Kosaki overgrowth syndrome

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Kosaki overgrowth syndrome: A novel pathogenic variant in PDGFRB and expansion of the phenotype including cerebrovascular complications

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Abstract
Heterozygous activating variants in platelet-derived growth factor, beta (PDGFRB) are associated with phenotypes including Kosaki overgrowth syndrome (KOGS),...
Penttinen syndrome and infantile myofibromatosis (IM). Here, we present three new cases of KOGS, including a patient with a novel de novo variant c.1477A > T p. (Ser493Cys), and the oldest known individual age 53 years. The KOGS phenotype includes characteristic facial features, tall stature, scoliosis, hyperelastic thin skin, lipodystrophy, variable intellectual and neurological deterioration, and abnormalities on brain imaging. Long-term outcome is unknown. Our cases confirm the phenotypic spectrum includes progressive flexion contractures, camptodactyly, widely spaced teeth, and constriction rings. We also propose novel occasional features including craniosynostosis, ocular pterygia, anterior chamber cleavage syndrome, early osteoporosis, increased pigmentation, recurrent haematomas, predisposition to cellulitis, nail dystrophy, carpal tunnel syndrome, recurrent hypoglycaemia in infancy, joint dislocation, and splenomegaly. Importantly, we report fusiform aneurysm of the basilar artery in two patients. Complications include thrombosis and stroke in the oldest reported patient and fatal rupture at the age of 21 in the patient with the novel variant. We conclude that cerebrovascular complications are part of the phenotypic spectrum of KOGS and KOGS-like disorders and suggest vascular imaging is indicated in these patients.

**KEYWORDS**

fusiform aneurysm, KOGS, Kosaki overgrowth syndrome, long-term outcome, PDGFRB, vascular

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**INTRODUCTION**

PDGFRB (OMIM #173410) encodes platelet-derived growth factor receptor beta, a tyrosine kinase receptor involved in activation of multiple signalling pathways including cellular proliferation and survival.1 Activating missense mutations are associated with infantile myofibromatosis (IM) (OMIM #228550; p.(Pro560Leu), p.(Arg561Cys), p.(Lys567Glu), and p.(Pro660Thr)).2-5 premature ageing syndrome, Penttinen type (OMIM #601812; p.(Val665Ala)),6 and Kosaki overgrowth syndrome (KOGS) (OMIM #616592; p.(Trp566Arg) and p.(Pro584Arg)).7,8 Novel PDGFRB variants including p.(Asn666His),9 p. (Arg561_Tyr562delinsHis),10 and p.(Asn666Ser)11 have also been reported in patients with phenotypes overlapping these disorders. A schematic representation of the PDGFRB protein with the location of activating variants is shown in Figure 1. Loss-of-function variants are associated with idiopathic basal ganglia calcification (IBGC) syndrome (OMIM #615007; p.(Leu658Pro) and p.(Arg987Trp)),12 Somatic activating mutations have been identified in tissue from fusiform cerebral aneurysms p.(Tyr562Cys).13 Somatic rearrangements with a t(5;12) translocation leading to a ETV6-PDGFRB fusion gene are associated with myeloproliferative disorder with eosinophilia (OMIM #131440).14

KOGS was first described in 2015 and to date, six patients have been reported with ages ranging from 3 to 19.7,8,15,16 The phenotype includes characteristic facial features, postnatal tall stature, long hands, and...
and feet, variable intellectual disability and neurological deterioration, scoliosis, hyperelastic thin and fragile skin, lipodystrophy, abnormalities on brain magnetic resonance imaging (MRI) including white matter lesions, ventricular enlargement/hydrocephalus and arachnoid cysts, and myofibromas in some individuals. Long-term outcome has not previously been reported and is of great interest given the apparently progressive course of this disorder.

Here, we report three new individuals with KOGS including the oldest patient at the age of 53 and expand the phenotype of this disorder. We describe a young adult with a novel variant in PDGFRB c.1477A > T p.(Ser493Cys), adding to our knowledge of the genotype-phenotype correlations in PDGFRB-related disorders. Importantly, we report cerebrovascular complications in both adults, highlighting the morbidity and mortality associated with this group of disorders.

