Kosaki overgrowth syndrome

Foster, Alison; Chalot, Basile; Antoniadi, Thalia; Schaefer, Elise; Keelagher, Rebecca; Ryan, Gavin; Thomas, Quentin; Philippe, Christophe; Bruel, Ange-Line; Sorlin, Arthur; Thauvin-Robinet, Christel; Bardou, Marc; Luu, Maxime; Quenardelle, Veronique; Wolff, Valerie; Woodley, Jessica; Vabres, Pierre; Lim, Derek; Igbokwe, Rebecca; Joseph, Annie

DOI:
10.1111/cge.13752

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Foster, A, Chalot, B, Antoniadi, T, Schaefer, E, Keelagher, R, Ryan, G, Thomas, Q, Philippe, C, Bruel, A-L, Sorlin, A, Thauvin-Robinet, C, Bardou, M, Luu, M, Quenardelle, V, Wolff, V, Woodley, J, Vabres, P, Lim, D, Igbokwe, R, Joseph, A, Walker, H, Jester, A, Ellenbogen, J, Johnson, D, Rooke, B, Moss, C, Cole, T & Faivre, L 2020, 'Kosaki overgrowth syndrome: A novel pathogenic variant in PDGFRB and expansion of the phenotype including cerebrovascular complications', *Clinical Genetics*. https://doi.org/10.1111/cge.13752

Received: 30 March 2020 | Accepted: 31 March 2020
DOI: 10.1111/cge.13752

ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

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

Alison Foster[1,2] | Basile Chalot[3,4,5] | Thalia Antoniadi[6] | Elise Schaefer[7] | Rebecca Keelagher[6] | Gavin Ryan[6] | Quentin Thomas[8] | Christophe Philippe[4,5] | Ange-Line Bruel[4,5] | Arthur Sorlin[3,4,5] | Christel Thauvin-Robinet[3,4,5] | Marc Bardou[9,10] | Maxime Luu[9,10] | Veronique Quenardelle[11] | Valerie Wolff[11,12] | Jessica Woodley[6] | Pierre Vabres[13] | Derek Lim[2] | Rebecca Igbokwe[2] | Annie Joseph[14] | Harriet Walker[15] | Andrea Jester[15] | Jonathan Ellenbogen[16] | Diana Johnson[17] | Bethanie Rooke[18] | Celia Moss[1,18] | Trevor Cole[2] | Laurence Faivre[3,5]

[1]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK

[2]West Midlands Regional Genetics Service and Birmingham Health Partners, Birmingham Women's and Children's Hospitals NHS Foundation Trust, Birmingham, UK

[3]Centre de Génétique et Centre de référence « Anomalies du Développement et Syndromes Malformatifs », Hôpital d'Enfants, Centre Hospitalier Universitaire de Dijon, Dijon, France

[4]Laboratoire de Génétique chromosomique et moléculaire, UF Innovation en diagnostic génomique des maladies rares, Centre Hospitalier Universitaire de Dijon, Dijon, France

[5]UMR-Inserm 1231 GAD team, Génétique des Anomalies du développement, Université de Bourgogne Franche-Comté, Dijon, France

[6]West Midlands Regional Genetics Laboratory, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

[7]Service de génétique médicale - Hôpitaux Universitaires de Strasbourg, Institut de Génétique Médicale d'Alsace, Strasbourg, France

[8]Service de Neurologie, Centre Hospitalier Universitaire de Dijon, Dijon, France

[9]Service de Pharmacologie et Centre d'Investigation Clinique, Centre Hospitalier Universitaire de Dijon, Dijon, France

[10]INSERM CIC 1432, Université de Bourgogne Franche-Comté, Dijon, France

[11]Stroke Unit, University Hospital, Strasbourg, France

[12]Federation of Translational Medicine of Strasbourg, University of Strasbourg, Strasbourg, France

[13]Service de Dermatologie, CHU de Dijon, Université de Bourgogne, France

[14]Ophthalmology Department, Royal Stoke University Hospital, Stoke-on-Trent, UK

[15]Hand and Upper Limb Service, Plastic and Reconstructive Surgery, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

[16]Paediatric Neurosurgery, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

[17]Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, Sheffield, UK

[18]Department of Dermatology, Birmingham Children's Hospital, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

Correspondence
Alison Foster, Clinical Genetics Unit, Birmingham Women's Hospital, Edgbaston, Birmingham B15 2TG, UK.
Email: alison.foster10@nhs.net

Abstract

Heterozygous activating variants in platelet-derived growth factor, beta (*PDGFRB*) are associated with phenotypes including Kosaki overgrowth syndrome (KOGS),

Laurence Faivre, Centre de Génétique, Hôpital d'Enfants, Centre Hospitalier Universitaire de Dijon, 14 rue Paul Gaffarel, BP 77908, 21079 Dijon cedex, France.
Email: laurence.faivre@chu-dijon.fr

Funding information
Burgundy Regional Council; National Institute for Health Research; European Union

