



# Shprintzen–Goldberg syndrome with a novel missense mutation of *SKI* in a 6-month-old boy

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The Shprintzen–Goldberg syndrome (SGS) is an extremely rare genetic disorder caused by heterozygous variant in *SKI*. SGS is characterized by neurodevelopmental impairment with skeletal anomaly. Recognition of SGS is sometimes quite challenging in practice because it has diverse clinical features involving skeletal, neurological, and cardiovascular system. Here we report a case of a 6-month-old boy who initially presented with developmental delay and marfanoid facial features including prominent forehead, hypertelorism, high arched palate and retrognathia. He showed motor developmental delay since birth and could not control his head at the time of first evaluation. His height was above 2 standard deviation score. Arachnodactyly, hypermobility of joints, skin laxity, and pectus excavatum were also noted. Sequencing for *FBN1* was negative, however, a novel missense variant, c.350G>A in *SKI* was identified by sequential whole exome sequencing. To our knowledge, this is the first case with SGS with phenotypic features of SGS overlapping with those of the Marfan syndrome, diagnosed by next generation sequencing in Korea.

**Key words:** Rare disease, Marfan syndrome, Neurodevelopmental disorder, *SKI*.

## Introduction

The Shprintzen–Goldberg syndrome (SGS; MIM 182212) is an extremely rare genetic disorder which involves multi-organ systems. It was first described as a craniosynostosis syndrome with some skeletal anomalies including distinctive facial features, scoliosis or arachnodactyly [1,2]. Patients with SGS usually have cardiovascular and ophthalmologic manifestations, also highlighted in Marfan syndrome (MFS) or Loeys–Dietz syndrome (LDS) [3]. Despite of these clinical similarities, obvious neurodevelopmental features, such as infantile hypotonia, early developmental delay, and intellectual disability, distinguish SGS as a different disease entity from MFS or LDS since pre-genetic

era [4]. In 2012, *SKI* gene (MIM 164780) have been identified as causative gene for SGS using whole exome sequencing (WES) [5]. It is an avian sarcoma viral oncogene homolog, associated with the function of TGF- $\beta$  signaling, which is known for molecular basis of MFS and LDS. However, diagnosis of SGS is still very challenging due to its rarity and its phenotypical change over time.

As the number of next generation sequencing (NGS) increases, molecular diagnosis become relatively easy in rare diseases. In case of SGS, early presenting symptom is hypotonia or developmental delay, whereas marfanoid features are quite tricky to detect especially in infants and toddlers. Numerous patients showing nonspecific symptoms are usually diagnosed through

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NGS. However, in-depth phenotyping is always essential by allowing the "clinical" diagnosis possible as well as providing key clues for analyzing genomic data.

Here, we report a case of a 6-month-old boy with SGS, who initially presented with global developmental delay and distinctive facial features.

Review of medical records and its secondary utilization were approved by the Seoul National University Hospital Institutional Review Board (IRB no. 1101-110-353).

## Case

The patient was 6-month-old boy born from non-consanguineous and healthy parents at gestational age 40 weeks 6 days. His birth weight was 3.85 kg (+0.59 standard deviation score [SDS]), height was 57 cm (+2.60 SDS) and head circumference was 37.2 cm (+1.52 SDS). Although there were no abnormal findings in prenatal examination, he was hospitalized to neonatal intensive care unit (NICU) for 7 days because of mild meconium staining. In NICU, he was noted to have dysmorphic face with high arched palate, micrognathia, and nevus flammeus on his forehead. Brain ultrasonography revealed thinning of corpus callosum and mild ventriculomegaly, and echocardiography indicated small atrial septal defect. Right retinal hemorrhage was noted immediately after birth which was spontaneously resolved. He was discharged without any complications and received regular outpatient check-up. At 6 months old, he was referred to our clinic due to developmental delay with dysmorphic face. At his first visit, he could not control his head completely but could only try to roll over. Appropriate eye contact with parents and visual following was observed. Distinctive facial features, including prominent forehead, midface hypoplasia,