2 | MATERIALS AND METHODS

Patients have been collected through a collaboration call launched within the European Reference Network ITHACA. Clinical information has been gathered. All variant descriptions in this article and in the cited literature refer to (NM_002609.3).

Exome capture and sequencing was performed at the Centre National de Génotypage (CNG) in patient 1 from 1 μg of genomic DNA per individual using the SureSelect Human All Exon v5_51Mb kit (Agilent, Santa Clara, California). The resulting libraries were sequenced on a HiSeq 2000 (Illumina, San Diego, California) according to the manufacturer’s recommendations for paired-end 76 bp reads. Raw data were processed as previously described (Thevenon, 2016). A recurrent PDGFRB chr5:g.149505064G > C, c.1751C > G, p.(Pro584Arg) variant was reported as pathogenic in ClinVar.

Patient 2 underwent next generation sequencing (NGS) on a custom-targeted panel of 44 overgrowth genes as part of the Phenotyping of Overgrowth Disorders (POD) research study (CPMS 19361) in the West Midlands Regional Genetics Laboratory (WMRGL) in the United Kingdom. The 2 μg of DNA extracted from lymphocytes underwent SureSelect QXT target enrichment (Agilent) and libraries were sequenced on the MiSeq (Illumina) according to manufacturer’s protocols. SureCall (Agilent) software was used for bioinformatic analysis. A pathogenic variant c.1751C > G p.(Pro584Arg) was identified in PDGFRB. Bi-directional Sanger sequencing on the ABI3730 of exon 12 of the PDGFRB gene confirmed the heterozygous presence of c.1751C > G p.(Pro584Arg) variant. Sanger sequencing of parental samples did not identify the variant.

Patient 3, together with parents, was recruited to the 100 000 Genomes Project. DNA was extracted from lymphocytes at the WMRGL and sent to Illumina for Whole Genome Sequencing. Sequencing data were passed through Genomics England’s bioinformatics pipeline for alignment, annotation and variant calling. Based on the Human Phenotype Ontology terms entered for this patient, the following gene panels were applied: Ehlers Danlos syndromes v1.43, Inherited bleeding disorders v1.153, Intellectual disability v2.800 (panelapp.genomicsengland.co.uk). The c.1477A > T p.(Ser493Cys) variant, with de novo inheritance, was identified in the PDGFRB gene in the heterozygous state. Results were analysed by the WMRGL and discussed at a multidisciplinary team meeting. This variant was classified as likely pathogenic according to ACMG and ACGS variant interpretation guidelines with the following lines of evidence: in silico tools predict the variant is damaging, the variant is not present in gnomAD, it is a de novo variant with a specific phenotype, and missense variants are constrained within this region of PDGFRB.

3 | RESULTS

3.1 | Patient 1

The patient (Figures 2 and 3) was a 53-year-old of French origin initially published in 1974 by Stoll et al. He was born after an uneventful pregnancy to healthy unrelated parents. His four older brothers were in good health. No particular events were noted during the neonatal period and the first year of life. At the age of 15 months dolichocephaly, tall stature, hyperelasticity and skin hyperpigmentation were noted. A right corneal dystrophy was diagnosed age 5.5 years.

He was referred to a genetic clinic at the age of 8. His height was 143 cm (+ 4 standard deviations [SD]) with an arm span of 142 cm and weight 29 kg (+2.4 SD). He had progressive dysmorphic facial features including hyperostosis of metopic and sagittal sutures that led to suspicion of craniosynostosis, wide spaced eyes, wide nasal base and bridge, long philtrum, micrognathia, thin and fragile gums, and high narrow palate. The skin was atrophic, hyperelastic and hyperpigmented, with hypertrophic and dystrophic scars. The joints were stiff, especially the knees and the ankles. A progressive semi-flexed position of the fingers, bilateral clinodactyly of the fifth fingers, pes cavus and claw toes were noted. Total intellectual quotient (IQ) was measured at 105. Global hypotonia was noted. Skeletal survey revealed global demineralization, enlarged phalanges, and bone age advanced by 3 years. A skin biopsy showed atrophic epidermal and dermal layers, increased epidermal melanin pigmentation, and increased dermal elastic fibres. The initial differential diagnoses were Shprintzen-Goldberg syndrome (SGS) or atypical Ehlers Danlos syndrome.