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

1 | 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

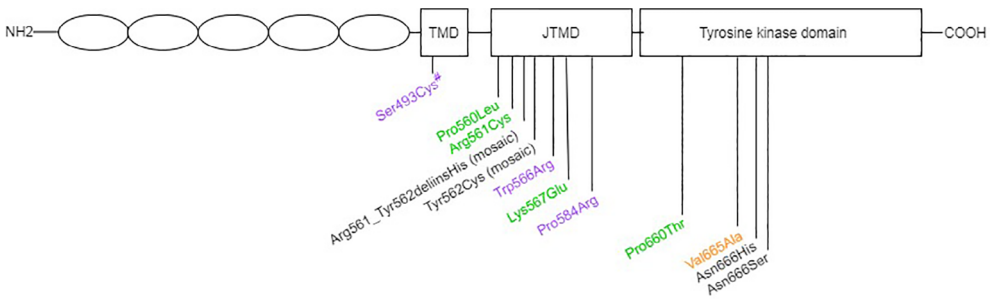

FIGURE 1 Schematic representation of the PDGFRB protein with location of activating mutations associated with Kosaki overgrowth syndrome, Pentinnen syndrome, infantile myofibromatosis, and other overlapping phenotypes [Colour figure can be viewed at wileyonlinelibrary.com]

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[7,8,15-17]. 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).[18] 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[19,20] 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.[21] 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 melanic 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 arachnoidian 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

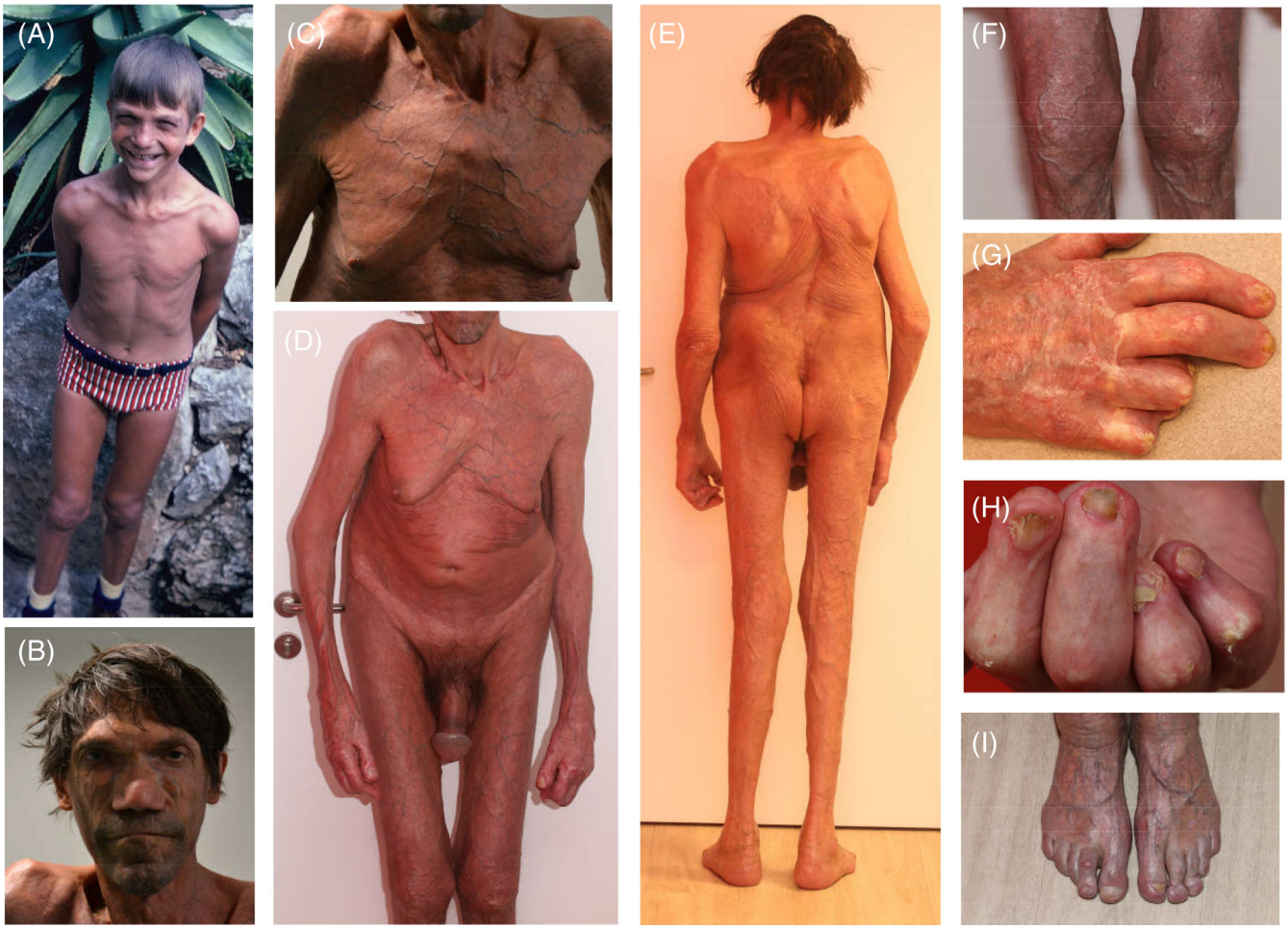

FIGURE 2 Clinical features of patient 1. A, During childhood. B-E, Age 53 years. Facial features, A and B, include supraorbital ridge, deep-set eyes, ptosis, hypertelorism, wide nasal bridge and base, mandibular hypoplasia, thin lips, smooth philtrum and square chin. Skin is atrophic with absence of subcutaneous fat, diffuse erythrosis, and abnormal blood vessels, C and D. Marfanoid habitus with tall stature, severe scoliosis, stiff joints, amyotrophia, and large penis, D-F. Hypertrophic, retractile and sometimes calcified scars, camptodactyly of 2-5th fingers, severe nail dystrophia, and Ainhum circumferential constriction of the second and third toe of the left foot, G-I [Colour figure can be viewed at wileyonlinelibrary.com]

