al., 2019). We then compared these data with the results already available for the two differential diagnoses of SGS: Marfan syndrome and LDS (Loeys and Dietz, 2008) (see Table 1).

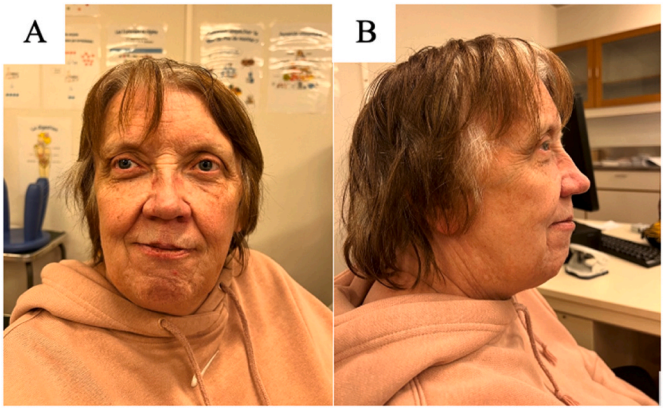

Fig. 3. Clinical features of our patient's mother
A and B: horizontal palpebral fissures, no hypo- or hypertelorism, no eno- or exophthalmos but malar hypoplasia.

4.1. Genotype-phenotype correlation

First, we evaluated the genotype-phenotype correlation among the three mutational hotspots in *SKI*. We divided the fifty-three patients described in the literature and our two patients into three groups, according to the location of the *SKI* pathogenic variants. The first group consisted of the thirty-two patients harboring a pathogenic variant in the amino acids 20 to 35 of the R-SMAD interacting domain (Au et al., 2014; Carmignac et al., 2012; Doyle et al., 2012; O'Dougherty et al., 2019; Saito et al., 2017; Schepers et al., 2015). The second group represented the twelve patients with a pathogenic variant in amino acids 94 to 117 of the DHD transcription regulatory domain (Au et al., 2014; Carmignac et al., 2012; Doyle et al., 2012; Schepers et al., 2015; Zhang et al., 2019). The eleven patients with a pathogenic variant in threonine 180 of DHD were included in group three (Arnaud et al., 2020).

In these patients, twenty-two different pathogenic variants were described. All of these variants were located within exon 1 of *SKI*. Among these twenty-two variants, we found a majority of missense variants: 86.4% were missense variants versus 13.6% inframe deletions. These variants were *de novo* in 87.5% of cases. Among these twenty-two pathogenic variants, we distinguished three more recurrent variants, occurring in 6, 5 and 6 cases respectively (Fig. 4). The first recurrent variants were located within amino acids 20 to 35 of the R-SMAD domain: *p.Leu32Val* and *p.Pro35Ser*. The last recurrent variant was located within the threonine 180 of the DHD, *p.Thr180Met*.

Autosomal dominant transmission has been described in only one family (Carmignac et al., 2012). We report the second family with autosomal dominant transmission. Germline mosaicism has also been described in two families (Carmignac et al., 2012; Schepers et al., 2015). All the other cases were due to *de novo* mutation.

There was no significant sex ratio difference between our three groups ($p > 0.05$): patients harboring a *SKI* pathogenic variant were 47.3% male and 52.7% female. The average age at diagnosis was eighteen years and three months. In groups 1 and 2, the mean age at diagnosis was seventeen years and four months, and seventeen years and seven months respectively. The average age at diagnosis was significantly higher in group 3 ($p < 0.05$), with an average age of nineteen years and nine months.

We compared the clinical features of these three groups (Fig. 5). Craniosynostosis was significantly more present in group 1 ($p < 0.001$), as it was present in 86.2% of group 1 patients, versus 41.7% of group 2 patients. No cases of craniosynostosis at all were reported in group 3.

We found scaphocephaly or dolichocephaly in 90% of group 1 patients and 90.9% of group 2 patients. In contrast, only 11.1% of group 3 patients had dolichocephaly. This difference is statistically significant ($p < 0.001$).

92.4% of patients with SGS had hypertelorism. 96.9% of group 1 patients and all patients in group 2 were hyperteloric. The presence of this physical feature was slightly less frequent in group 3 with 70% of patients presenting with hypertelorism ($p < 0.05$).