Pterygia of the right eye at the age of 10 and the left eye at the age of 32 were treated with keratoplasty, but recurrence in both eyes resulted in visual impairment. Early osteoporosis was diagnosed at the age of 37, but the presence of plantar calcifications ruled out treatment with bisphosphonates. Scoliosis was rapidly progressive and not amenable to surgical intervention. At the age of 53, he presented with an ischaemic stroke caused by a basilar artery aneurysm thrombosis. MRI investigations discovered generalised dolichoectasia of the cerebral arteries, and arachnoid cysts of the temporal lobes, frontoparietal areas and posterior fossa associated with a Dandy-Walker malformation (Figure 2). Heart and vascular ultrasounds found normal aortic diameters and no other vessel ectasia. AngioMRI
revealed a sinuous thoracic aorta. Long-term treatment with low-dose aspirin was initiated. Sequencing of the SKI gene was negative.

Exome sequencing revealed a recurrent PDGFRB chr5: g.149505064G > C, c.1751C > G, p.(Pro584Arg) variant reported as pathogenic in ClinVar. Clinical re-evaluation showed evolving physical features but no cognitive decline. General examination revealed marfanoid habitus with tall stature (188 cm) despite severe scoliosis, stiff joints, amyotropia, and large penis. D-F. Hypertrophic, retractile and sometimes calcified scars, camptodactyly of 2-5th fingers, severe nail dystrophy, and Ainhum circumferential constriction of the second and third toe of the left foot, G-I [Colour figure can be viewed at wileyonlinelibrary.com]

3.2 | Patient 2

Patient 2 (Figure 4) was born at 37 weeks gestation weighing 3.7 kg (+1.9 SD) following induction of labour for prolonged rupture of the membranes and oligohydramnios. His parents were unrelated white British and his younger sibling and two elder maternal half siblings were healthy. At 48 hours of age, he had a bilateral orchidopexy for suspected testicular torsion and was noted to have cryptorchidism.
Multiple suture craniosynostosis (sagittal, coronal, and metopic) was diagnosed by 14 months of age. Bilateral periventricular cystic foci were identified on MRI brain scan. At six years of age, he developed obstructive ventriculomegaly with tonsillar descent and required insertion of a ventriculo-peritoneal (VP) shunt. Subsequent visual impairment was attributed to the period of raised intracranial pressure and to enlargement of mid brain cysts. Visual acuities were perception of light only in the right eye and 0.6 at 10 cm in the left eye (Kay Picture Test Linear Crowded Book). He also had conductive hearing loss due to glue ear and required hearing aids. Primary dentition was lost prematurely at the age of three years. He developed contractures of the digits of both hands and equinovarus of the feet and ankles requiring orthotic treatment with boots. Hand and foot X-rays showed widening of the metacarpals, metatarsals, and phalanges.

Early developmental milestones were normal, including walking at the age of 14 months and an Ages and Stages Questionnaire (ASQ) developmental assessment at the age of four identified no developmental concerns. He was moved from mainstream education to special education at the age of six primarily due to visual impairment. Primary dentition was lost prematurely at the age of three years. He developed contractures of the digits of both hands and equinovarus of the feet and ankles requiring orthotic treatment with boots. Hand and foot X-rays showed widening of the metacarpals, metatarsals, and phalanges.

On examination in the genetics clinic at the age of six, he had a tanned appearance with no history of sun exposure and out of keeping compared to other family members and ethnic background. Other dermatological features included hyperelastic soft thin skin, lax skin on the palms, pigmented lesions on the thighs, pectus excavatum, reduced extension at the elbow, broad hands, progressive flexion contractures of the fingers and toes, and widely spaced teeth. Dysmorphic facial features consisted of brachycephaly, sloping forehead, prominent supraorbital ridges, widely spaced eyes, proptosis, downslanting palpebral fissures, wide nasal bridge, wide nasal base, wide nasal tip, malar flattening, midface retrusion, smooth philtrum, thin vermilion of the upper lip, everted vermilion of the lower lip, and prominent ears with forward facing and uplifted earlobes (Figure 3). At the age of six, his height was 132.5 cm (+2.8 SD), head circumference 51.0 cm (−1.5 SD) and weight 27.8 kg (+1.7 SD).