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, dolichostenomelia, minor pectus carinatum, and stiff joints with genu valgum and amyotrophy. Macropenis was noted with enlarged glans. Facial features included marked supraorbital ridges, broad nasal tip with large bridge and base, wide spaced eyes, ptosis, mandibular hypoplasia, slightly low set ears, smooth philtrum, thin upper-lip and square chin. Hairs were fine with generalised hypotrichosis. Dermatologic features were particularly marked, with diffuse erythrosis, absence of subcutaneous fat, atrophic and fragile skin with generalised abnormal appearance of blood vessels and hypertrophic, retractile and sometimes calcified scars of the extremities, secondary to minor injuries. There was no cutis laxa, skin hyperelasticity or dental anomaly. There was camptodactyly of 2-5th fingers, Ainhum circumferential constriction of the second and third toe of the left foot, severely dystrophic nails and pterygia of two toenails. Re-evaluation of cerebral MRIs and CT scans did not reveal cerebral calcification. Compassionate use of tyrosine kinase inhibitors was discussed but declined by the patient.

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.

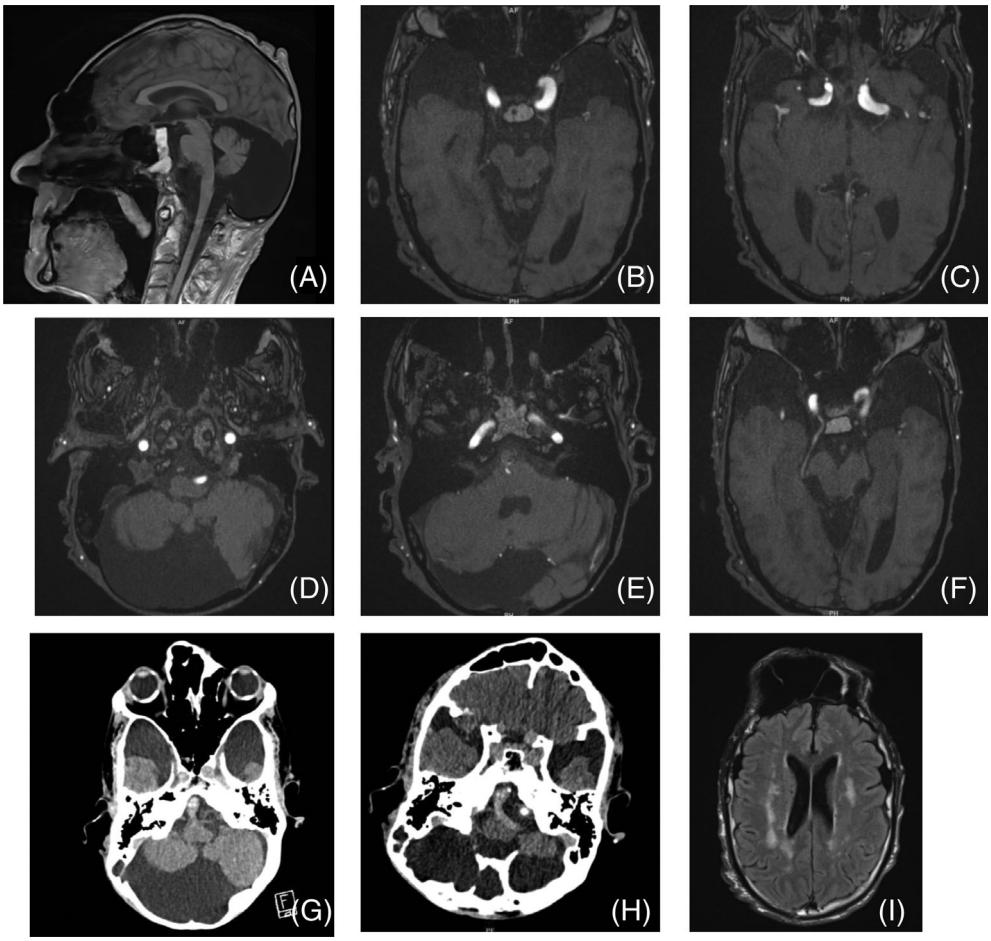

FIGURE 3 Imaging of patient 1. A, Sagittal view of a T1-weighted cerebral MRI showing a large posterior fossa cyst in continuity with the fourth ventricle associated with an elevated tent and diffuse hypoplasia of the cerebellum (Dandy-Walker syndrome). B-F, Axial views of a Time Of Flight (ToF)-weighted 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

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. Hearing impairment, flexion contractures of the fingers, and frequent hospital admissions with recurrent VP shunt blockages were also contributing factors.

