Activating variants in PDGFRB result in a spectrum of disorders responsive to imatinib monotherapy

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Data sharing and availability

Data available on request from the authors.
ABSTRACT

Purpose:
More than 50 individuals with activating variants in the receptor tyrosine kinase PDGFRB have been reported, separated based on clinical features into solitary myofibromas, infantile myofibromatosis, Penttinen syndrome with premature aging and osteopenia, Kosaki overgrowth syndrome and fusiform aneurysms. Despite their descriptions as distinct clinical entities, review of previous reports demonstrates substantial phenotypic overlap.

Methods:
Case series (n=12) and literature review

Results:
We describe five patients with PDGFRB activating variants whose clinical features overlap multiple diagnostic entities. Seven additional patients from a large family had variable expressivity and late-onset disease, including adult onset features and two individuals with sudden death. Three patients were treated with imatinib and had robust and rapid response, including the first two reported infants with multicentric myofibromas treated with imatinib monotherapy and one with a recurrent p.Val665Ala (Penttinen) variant. Along with previously reported individuals, our cohort suggests infants and young children had few abnormal features, while older individuals had multiple additional features, several of which appeared to worsen with advancing age.

Conclusion:
Our analysis supports a diagnostic entity of a spectrum disorders due to activating variants in
\textit{PDGFRB}. Differences in reported phenotypes can be dramatic and correlate with advancing
age, genotype, and to mosaicism in some individuals.

Keywords: myofibromatosis, fusiform aneurysm, Penttinen syndrome, Kosaki overgrowth
syndrome, imatinib
INTRODUCTION

Several clinical entities have been attributed to constitutional or mosaic pathogenic variants in the receptor tyrosine kinase PDGFRB (Supplementary Table 1 online). Loss-of-function variants have been associated with idiopathic basal ganglia calcifications (MIM 615007), also called Fahr disease.

Constitutional gain-of-function (GOF) or activating variants have been associated with several reportedly distinct phenotypes attributed to different pathogenic variants including (from less to more severe) infantile myofibromatosis (MIM 228550), fusiform aneurysms, Kosaki overgrowth syndrome (p.Pro584Arg; MIM 616592), Penttinen premature aging syndrome (p.Val665Ala; MIM 601812), and in many individuals with features that do not clearly fit within any of these diagnostic category (Aminkeng, 2015; Bredrup et al., 2019; Cheung et al., 2013; Guimier et al., 2019; Johnston et al., 2015; Lepelletier et al., 2017; Martignetti et al., 2013; Pond et al., 2018; Takenouchi et al., 2015; Zarate et al., 2019; Zhang et al., 2018).

Postzygotic (mosaic) GOF variants have also been described, including two individuals with segmental mosaicism involving multiple tissues. The first was an infant with multicentric myofibromas and segmental skin changes typical of Penttinen syndrome; the p.Val665Ala mutation was found in affected skin but not in surrounding unaffected skin (Zhong et al., 2018). The second was a man with segmental overgrowth, thin, discolored skin and multiple intra- and extracranial fusiform aneurysms with a different GOF variant (Karasozen et al., 2019). Notably,
fusiform cerebral, coronary and renal aneurysms have all been reported in individuals with constitutional PDGFRB GOF phenotypes (Brasseur et al., 2010; Frezin, Fusaro, Reding, & Godefroid, 2015; Zarate et al., 2019; Zufferey et al., 2013). More restricted mosaic GOF variants of PDGFRB found only in affected tissue have been seen in sporadic myofibromas, and less often in myopericytomias and fusiform aneurysms (Arts et al., 2016; Hung & Fletcher, 2017; Zhong et al., 2018)(Karasozen et al., 2019). None of these reports described deep sequencing in affected tissue to detect potential second pathogenic variants, although one described three different pathogenic variants in PDGFRB in three myofibromas in a single individual (Arts et al., 2016). Mosaic variants in PDGFRB (p.Asn666Ser) were also found in 9% of individuals with unicentric Castleman disease, a condition in which overgrowth of a lymph node is associated with systemic inflammatory symptoms and multiple organ dysfunction due to dysregulation of cytokines (Li et al 2019).

One or more key features have been described for each of these described entities that allow for some affected individuals to fit clearly within a diagnostic category, while other individuals have features that span or extend beyond current diagnostic entities or “bins”. For example, several individuals with germline pathogenic variants at amino acid 665 have progressive acro-osteolysis, as described in Penttinen syndrome, while this has not been seen with other GOF mutations. However, other features appear to be common to all patients with GOF variants of PDGFRB, especially myofibromas and risk for aneurysms. This pattern is analogous to FGFR2-associated craniosynostosis syndromes, in which all GOF pathogenic variants are associated with major features such as multisuture craniosynostosis, midface retrusion, and multilevel...
airway obstruction, while some variants are associated with less common but easily recognized features such as polysyndactyly in Apert syndrome.

Treatment of two siblings with infantile myofibromatosis with imatinib, a tyrosine kinase inhibitor that downregulates PDGFRB, in addition to vinblastine led to reduction in size of myofibromas within four weeks, while treatment of one boy with a severe GOF-associated phenotype led to sustained improvement of multiple features over one year of therapy (Mudry et al., 2017; Pond et al., 2018).