Clinical array-comparative genomic hybridisation (aCGH) and craniosynostosis screen (sequencing of FGFR1 exon 7, FGFR3 exons IIIa and IIIc, FGFR3 exons 7 and 10, TWIST exon 1, FGFR2 exons 3, 5, 11, 14, 15, 16, 17 and 18 and MLPA of TWIST1, RUNX2, ALX1, ALX3, ALX4, MSX2, and EFNB1) did not identify any probably pathogenic variants. A de novo pathogenic variant c.1751C > G, p. (Pro584Arg) was identified in PDGFRB on an NGS panel of overgrowth genes.

Subsequent echocardiogram at the age of seven was normal. Further vascular investigations are planned.

**FIGURE 3** Imaging of patient 1. A, Sagittal view of a T1-weighted cerebral MRI showing a large posterior fossa cyst in continuity with the fourth ventricle associated with an elevated tent and diffuse hypoplasia of the cerebellum (Dandy-Walker syndrome). B-F, Axial views of a Time Of Flight (ToF)-weighted cerebral MRI, B, C, D, Diffuse dolichoectasia of internal carotid and vertebral arteries. E, Thrombosis of fusiform aneurysm of the basilar artery. F, Bilateral fetal posterior cerebral arteries. G-H, Axial views of a cerebral computerised tomography (CT) scan revealing the Dandy Walker malformation, bilateral subarachnoid cysts of the anterior temporal lobes, and thrombosis of the fusiform aneurysm of the basilar artery. I, Axial view of a T2 Fluid Attenuated Inversion Recovery (FLAIR) cerebral MRI showing mild merging punctiform hypersignal of the white matter linked to a microangiopathy and bilateral asymmetrically pneumatized frontal sinus.
Bilateral carpal tunnel release was performed for severe median nerve compression at the age of eight.

3.3 | Patient 3

Patient 3 (Figure 5) was born to unrelated healthy parents and had two healthy elder sisters. His mother had hypertension from 34 weeks of pregnancy and labour was induced at term. Despite a normal birth weight of 3.26 kg, he appeared extremely thin with wrinkled skin. He also had extremely pale hair and irides and diastasis recti.

He had recurrent hypoglycaemic episodes between the ages of five months and three years. Extensive metabolic investigations were unremarkable and he was diagnosed with ketotic hypoglycaemia that resolved with age. Early developmental milestones were normal.

At the age of 10, a yellow ring around the iris was noted. An ophthalmology review identified a minor variant of a Rieger-like anterior chamber cleavage syndrome, with significant thickening of the peripheral millimetre of the iris, prominence of corneal nerves bilaterally and prominent Schwalbe’s lines on the right. Vision was normal.

He had recurrent haematomas and cellulitis of the lower limbs, and surgical intervention was technically difficult because of abnormal
blood vessels. He had pain in his joints and the soles of the feet from early childhood.

On review in the genetics clinic age of 11, his height was 143.9 cm (50th centile), weight 42.7 kg (+1.1 SD) and OFC 56.5 cm (+1.0 SD). He had low body fat and a muscular build. The right leg and foot were smaller than the left due to a fractured tibia and treatment with plaster at the age of four with subsequent muscle wasting. He had a tanned appearance. The skin was soft and lax with wrinkled palms and soles, mobile prominent veins and varicosities on distal upper and lower limbs, easy bruising, numerous non-atrophic scars, and little body hair. He had hypermobility of small joints, left knee, and spine; and divarification of the rectus muscles. Dentition was at least two years advanced with prominent gums and wide spaced teeth. Hands and feet were large with broad digits. Facial features of prominent supraorbital ridges, broad nose and broad nasal bridge were noted. A pulsatile lump was present on the occiput and confirmed to be a vascular malformation when surgically removed at the age of 12. Shoulder dislocation occurred at the age of 15. He attended mainstream school with some learning support but did not require a statement of special educational needs and went on to attend university. At the age of 20, his height was 185.4 cm (+1.2 SD) and weight was 97.4 kg (+1.9 SD) and splenomegaly was noted.