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.

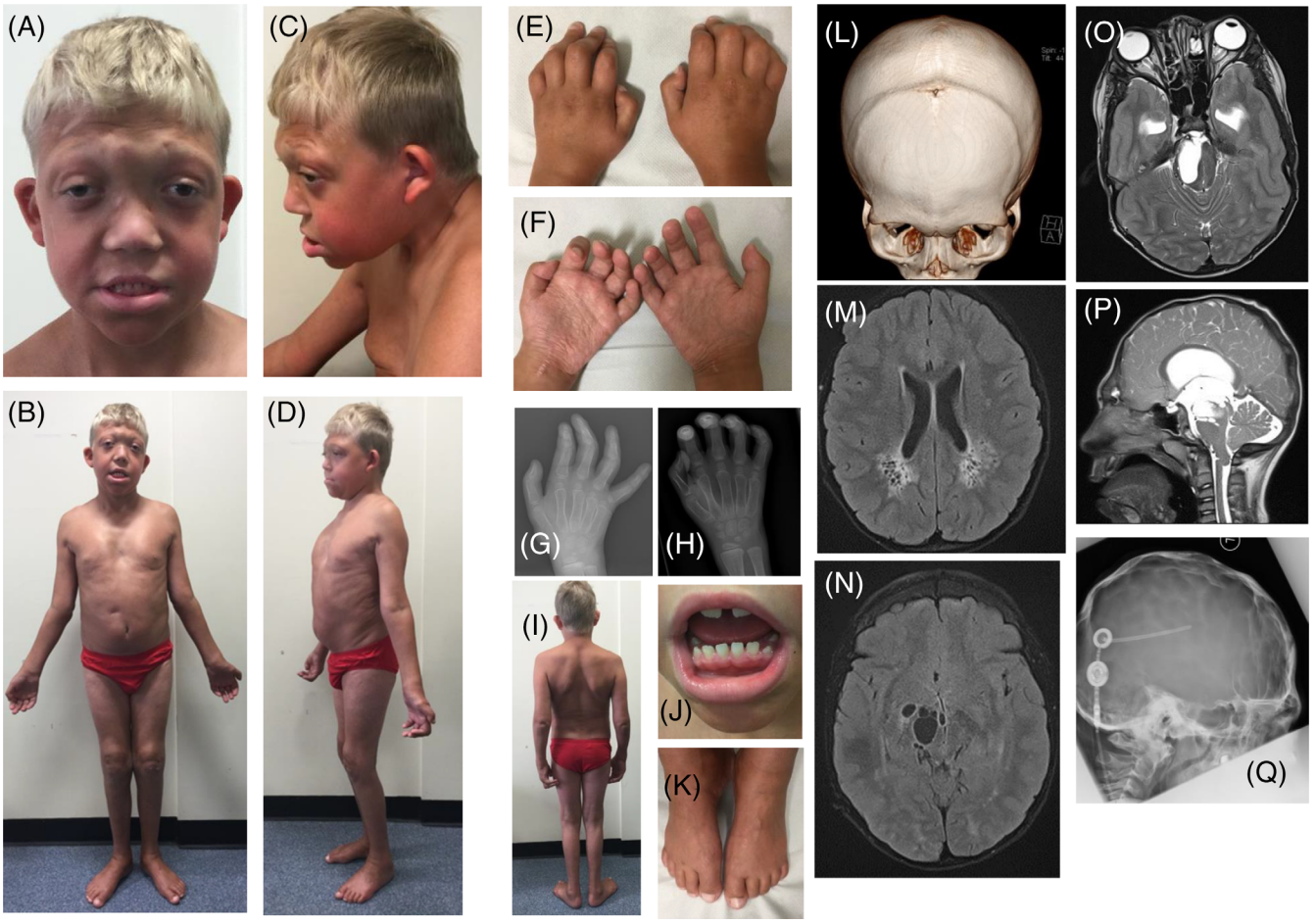

FIGURE 4 Clinical features and imaging of patient 2. Features of the face and cranium, A-D, brachycephaly, sloping forehead, prominent supraorbital ridge, wide spaced eyes, proptosis, downslanting palpebral fissures, wide nasal bridge, wide nasal base, wide nasal tip, malar flattening, midface retrusion, smooth philtrum, thin vermilion of the upper lip, everted vermilion of the lower lip, protruding ears with forward facing and uplifted earlobes, widely spaced teeth and class III malocclusion resulting from midface retrusion (J). Tanned appearance with thin hyperelastic skin and wrinkled palms, B,D,F. Tall body habitus with pectus excavatum and reduced extension of the elbows, B,D. Progressive flexion contractures of the fingers and short wide thumbs, E,F. Broad feet (K). Hand and foot x-rays age three, G, and five, H: Widening of metacarpals and phalanges with a degree of carpal crowding and some widening of the metatarsals and phalanges; progression of contractures. L: CT head age 18 months with almost complete fusion of the sagittal, coronal and metopic sutures. M and N: MRI head age three showing generalised parenchymal volume loss, bilateral posterior periventricular T2 high and flair high signal with focal areas of low signal in keeping with cystic changes, right cerebral peduncle T2 high signal and Wallerian degeneration with severe cystic gliosis, and small foci of flair hyperintensity in the bilateral centrum ovale suggesting acute ischaemic foci. O and P: MRI head age five showing foci in the right midbrain occluding the third ventricle and cerebral aqueduct causing increase in size of the bilateral lateral ventricles and third ventricle, mild mass-effect with midline shift, inferior descent of the brainstem and cerebellar tonsils and possible compression of the optic nerve/chiasm. Q: CT head age five showing copper beaten skull related to chronic raised intracranial pressure [Colour figure can be viewed at wileyonlinelibrary.com]