Proptosis was statistically more found in group 1 with 90.6% of patients presenting this physical feature ($p < 0.001$). We found proptosis in 70% of group 2 patients and 40% of group 3 patients. Among the patients in group 3, 40% had enophthalmos.

Malar hypoplasia was described in only twenty-two patients in group 1 and five patients in group 2. It was found in 70% of group 3 patients. Even if this difference is statistically significant ($p < 0.05$), we must be careful with the interpretation of this sign since information was missing for many patients.

Microretrognathia was described in 96.5% of group 1 patients. It was

Table 1
Comparison of clinical features of Marfan syndrome, Loeys-Dietz syndrome by associated genes and Shprintzen-Goldberg syndrome by mutational hotspots.

Clinical features	Marfan syndrome	Loeys-Dietz syndrome					Shprintzen-Goldberg syndrome (*SKI*)		
	FBN1	*TGFBR1*	*TGFBR2*	*SMAD3*	*TGFB2*	*TGFB3*	R-SMAD	DHD 94-117	DHD 180
Cranyosynostosis	–	+	+	+	–	–	+++	++	–
Hypertelorism	–	++	+	+	+	+	+++	+++	+++
Proptosis	–	+	+	–	+	–	+++	+++	++
Malar hypoplasia	++	++	+	+	+	–	+++	++	+++
Abnormal palate	–	++	+	+	+	+	++	++	+++
Retrognathia	++	++	+	–	+	–	+++	+++	++
Pectus deformity	++	++	++	++	++	+	+++	++	+++
Scoliosis	++	++	++	++	+	+	+++	++	++
Joint hypermobility	++	+++	++	+	++	+	++	++	+++
Dolichostenomelia	++	+	+	+	+	–	N/A	N/A	++
Arachnodactyly	+++	++	++	+	++	++	+++	+++	+++
Foot malposition	–	++	+	++	++	+	+++	++	+++
Developmental delay	–	+	+	+	+	–	+++	++	+
Mitral valve prolapse	++	+	+	++	+	+	+	+	++
Aortic aneurysm	+++	++	++	++	++	+	+	+	++
Arterial tortuosity	–	++	++	+	+	+	+	–	–
Hernias	+	+	+	+	++	+	+	+	+
Ectopia lentis	++	–	–	–	–	–	–	–	–
Striae	++	+	+	+	+	+	–	–	+

Estimated frequency of clinical features present in patients with Marfan syndrome, the different types of Loeys-Dietz syndrome and Shprintzen-Goldberg syndrome. - = the clinical feature is not present, + = the clinical feature is rarely present, ++ = the clinical feature is sometimes present, +++ = the clinical feature is frequent.