Cranial MRI scan showed hypoplasia of both superior and inferior cerebellar vermis and prominent posterior fossa subarachnoid spaces with bilateral subcortical high signal areas. Other investigations including bone age, metabolic studies (urinary GAGs and AA, oligosaccharides, sialic acid, MCAD screen), platelets, bleeding time and clotting screen, chromosomal analysis, CGH array, FLNA, fibroblast analysis for collagen type I, III and V, and molecular analysis of COL3A1 and COL5A1 were unremarkable. At the age of 20, skeletal survey reported significant prominence of the frontal bone, which was unaerated and slightly increased bone density with undermodelling of...
the distal femur and proximal tibia with possible mild elongation of the metacarpals and metatarsals. EMG showed no evidence of myotonia and nerve conduction studies showed normal motor and sensory conduction in the upper and lower limbs.

A 3 cm soft mobile lump that developed on the left shin at the age of 14 was reported as a benign angiofibromatous lesion with unusual histology.

At the age of 21, he had a fatal stroke. CT and MRI images showed a basilar artery aneurysm thrombosis with subsequent dissection of the aneurysm and subarachnoid haemorrhage. Multiple foci of signal change in the supratentorial white matter in keeping with chronic small vessel ischaemia were also seen. Post-mortem examination confirmed a ruptured fusiform aneurysm of the basilar artery measuring up to 2.5 cm in maximum diameter. The vertebral arteries were normal and the aorta was unremarkable. The coronary arteries showed moderate calcified atheroma.

This patient was posthumously recruited to the 100 000 Genomes Project. Whole genome sequencing identified a previously unreported de novo variant c.1477A > T p.(Ser493Cys) in PDGFRB.

**DISCUSSION**

KOGS is an ultra-rare disorder largely underdiagnosed with only six cases reported worldwide. Although a recognisable phenotype, the majority of cases have been following a genotype-first approach, due to lack of knowledge of the disorder. A number of key features have been identified but each reported case has expanded the spectrum, leading to a heterogeneous phenotype with constant, occasional and rare features (Figure 6). Characteristic facial features include wide spaced eyes, downslanting palpebral fissures, wide nasal bridge and nasal base, broad nasal tip, pointed chin, prominent supraorbital ridges, underdeveloped malae, cupid bow shaped and thin upper lip, proptosis and smooth philtrum. Tall stature, MRI abnormalities including white matter lesions, arachnoid cysts, Dandy-Walker malformation and hydrocephalus, abnormal cranial shape, thin fragile hyperelastic skin, scoliosis, premature ageing, lipodystrophy, sparse hair, hypotonia in infancy, delayed speech and language, intellectual disability, neurological deterioration, and myofibroma are also recognised features. Our cases confirm that several features previously reported in only a single individual with KOGS, including camptodactyly, progressive joint contractures, widely spaced teeth, and constriction rings are part of the phenotypic spectrum. We also report novel features including craniosynostosis, ocular pterygia, anterior chamber cleavage syndrome, early osteoporosis, enlarged penis, diffuse erythrosis, increased pigmentation, recurrent haematomas, predisposition to cellulitis, nail dystrophy, carpal tunnel syndrome, recurrent hypoglycaemia in infancy, muscular build, joint dislocation, and splenomegaly (Table 1). In one of our patients visual impairment resulted from KOGS-related obstructive ventriculomegaly and mid brain cysts.

The identification of the oldest patient provides valuable information about the natural history of KOGS in later life. This individual has normal intellectual functioning at the age of 53, demonstrating the progressive neurological deterioration and intellectual disability in other reported individuals is not universal. Cerebral angioMRI revealed both large vessel and small vessel anomalies with enlarged and dysplastic cervical and intracranial arteries (internal carotids, vertebral arteries, basilar artery) and a fusiform aneurysm of the basilar artery, and punctiform hypersignal of the subcortical white matter related to microvascular angiopathy too extensive for age. A vascular phenotype was also unfortunately diagnosed post-mortem in patient 3, following investigation of sudden death at the age of 21 from a ruptured fusiform aneurysm of the basilar artery.
### TABLE 1  Clinical characteristics of patients reported with KOGS and the presently reported patients