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

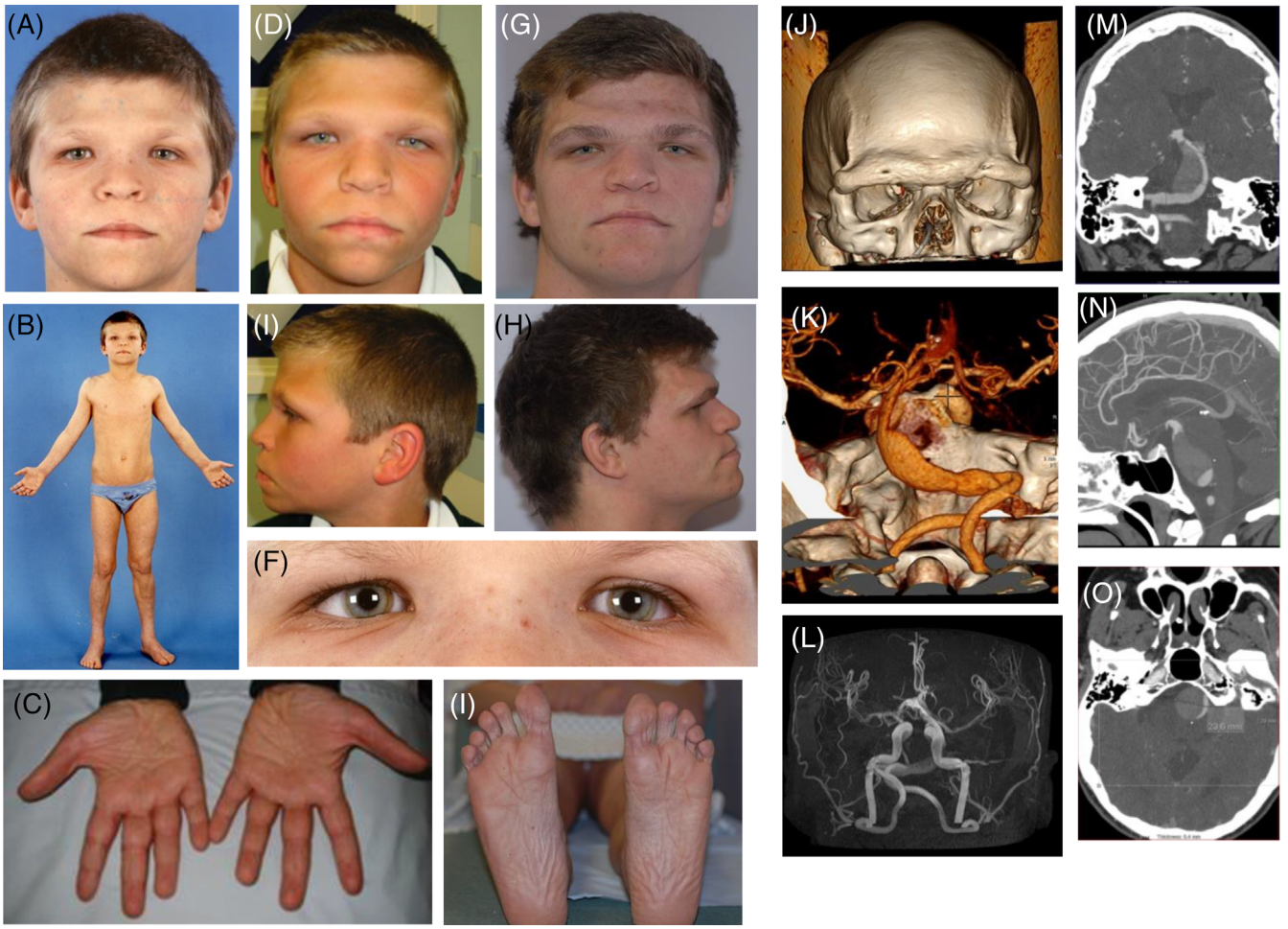

FIGURE 5 Clinical features and imaging of patient 3. Facial features: prominent supraorbital ridges, broad nose and broad nasal bridge age 9, A, age 11, D,I, and age 20, G,H. Yellow ring around the iris, F. Reduced subcutaneous fat, B. Large hands with broad digits, C, and thin hyperelastic skin with wrinkled palms and soles, C,I. J,K: Intracranial CT angiogram showing prominent frontal bone and thrombosis of a large fusiform aneurysm of the basilar artery, the majority of which is thrombosed. L-O, MRA head showing large fusiform aneurysm of the basilar artery indenting the brain stem and including an area of thrombosis, multiple foci of signal change in the supratentorial white matter in keeping with chronic small vessel ischaemia, and multiple areas of presumed dural ectasia with thinning of the skull vault and skull base [Colour figure can be viewed at wileyonlinelibrary.com]

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, wide spaced eyes, 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*.