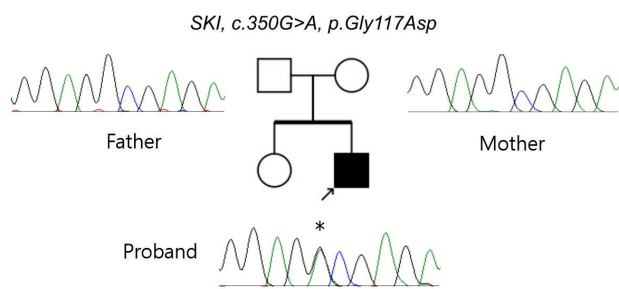
micrognathia, hypertelorism, and low set ears were noted. His height was +3.3 SDS whereas his weight was -0.94 SDS and head circumference was +0.72 SDS (body mass index was 12.45 kg/m<sup>2</sup>).

He showed joint and skin laxity, pectus excavatum, and arachnodactyly (Fig. 1). Muscle tone was slightly decreased but deep tendon reflexes were physiologic without any pathologic reflexes. Follow-up ophthalmologic examination on iris, retina, and fundus was all clear. Echocardiography indicated no remained atrial septic defect but mild dilatation of aortic annulus (z-score 1.7) and sinus (z-score 2.3). X-ray on skeletal system (skull, spine, hip and limbs) was unremarkable. Brain magnetic resonance imaging indicated prominent subarachnoid spaces and focal dural ectasias of distal optic nerve. Being suspicious of MFS, Sanger sequencing for *FBN1* was conducted at first, which was negative. There were no pathogenic variants in gene related to marfanoid features such as *FBN1*. Sequential WES was performed for diagnosis. Genomic DNA was extracted from peripheral blood leukocyte using QIAamp DNA Blood Midi Kit according to the manufacture's instruction (Qiagen, Valencia, CA, USA). WES was performed using an Illumina Highseq 2500. A novel heterozygous missense variant c.350G>A in *SKI* gene (NM\_003036.3; p.Gly117Asp) was identified. Although we suspected MFS or LDS first, we conducted WES as a second diagnostic process because of patient's severe retardation and need for early diagnosis. However we reviewed the WES data focusing on the genes related to MFS and LDS *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, and *SMAD3* again, and no significant variants were identified.

The variant was classified as pathogenic according to the guideline of the American College of Medical Genetics and Genomics [6]. It was identified as *de novo* after segregation test (PS2, Fig. 2) and his mutation was positioned in the Dachshund-



**Fig. 1.** Clinical features of the patient at 11 months. (A) Arachnodactyly of fingers. (B) Arachnodactyly of toes.



**Fig. 2.** Sanger sequencing of the patient and his parents. Pedigree with results of Sanger sequencing of whole family. Sanger trace revealed *A de novo* missense variant of c.350G>A, p.Gly117Asp.

homology domain (DHD), the mutational hot spot of the SGS (PM1). The variant was not observed in population database such as gnomAD or 1000genome (PM2). And Doyle et al. [7] have reported a SGS patient with *SKI* variant, p.Gly117Arg, resulting in different amino acid change at the same protein position (PM5). The location of the variant was also highly conserved over multiple species such as zebrafish or lamprey, as well as other vertebrates [8].

His latest follow-up was at his age of 20-month-old and he was able to creep independently and sit with support with rehabilitation. He seemed to recognize his parents but could not speak any single words.

## Discussion

Clinical manifestation of SGS is quite characteristic although there are some similarities with MFS or LDS based on their molecular mechanism. The disease had been recognized in early 1980s, long before the identification of causative gene [1]. However, those distinctive features appear sequentially making clinical diagnosis challenging in practice, especially in younger patients. As NGS technique developed and became easily accessible, diagnostic method of rare genetic disorder have changed dramatically. Early diagnosis using NGS has many strengths: lower entire medical cost with early emotional stability, and establishment of practical guideline. Thus, NGS is an irreplaceable tool in rare disease diagnostics. Nevertheless, thorough phenotyping is still important as clinical suspicion is essential for analyzing NGS data. Numerous articles reported how insufficient or wrong phenotyping made NGS data useless [9]. Because our patient was suspected as MFS or other connective tissue diseases, NGS data analysis was initially focused on these diseases, led to his confirmative diagnosis. Under cost limited situ-

ation, single gene test accompanied with in-depth phenotyping would be the best choice in practice, as Doyle et al. reported how they conducted single gene sequencing only among selected patients with specific characteristics after identifying variant of *SKI* in index case [7,9].