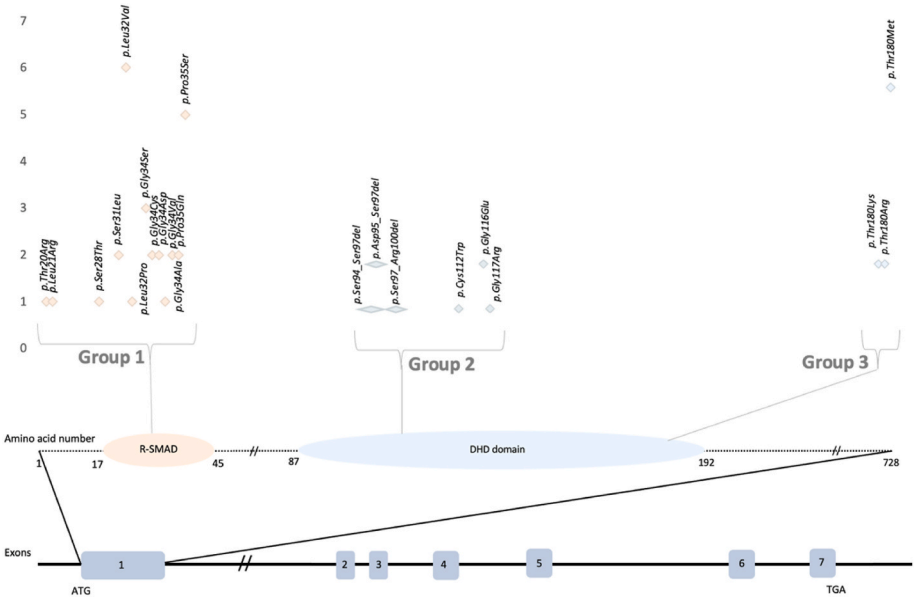

Fig. 4. Currently reported pathogenic variants in *SKI*
Twenty-two pathogenic variants have been reported among the three mutational hotspots in *SKI*: the small mothers against decapentaplegic receptor domain (group 1), amino acids 94 to 117 of Daschund homology domain (group 2), threonine 180 of Daschund homology domain (group 3), all within exon 1 of *SKI*. We distinguished three more recurrent variants: *p.Leu32Val* and *p.Pro35Ser* within the small mothers against decapentaplegic receptor (R-SMAD) domain and *p. Thr180Met* within the threonine 180 of the Dachshund homology domain (DHD).

also found in 72.7% of group 2 patients and 54.5% of group 3 patients. This difference is also statistically significant ($p < 0.01$).

Some patients may also have low implanted ears. Eighteen patients in group 1, five patients in group 2, and one patient in group 3 had this dysmorphic feature. Even if this difference was statistically significant ($p < 0.001$), we must be careful with the interpretation since information was missing for many patients.

Joint contractures were significantly more described in groups 1 and 2, with 88.9% and 90%, respectively ($p < 0.01$). In the third group, only 45.4% of patients had joint contractures.

To our knowledge, no other patients were described with stretch marks or severe acute eczema.

We also compared the neurological disorders among these three groups (Fig. 6). The presence of intellectual disability and/or developmental delay was common in group 1 and group 2. Fourteen patients in group 1 and six patients in group 2 had an intellectual disability. The developmental delay concerned 95.8% of group 1 patients and five patients in group 2. No intellectual disability was described in group 3 ($p < 0.001$). Developmental delay was described in only 30% of the patients in group 3 ($p < 0.001$). Patients showed hypotonia, with statistically significant difference between the three groups ($p < 0.01$). However, data on this feature was frequently lacking.

There was no significant difference in cardiac involvement between these three groups ($p > 0.05$).

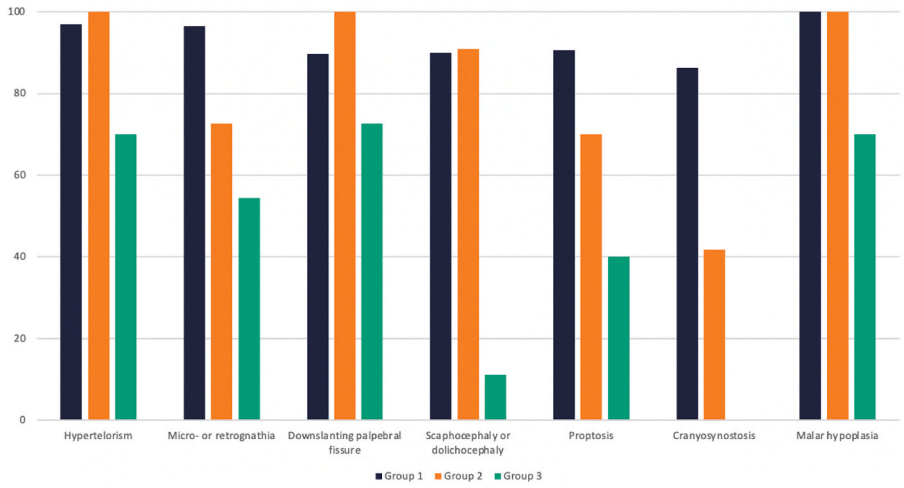

Fig. 5. Facial features comparison across the three groups of SGS patients
Facial dysmorphic features within group 1 (R-SMAD), group 2 (DHD amino acids 94–117) and group 3 (DHD amino acid 180) in percentage.