4 | 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 diagnosed 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.[15] 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.[15,16] 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[7,8,15] 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[7,8] 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.

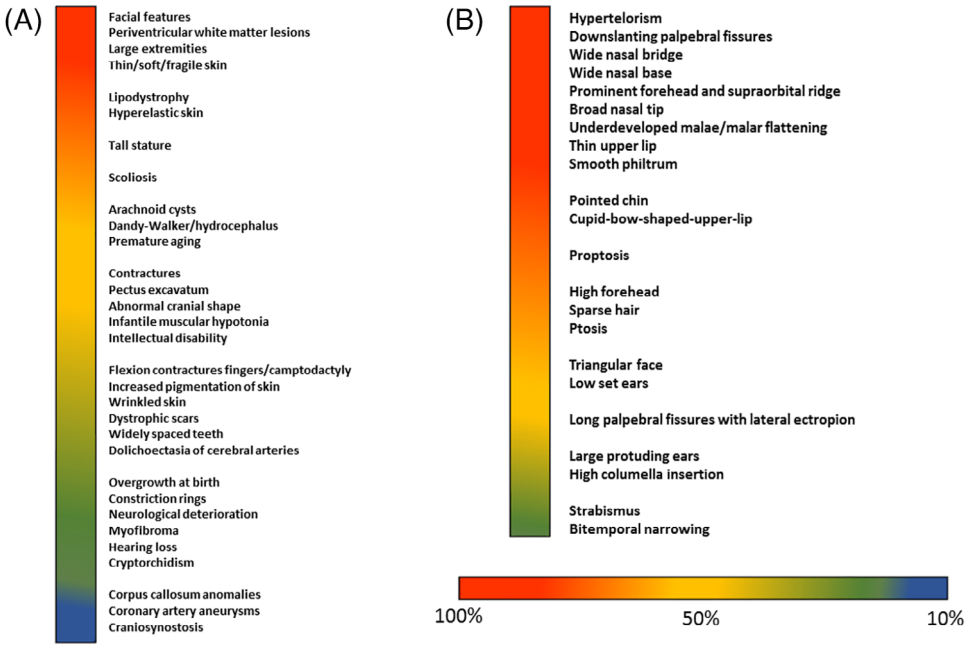

FIGURE 6 Frequency of general clinical features, A, and facial features, B, in published patients with KOGS [Colour figure can be viewed at wileyonlinelibrary.com]

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)	Reference 15	Reference 16	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	F	M	M	M
Growth pattern									
Overgrowth at birth	–	–	–	–	+	+	–	–	–
Tall stature (Height SD)	+ (+4.8)	nk	+	+	+	+ (+6.1)	+ (+4.0)	+ (+2.8)	– (0.0)
Large extremities	+	+	+	+	+	+	+	+	+
Skeletal features									
Scoliosis	+	+	–	+	+	+	+	–	–
Camptodactyly/flexion contractures of fingers	nk	nk	nk	nk	+	–	+	+	–
Contractures	nk	nk	nk	nk	+	+	+	+	–
Pectus excavatum	nk	nk	–	+	–	+	+	+	–
Abnormal cranial shape	+	+	nk	nk	+	nk	–	+(craniosynostosis)	–
Dermatological features									
Hyperelastic skin	+	+	+	+	+	+	–	+	+
Thin/soft/fragile skin	+	+	+	+	+	+	+	+	+
Increased skin pigmentation	–	–	–	–	–	–	+	+	+
Wrinkled skin	nk	nk	nk	+	nk	nk	–	+	+
Dystrophic scars	–	–	–	+	–	–	+	–	–
Constriction rings	–	–	+	–	–	–	+	–	–
Lipodystrophy	+	+	–	+	+	+	+	+	+
Premature ageing	nk	nk	–	+	+	+	+	+	–
Widely spaced teeth	nk	nk	nk	nk	+	nk	–	+	+
Neurological features									
Intellectual disability	+	+	+	+	–	–	–	–	–
Neurological deterioration	+	+	nk	nk	–	–	-	–	–
Infantile muscular hypotonia	nk	nk	+	+	+	–	+	-	–
Cerebral MRI									
Periventricular white matter lesions	+	+	+	+	+	+	+	+	+

(Continues)

TABLE 1 (Continued)