|                          | Patient 1 (Reference 7) | Patient 2 (Reference 7) | Patient 1 (Reference 8) | Patient 2 (Reference 8) | Current report Patient 1 | Current report Patient 2 | Current report Patient 3 |
|--------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------------------|--------------------------|-------------------------|
| **Demographics**         |                         |                         |                         |                         |                          |                          |                         |
| Age                      | 14                      | 17                      | 3                       | 15                      | 10                       | 19 (deceased)           | 53                      | 6                       | 22 (deceased)           |
| Sex                      | F                       | F                       | F                       | F                       | M                        | M                        | M                       |
| **Growth pattern**       |                         |                         |                         |                         |                          |                          |                         |
| Overgrowth at birth      | −                       | −                       | −                       | −                       | +                        | +                        | −                       | −                       |
| Tall stature (Height SD) | (+4.8)                  | nk                      | +                       | +                       | +                        | +                        | +                       | (0.0)                   |
| Large extremities        | +                       | +                       | +                       | +                       | +                        | +                        | +                       |
| **Skeletal features**    |                         |                         |                         |                         |                          |                          |                         |
| Scoliosis                | +                       | +                       | −                       | nk                      | nk                       | +                        | +                       |
| Camptodactyly/flexion contractures of fingers | nk | nk | nk | nk | + | − | + |
| Contractures             | nk                      | nk                      | nk                      | nk                      | nk                       | +                        | +                       |
| Pectus excavatum         | nk                      | nk                      | −                       | +                       | −                        | +                        | +                       |
| Abnormal cranial shape   | +                       | +                       | nk                      | nk                      | nk                       | nk                       | −                       |
| **Dermatological features** |                         |                         |                         |                         |                          |                          |                         |
| Hyperelastic skin        | +                       | +                       | +                       | +                       | +                        | +                        | +                       |
| Thin/soft/fragile skin   | +                       | +                       | +                       | +                       | +                        | +                        | +                       |
| Increased skin pigmentation | −                  | −                       | −                       | −                       | −                        | −                        | −                       |
| Wrinkled skin            | nk                      | nk                      | nk                      | nk                      | nk                       | nk                       | nk                      |
| Dystrophic scars         | −                       | −                       | −                       | +                       | −                        | +                        | −                       |
| Constriction rings       | −                       | −                       | +                       | −                       | −                        | +                        | −                       |
| Lipodystrophy            | +                       | +                       | −                       | +                       | +                        | +                        | +                       |
| Premature ageing         | nk                      | nk                      | −                       | +                       | +                        | +                        | +                       |
| Widely spaced teeth      | nk                      | nk                      | nk                      | nk                      | nk                       | nk                       | nk                      |
| **Neurological features** |                         |                         |                         |                         |                          |                          |                         |
| Intellectual disability  | +                       | +                       | +                       | +                       | −                        | −                        | −                       |
| Neurological deterioration| +                       | nk                      | nk                      | nk                      | −                        | −                        | −                       |
| Infantile muscular hypotonia | nk                 | nk                      | +                       | +                       | +                        | +                        | −                       |
| **Cerebral MRI**         |                         |                         |                         |                         |                          |                          |                         |
| Periventricular white matter lesions | +               | +                       | +                       | +                       | +                        | +                        | +                       |