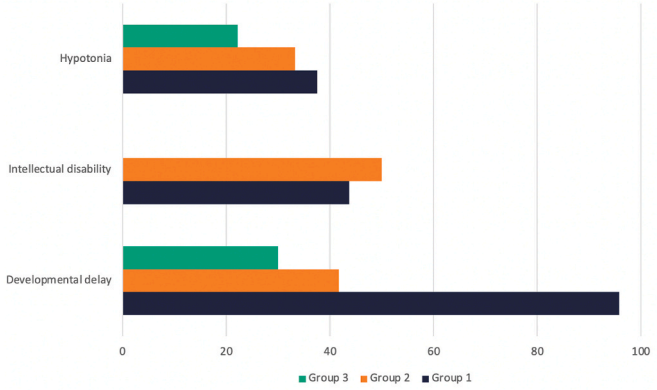

Fig. 6. Neurological symptoms across the three SGS groups
Neurological impairments withing group 1 (R-SMAD), group 2 (DHD amino acids 94–117) and group 3 (DHD amino acid 180) in percentage.

4.2. Differential diagnosis

Dysmorphic features and orthopedic involvement seemed more severe in patients with SGS, especially in the first group when compared to Marfan syndrome or LDS patients. Developmental delay was mostly present in the first two groups of patients with SGS. Pectus deformities and scoliosis seemed to be common in all patients with Marfan syndrome, LDS or SGS. Cardiac involvement was more common in Marfan syndrome, with a predominance of aortic aneurysms. Cardiac involvement was also common in patients with LDS types I and II and in patients with SGS. Hernias were also present in a similar way in all patients. Ectopia lentis was only described in patients with Marfan syndrome.

The initial suspected diagnosis for our patient was Marfan syndrome as the Marfan systemic score was positive (11/20). The patient did not present craniosynostosis or developmental delay, features that are more specific to SGS. He also presented stretch marks which were not described yet in SGS, but present in Marfan and LDS patients. The absence of intellectual deficiency can be explained by the mutation location on the threonine 180 of the DHD. Further functional analyses should be performed to understand the role of this specific amino acid in SKI.

The Shprintzen-Goldberg syndrome diagnosis in our patients allowed us to diagnose a dilated ascending aorta at 4,1 cm (+2.69 standard deviations) in the mother. Genetic diagnosis can be useful to adapt a patient's management. Thoracic aortic aneurysm and dissection (TAAD) has a high mortality rate if undetected, especially in syndromic conditions. The surgical intervention criteria have been adapted depending on the gene involved. Prophylactic surgical intervention is recommended when the ascending aorta diameter is between 4 and 4.5 cm for patients carrying a pathogenic variant in *TGFBR1*, *TGFBR2* and *SMAD3*, in other words, Loeys-Dietz syndrome type 1, type 2, and type 3. Marfan syndromes are operated when the ascending aorta diameter reaches 5 cm or less, while Loeys-Dietz syndromes type 4, with a pathogenic variant in TGFB2, are operated between 4.5 and 5 cm. For patients with Shprintzen-Golberg syndrome and Loeys-Dietz syndrome type 5, with a pathogenic variant in TGFB3, no adaptation of the standard procedure is advised yet. The prophylactic surgical intervention is performed when the ascending aorta dimension is between 5 and 5.5 cm (Ostberg et al., 2020). No prophylactic surgical intervention was recommended in our patient's mother.

5. Conclusion

In this report, we present an additional case of SGS with a variant in threonine 180 of DHD of SKI gene. Our genotype-phenotype correlation supports previous findings that patients with mutations in this domain present a milder phenotype compared to other SGS patients. Interestingly our patient presented severe stretch marks. To our knowledge, no other SGS patient was described with this skin feature. Skin involvement may be part of SGS's clinical spectrum, but further studies should be performed to precise the genotype-phenotype correlation. Finally, our study highlights that a clinical diagnosis without molecular confirmation may lead to mismanagement, notably of cardiovascular risk. Genetic diagnosis may be essential to adapt genetic counseling and surgical management.

CRediT authorship contribution statement

Camille Chatelain: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Léna Kukor:** Data curation. **Sophie Bailleux:** Validation. **Vincent Bours:** Validation. **Saskia Bulk:** Writing – review & editing. **Elisa Docampo:** Writing – review & editing, Validation, Supervision, Conceptualization.

Disclosures

None.

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Data availability

Data will be made available on request.

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