With WES, our patient was found to have a heterozygote missense variant in exon 1 of the *SKI* gene (NM\_003036.3; c.350G>A, p.Gly117Asp). To date, 35 different variants were reported in human gene mutation database [10]. Among them, 18 (51.4%) were located in R-SMAD binding domain and DHD domain as our patient. It is located in a mutational hot spot and different amino acid change at the same residue has been already reported as pathogenic. He was the first Korean case of SGS diagnosed with NGS.

Patients with *SKI* mutation in this region are reported to have relatively homogeneous clinical course, like our patient. Au et al. [2] reported a patient with a missense mutation in *SKI* exon 1 c.347G>A (p.gly116Glu). He was referred to hospital at age of 3 years with dysmorphic features including marfanoid habitus and developmental delay. At 3 years, He could not walk independently because of joint laxity and hypotonia, and had significant expressive speech delay. Our case also had marfanoid facial features and decreased muscle tone. Furthermore, he showed motor and speech developmental delay in toddler. Aortic root dilatation was presented in patients with *SKI* mutation in DHD domain reported Doyle et al. [7] Because our case had mild dilatation of aortic annulus and sinus, regular echocardiography and cardiac examinations were required.

In conclusion, we reported a boy clinically suspected to have MFS or other connective tissue disease, who eventually diagnosed as SGS using NGS in very young age, the Korean first patient.

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## References

- Shprintzen RJ, Goldberg RB. A recurrent pattern syndrome of craniosynostosis associated with arachnodactyly and abdominal hernias. *J Craniofac Genet Dev Biol* 1982;2:65-74.
- Au PY, Racher HE, Graham JM Jr, Kramer N, Lowry RB, Parboosingh JS, et al. De novo exon 1 missense mutations of *SKI* and Shprintzen-Goldberg syndrome: two new cases and a clinical review. *Am J Med*

- Genet A 2014;164A:676–84.
3. Grealley MT. Shprintzen–Goldberg syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, eds. GeneReviews®. Seattle (WA): University of Washington, 1993.
  4. Bari A, Sadaqat N, Nawaz N, Bano I. Shprintzen–Goldberg syndrome: a rare disorder. J Coll Physicians Surg Pak 2019;29:S41–2.
  5. Carmignac V, Thevenon J, Adès L, Callewaert B, Julia S, Thauvin-Robinet C, et al. In-frame mutations in exon 1 of *SKI* cause dominant Shprintzen–Goldberg syndrome. Am J Hum Genet 2012;91:950–7.
  6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–24.
  7. Doyle AJ, Doyle JJ, Bessling SL, Maragh S, Lindsay ME, Schepers D, et al. Mutations in the TGF- $\beta$  repressor *SKI* cause Shprintzen–Goldberg syndrome with aortic aneurysm. Nat Genet 2012;44:1249–54.
  8. University of California Santa Cruz Genome Browser. [[https://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=chr1%3A2160555%2D2160555&hg-sid=841421989\\_awaDDAaSxQIAvGr6coJIPBOOYJZz](https://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=chr1%3A2160555%2D2160555&hg-sid=841421989_awaDDAaSxQIAvGr6coJIPBOOYJZz)]
  9. Pena LDM, Jiang YH, Schoch K, Spillmann RC, Walley N, Stong N, et al. Looking beyond the exome: a phenotype-first approach to molecular diagnostic resolution in rare and undiagnosed diseases. Genet Med 2018;20:464–9.
  10. The human gene mutation database. [<http://www.hgmd.cf.ac.uk/ac/index.php>]