(Continues)
|                  | Patient 1 (Reference 7) | Patient 2 (Reference 7) | Patient 1 (Reference 8) | Patient 2 (Reference 8) | Reference 15 | Reference 16 | Current report Patient 1 | Current report Patient 2 | Current report Patient 3 |
|------------------|-------------------------|-------------------------|-------------------------|-------------------------|--------------|--------------|---------------------------|---------------------------|---------------------------|
| **Dandy-Walker** | −                       | −                       | +                       | +                       | +            | +            | +                         | +                         | +                         |
| malformation/cerebellar hypoplasia/hydrocephalus |                         |                         |                         |                         |              |              |                           |                           |                           |
| **Arachnoid cysts** | −                       | −                       | +                       | −                       | +            | +            | +                         | +                         | −                         |
| **Corpus callosum anomalies** | −                       | −                       | −                       | −                       | +            | −            | −                         | −                         | −                         |
| **Vascular** |                         |                         |                         |                         |              |              | + (cervical, vertebral) | −                         | + (basilar artery) |
| Dolichoectasia of cerebral arteries | −                       | −                       | −                       | −                       |              |              | +                         | −                         | −                         |
| Coronary artery aneurysms | nk                     | nk                     | nk                     | nk                     | +            | −            | −                         | −                         | −                         |
| **Others** |                         |                         |                         |                         |              |              |                           |                           |                           |
| Facial features | +                       | +                       | +                       | +                       | +            | +            | +                         | +                         | +                         |
| Myofibroma | +                       | −                       | +                       | −                       | +            | +            | +                         | −                         | −                         |
| Hearing loss | −                       | −                       | −                       | −                       | −            | −            | −                         | −                         | −                         |
| Cryptorchidism | na                     | na                     | na                     | na                     | +            | −            | −                         | −                         | −                         |
| **Other features** |                         |                         |                         |                         |              |              | +                         | −                         | −                         |
| Cardiac valvulopathy |                         |                         |                         |                         |              |              |                           |                           |                           |
| Hydrocephrosis |                         |                         |                         |                         |              |              | +                         | −                         | −                         |
| Epilepsy |                         |                         |                         |                         |              |              |                           |                           |                           |
| Ocular pterygia |                         |                         |                         |                         |              |              | +                         | −                         | −                         |
| Osteoporosis |                         |                         |                         |                         |              |              |                           |                           |                           |
| Diffuse erythrosis |                         |                         |                         |                         |              |              |                           |                           |                           |
| Plantar calcifications |                         |                         |                         |                         |              |              |                           |                           |                           |
| Visual impairment |                         |                         |                         |                         |              |              | +                         | −                         | −                         |
| Mild anterior chamber cleavage syndrome |                         |                         |                         |                         |              |              |                           |                           |                           |
| Joint dislocation |                         |                         |                         |                         |              |              |                           |                           |                           |
| Vascular malformation |                         |                         |                         |                         |              |              |                           |                           |                           |
| Splenomegaly |                         |                         |                         |                         |              |              |                           |                           |                           |
| **Genetics** |                         |                         |                         |                         |              |              | +                         | −                         | −                         |
| Variant | c.1751C > G            | c.1751C > G            | c.1696 T > C            | c.1696 T > C            | c.1751C > T | c.1696 T > C | +                         | −                         | −                         |
| Protein | p.(Pro584Arg)          | p.(Pro584Arg)          | p.(Trp566Arg)           | p.(Trp566Arg)           | p.(Pro584Arg)| p.(Trp566Arg) | p.(Pro584Arg)            | p.(Pro584Arg)            | p.(Ser493Cys)              |

**Abbreviations:** KOGS, Kosaki overgrowth syndrome +, present; −, absent; nk, not known; na, not applicable; nc, not confirmed.
A vascular phenotype has been previously reported in KOGS, in a patient with saccular aneurysms in both coronary artery systems and mild tortuosity of the cervical vertebral arteries. This individual died suddenly at the age of 19 without post-mortem examination. The vascular findings in our cases confirm that vascular features are part of the phenotypic spectrum of KOIS and are associated with both known KOIS-genotypes c.1696 T > C p.(Trp566Arg) and c.1696 T > C p.(Trp566Arg) and also with the novel PDGFRB variant c.1477A > T p.(Ser493Cys). Echocardiograms have been performed on three younger individuals with molecularly confirmed KOIS, including our patient 2 at the age of six, and no other vascular anomalies have been identified. However, several features of KOIS such as the prematurely aged appearance are progressive, and it is probably that vascular complications may develop with age. Given the morbidity and mortality associated with vascular phenotypes, we suggest that clinicians consider baseline vascular screening with echocardiogram, cerebral MRI and angioMRI for individuals with KOIS at diagnosis and again in adult life.