	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									
Dolichoectasia of cerebral arteries	–	–	–	–	–	+ (cervical, vertebral)	+	–	+ (basilar artery)
Coronary artery aneurysms	nk	nk	nk	nk	nk	+	–	–	–(atheroma)
Others									
Facial features	+	+	+	+	+	+	+	+	+
Myofibroma	+	–	+	–	–	–	–	–	nc
Hearing loss	–	–	–	–	–	+	–	+	–
Cryptorchidism	na	na	na	na	+	na	–	+	–
Other features	–	–	–	Cardiac valvulopathy		Hydronephrosis Epilepsy Spinal dural ectasia Diplegia	Ocular pterygia Osteoporosis Diffuse erythrosis Nail dystrophy Plantar calcifications	Visual impairment Carpal tunnel syndrome	Hypoglycaemia in infancy 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	c.1751C > G	c.1751C > G	c.1477A > T
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,[16] 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 KOGS and are associated with both known KOGS-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 KOGS, including our patient 2 at the age of six, and no other vascular anomalies have been identified. However, several features of KOGS 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 KOGS 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 Pentinnen syndrome and major dilatation of the left coronary system on echocardiogram age seven and a haemorrhagic stroke secondary to aneurysm of the basilar artery age nine have been reported.[22] She had many of the shared clinical features of a *PDGFRB*-related disorder—thin fragile skin, sparse hair, kyphoscoliosis, progressive joint contractures, tall stature (height > 3SD), ocular pterygia, MRI findings of hydrocephalus, arachnoid cysts, white matter lesions and multiple craniosynostosis—in addition to the characteristic progressive acro-osteolysis, nodular scarring and facial features of Penttinen syndrome. A molecular diagnosis in this case would provide further insight into the genotype-phenotype correlations between specific *PDGFRB* mutations and vascular complications. In addition, Karasozen 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[13] . Upregulation of PDGFRB expression has also been showed in aortic wall tissue from patients with thoracic aortic dissection.[23] 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 KOGS 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.[9] 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.[24] It has been established that the KOGS-specific pathogenic variants in *PDGFRB* are activating mutations that activate the PI3K-AKT pathway[16] and are responsive to imatinib[25] suggesting that individuals with KOGS 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 KOGS 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 KOGS 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.[6,22,26] Patient 3 also has novel features including recurrent hypoglycaemia in infancy, minor anterior chamber cleavage syndrome, recurrent haematomas and cellulitis 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 KOGS variants are in the juxtamembrane domain of the protein.

Recently, individuals with novel mutations in *PDGFRB* not previously associated with KOGS, 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)[11] and c.1996A > C p.(Asn666His),[9] 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),[10] a somatic loss-of-function variant in the juxtamembrane region, has a phenotype overlapping KOGS 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 KOGS, report a patient with a novel *PDGFRB* variant and a KOGS-like phenotype, and highlight the vascular risk in KOGS. We suggest that vascular investigations are indicated in individuals with KOGS and KOGS-like disorders. Therapeutic options are of great interest in the future clinical management of these patients.

ACKNOWLEDGEMENTS

The authors thank the patients and their families. Some authors of the manuscript are part of the European Reference Network ITHACA.

The authors thank the Burgundy Regional Council through the plan régional d'actions pour l'innovation (PARI 2017) and the European Union through the PO FEDER-FSE Bourgogne 2014/2020 programs. The Phenotyping of Overgrowth Disorders (POD) study (CPMS 19361) is funded by the National Institute for Health Research (NIHR) in the United Kingdom. This research was made possible through access to the data and findings generated by the 100 000 Genomes Project. The 100,000 Genomes Project is managed by Genomics England Limited (a wholly owned company of the Department of Health and Social Care). The 100 000 Genomes Project is funded by the National Institute for Health Research and NHS England. The Wellcome Trust, Cancer Research UK and the Medical Research Council have also funded research infrastructure. The 100 000 Genomes Project uses data provided by patients and collected by the National Health Service as part of their care and support.

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 corresponding author upon reasonable request.

ORCID

Alison Foster https://orcid.org/0000-0002-0216-3909
Ange-Line Bruel https://orcid.org/0000-0002-0526-465X