There are numerous other lines of evidence suggesting that vascular complications may be associated with the wider PDGFRB-spectrum disorders. A patient with a clinical diagnosis of Penttinen syndrome and major dilatation of the left coronary system showed recurrences and vascular complications. In addition, Karasoz et al reported a patient with saccular aneurysm in both coronary artery systems of the delineation of the phenotypes secondary to gain-of-function mutations and vascular complications. In addition, Karasoz et al reported the case of a 23-year-old man with progressive intracranial aneurysms and ipsilateral cutaneous phenotype with a somatic missense pathogenic variant p.(Tyr562Cys) within the PDGFRB gene predicted to generate a stream of hyperphosphorylation. Upregulation of PDGFRB expression has also been showed in aortic wall tissue from patients with thoracic aortic dissection. All these elements constitute strong arguments for activating mutations of the PDGFRB gene leading to global vascular pathology.

The high morbidity and mortality associated with vascular complications and the progressive natural history of KOIS make the possibility of therapeutic intervention an important consideration. To date, two individuals with other PDGFRB-related disorders have been treated with tyrosine kinase inhibitors. The patient reported by Pond et al was treated with imatinib with clinical improvement in contractures of the hands and decrease in coarseness of the facial features. Mudry et al reported a patient with a germline heterozygous c.1681C > A p.(Arg561Cys) missense mutation causing generalised infantile myofibromatosis. After failure of multiple lines of chemotherapy, the multiple tumours finally responded to a combination of sunitinib and vinblastine. It has been established that the KOIS-specific pathogenic variants in PDGFRB are activating mutations that activate the PI3K-AKT pathway and are responsive to imatinib suggesting that individuals with KOIS might also be candidates for treatment with tyrosine kinase inhibitors.

In this report, we also extend the genotype-phenotype correlations associated with PDGFRB related disorders. Our patient 3 with a novel PDGFRB variant c.1477A > T p.(Ser493Cys) shares many features with the KOIS phenotype including typical facial features, hyperelastic thin skin, lipodystrophy and MRI brain anomalies. His tanned appearance and wrinkled palms are strikingly similar to those of patient 2. His growth (on the 50th centile) is not typical of KOIS but given the small number of reported patients, it is possible that tall stature is not universal in this condition. Variability in height exists in other PDGFRB-spectrum disorders. For example, two of the five reported individuals with molecularly confirmed Penttinen syndrome have overgrowth. Patient 3 also has novel features including recurrent hypoglycaemia in infancy, minor anterior chamber cleavage syndrome, recurrent haematomas andcellulitis of the lower limbs, a muscular build, joint dislocation and splenomegaly. Further observations of patients with this novel variant will inform the medical community if these features are specific to this variant or not. Interestingly, this novel variant is located in the transmembrane domain of PDGFRB, whereas the other known KOIS variants are in the juxtamembrane domain of the protein.

Recently, individuals with novel mutations in PDGFRB not previously associated with KOIS, Penttinen or IM have been reported. Two different variants at the same amino acid in the tyrosine kinase hinge region of PDGFRB, c.1997A > G p.(Asn666Ser) and c.1996A > C p.(Asn666His), are both associated with Penttinen-like phenotypes, but the two patients reported by Bredrup et al have a more severe phenotype. The pterygium described in our patient 1 was also seen in Bredrup’s patient 2, and the carpal tunnel syndrome in our patient 2 also developed in the Pond patient. The case reported by Guimier et al c.1682_1684del p.(Arg561_Tyr562delinsHis), a somatic loss-of-function variant in the juxtamembrane region, has a phenotype overlapping KOIS and Penttinen but also has bilateral periventricular and basal ganglia calcifications as seen in IBGC 4 and multifocal myofibromatosis as seen in IM. This patient also has the wrinkled palms and soles seen in our patients 2 and 3. These novel variants, together with our variant, raise the question of the delineation of the phenotypes secondary to gain-of-function PDGFRB variants. The term of PDGFRB gene activation-related disorders might be more appropriate.

In conclusion, we describe here the long-term outcome in the oldest reported individual with KOIS, report a patient with a novel PDGFRB variant and a KOIS-like phenotype, and highlight the vascular risk in KOIS. We suggest that vascular investigations are indicated in individuals with KOIS and KOIS-like disorders. Therapeutic options are of great interest in the future clinical management of these patients.

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CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the

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