REFERENCES

1. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. *Genes Dev*. 2008;22(10):1276-1312. https://doi.org/10.1101/gad.1653708.
2. Cheung YH, Gayden T, Campeau PM, et al. A recurrent PDGFRB mutation causes familial infantile myofibromatosis. *Am J Hum Genet*. 2013;92(6):996-1000. https://doi.org/10.1016/j.ajhg.2013.04.026.
3. Martignetti JA, Tian L, Li D, et al. Mutations in PDGFRB cause autosomal-dominant infantile myofibromatosis. *Am J Hum Genet*. 2013;92(6):1001-1007. https://doi.org/10.1016/j.ajhg.2013.04.024.
4. Lepelletier C. Heterozygous PDGFRB mutation in a three-generation family with autosomal dominant infantile Myofibromatosis. *Acta Derm Venereol*. 2017;97:858-859. https://doi.org/10.2340/00015555-2671.
5. Murray N, Hanna B, Graf N, et al. The spectrum of infantile myofibromatosis includes both non-penetrance and adult recurrence. *Eur J Med Genet*. 2017;60(7):353-358. https://doi.org/10.1016/j.ejmg.2017.02.005.
6. Johnston JJ, Sanchez-Contreras MY, Keppler-Noreuil KM, et al. A point mutation in PDGFRB causes autosomal-dominant Penttinen syndrome. *Am J Hum Genet*. 2015;97(3):465-474. https://doi.org/10.1016/J.AJHG.2015.07.009.
7. Takenouchi T, Yamaguchi Y, Tanikawa A, Kosaki R, Okano H, Kosaki K. Novel overgrowth syndrome phenotype due to recurrent De novo PDGFRB mutation. *J Pediatr*. 2015;166(2):483-486. https://doi.org/10.1016/j.jpeds.2014.10.015.
8. Minatogawa M, Takenouchi T, Tsuyusaki Y, et al. Expansion of the phenotype of Kosaki overgrowth syndrome. *Am J Med Genet Part A*. 2017;173:2422-2427. https://doi.org/10.1002/ajmg.a.38310.
9. Pond D, Arts FA, Mendelsohn NJ, Demoulin J-B, Scharer G, Messinger Y. A patient with germ-line gain-of-function PDGFRB p.N666H mutation and marked clinical response to imatinib. *Genet Med*. 2018;20(1):142-150. https://doi.org/10.1038/gim.2017.104.
10. Guimier A, Gordon CT, Hully M, et al. A novel de novo *PDGFRB* variant in a child with severe cerebral malformations, intracerebral calcifications, and infantile myofibromatosis. *Am J Med Genet Part A* 2019;1–6. https://doi.org/10.1002/ajmg.a.61151.
11. Bredrup C, Stokowy T, Mcgaughran J, et al. A tyrosine kinase-activating variant Asn666Ser in PDGFRB causes a progeria-like condition in the severe end of Penttinen syndrome. *Eur J Hum Genet*. 2019;27:574-581. https://doi.org/10.1038/s41431-018-0323-z.
12. Nicolas G, Pottier C, Maltete D, Coutant S, Rovelet-Lecrux A. Mutation of the PDGFRB gene as a cause of idiopathic basal ganglia calcification. *Neurology*. 2013;80(2):181-187. https://doi.org/10.1212/WNL.0b013e31827ccf34.
13. Karasozen Y, Osbun JW, Parada CA, et al. Somatic PDGFRB activating variants in fusiform cerebral aneurysms. *Am J Hum Genet*. 2019;104(5):968-976. https://doi.org/10.1016/j.ajhg.2019.03.014.
14. Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. *N Engl J Med*. 2002;347(7):481-487. https://doi.org/10.1056/NEJMoa020150.
15. Gawliński P, Pelc M, Ciara E, et al. Phenotype expansion and development in Kosaki overgrowth syndrome. *Clin Genet*. 2018;93(4):919-924. https://doi.org/10.1111/cge.13192.
16. Zarate YA, Boccuto L, Srikanth S, et al. Constitutive activation of the PI3K-AKT pathway and cardiovascular abnormalities in an individual with Kosaki overgrowth syndrome. *Am J Med Genet Part A*. 2019;1–6. https://doi.org/10.1002/ajmg.a.61145.
17. Takenouchi T, Okuno H, Kosaki K. Kosaki overgrowth syndrome: a newly identified entity caused by pathogenic variants in platelet-derived growth factor receptor-beta. *Am J Med Genet Part C Semin Med Genet*. 2019;1–8. https://doi.org/10.1002/ajmg.c.31755.
18. Thevenon J, Duffourd Y, Masurel-Paulet A, et al. Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test. *Clin Genet*. 2016;89(6):700-707. https://doi.org/10.1111/cge.12732.
19. Richards S, Aziz N, Bale S, 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(5):405-423. https://doi.org/10.1038/gim.2015.30.
20. Ellard S, Baple E, Berry I, et al. ACGS Best Practice Guidelines for Variant Classification 2019. Association for Clinical Genomic Science Website. https://www.acgs.uk.com/quality/best-practice-guidelines. Accessed October 3, 2019.
21. Stoll C, Juif JG, Grosshans E, Brini A. Ehlers-Danlos syndrome associated with gigantism, craniosynostosis and melanoderma. *Pediatrie*. 1974;29(1):81-89.
22. Zufferey F, Hadj-Rabia S, De Sandre-Giovannoli A, et al. Acro-osteolysis, keloid like-lesions, distinctive facial features, and overgrowth: two newly recognized patients with premature aging syndrome, penttinen type. *Am J Med Genet Part A*. 2013;161(7):1786-1791. https://doi.org/10.1002/ajmg.a.35984.
23. Meng W, Liu S, Li D, et al. Expression of platelet-derived growth factor B is upregulated in patients with thoracic aortic dissection. *J Vasc Surg*. 2018;68(6):3S-13S. https://doi.org/10.1016/j.jvs.2018.01.052.
24. Mudry P, Slaby O, Neradil J, et al. Case report: rapid and durable response to PDGFR targeted therapy in a child with refractory multiple infantile myofibromatosis and a heterozygous germline mutation

of the PDGFRB gene. *BMC Cancer*. 2017;17(1):119. https://doi.org/10.1186/s12885-017-3115-x.

25. Arts FA, Chand D, Pecquet C, et al. PDGFRB mutants found in patients with familial infantile myofibromatosis or overgrowth syndrome are oncogenic and sensitive to imatinib. *Oncogene*. 2015;1-10. https://doi.org/10.1038/onc.2015.383.
26. Zhang Z, Zheng S, Zheng S, et al. Premature Aging Syndrome, Penttinen Type: Report of a Chinese Case with a PDGFRB mutation. *Acta Derm Venereol*. 2018;98:912-913. https://doi.org/10.2340/00015555-2993.

How to cite this article: Foster A, Chalot B, Antoniadi T, et al. Kosaki overgrowth syndrome: A novel pathogenic variant in *PDGFRB* and expansion of the phenotype including cerebrovascular complications. *Clin Genet*. 2020;1–13. https://doi.org/10.1111/cge.13752