Here we describe clinical and molecular data for 7 individuals from one multiplex family, and another 5 unrelated single affected individuals with PDGFRB GOF variants, including an update regarding therapy for one previously reported boy. Our analysis of these 12 and more than 60 previously reported affected individuals demonstrates overlapping phenotypes between all of the reported entities associated with GOF variants, which supports a single disease spectrum that we designate PDGFRB activating spectrum disorder (PAVS). Within this wide spectrum of overlapping phenotypes, we were also able to recognize two consistent subgroups with less severe and more severe features that correlate with the specific mutation: PAVS1, which includes infantile myofibromatosis and aneurysms in otherwise normal appearing individuals; and PAVS2, which is characterized by more severe multisystem abnormalities that are uniformly progressive if followed for several years, and encompasses the previously described diagnostic entities of Penttinen and Kosaki overgrowth syndromes.
Within each group we found several genotype-phenotype correlations as well as a contribution of mosaicism to the phenotype. Both subgroups had shared pathophysiology resulting in risk for recurrent myofibromas, aneurysms, skin changes, potential for overgrowth and progressive white matter disease or leukoencephalopathy. We also report rapid and dramatic response to imatinib monotherapy in three children with PDGFRB-activating variant spectrum disorders, two with PAVS1 and one with PAVS2. We propose that imatinib monotherapy may be effective in the treatment of patients with PAVS1 and PAVS2.

METHODS

The individuals reported in this study were recruited through IRB-approved protocols at Seattle Children’s Hospital and the Children’s Hospital of Philadelphia. PDGFRB GOF variants were detected by clinical or research exome sequencing (Table 1). We performed retrospective chart review for all subjects, including re-analysis of sequencing data.

Literature review

Our initial literature review identified reports of at least nine disorders distinguished by clinical or pathological criteria and associated with PDGFRB pathogenic GOF variants (Supplementary Table 1 online). However, several individuals in our series had features that overlapped with two or more of these entities, prompting us to review all reports with individually described data, which we separated into those with (PDGFRB+) and those without (PDGFRB-S or suspected)
molecular data. We excluded aggregated studies of sporadic myofibromas and aneurysms when individual-level data were not available, as well as individuals with loss-of-function variants.

RESULTS

We describe 12 affected or probably affected individuals from six families with pathogenic GOF variants of PDGFRB, including one new family with seven affected individuals (LR19-377a1-a7). The authors personally evaluated the proband and his mother (LR19-377a1 and LR19-377a2) and obtained relevant clinical information on other likely affected relatives from family members in person and by phone. A pedigree is shown in Supplementary Figure 1. In this family, the proband and his mother had genetic testing, while the remaining individuals were suspected to be affected based on their medical history. For additional details regarding clinical course for each patient please see Supplementary File. Two of our 5 single affected individuals were previously reported. Subject LR17-436, now 14 years old, was reported at age 9 as patient 3 (Johnston et al., 2015). We report several new clinical features as well as their response to treatment with imatinib. The neuroimaging features of subjects LR05-118 were recently reported (Aldinger et al., 2019), and here we describe her full phenotype and clinical course. For further details regarding their phenotypes, see the Supplementary text.

Clinical Reports
**LR19-377a1.** This infant boy had multicentric myofibromatosis including a large myofibroma at the base of the tongue causing upper airway obstruction. Next-generation sequencing was performed on blood and tissue (“OncoPlex Panel”, University of Washington, and identified two pathogenic PDGFRB GOF variants. The first presumably constitutional variant was seen in blood and myofibroma: c.1998C>A (p.Arg561Cys). The second GOF variant was detected in tumor only: c.1681C>T (p.Asn666Lys). These findings were confirmed by GeneDx exome sequencing, which was performed due to his severe clinical phenotype. He was started on imatinib monotherapy at one month of life. He underwent operative airway evaluation at that time showing severe tongue base obstruction (Grade IV laryngoscopy view), and then had rapid resolution of his myofibromas and airway obstruction allowing him to be discharged home with no respiratory support at seven weeks of life (Figure 1). His tumors were barely visible by two months on therapy, and imatinib was discontinued at four months, as he had no clinically significant disease at that time. Repeat imaging at 10 months of age showed recurrence of myofibromatosis, including re-growth of previous tumors and development of new tumors. Figure 1. Importantly, the mass at the base of tongue has not had regrowth and he remains free of respiratory obstruction.

**LR19-377a2.** The mother of proband LR19-377a1 had two masses identified at one month of age on her shoulder and abdomen that were surgically removed at four months. The pathological features were consistent with myofibromas. At five years, she developed another large abdominal mass that was surgically removed and pathologically confirmed to be...
consistent with myofibroma. Genetic testing from peripheral blood identified the same GOF variant first detected in her son: c.1998C>A (p.Arg561Cys).

LR19-377a3. The maternal grandmother developed a mass of her neck in adulthood that has not been removed or biopsied, but the consistency and appearance of the mass are similar to those of other family members with biopsy-proven myofibromatosis. She recalls no similar masses in childhood.

LR19-377a4. One maternal great uncle (brother of a3) passed away suddenly at age 60. He was in good health except for hypercholesterolemia. He developed progressive subcutaneous masses as an adult that were similar in appearance to other those in LR19-377a1 and LR19-377a2. No autopsy was performed.

LR19-377a5. Another great uncle (brother of a3 and a4) was well without significant medical problems until adulthood. As an adult he developed numerous masses similar in appearance to LR19-377a1, LR19-377a2 and LR19-377a4. He also had hypercholesterolemia managed with medication. In his early 50’s, he reported sudden onset of pain, and died en route to the hospital. His family does not recall where the pain was localized. No autopsy was performed.

LR19-377a6. The son of LR19-377a5 was healthy until early adulthood, when he also developed numerous subcutaneous masses similar in appearance to LR19-377a1, LR19-377a2, LR19-377a4 and LR19-377a5. He is otherwise in good health.
One individual in a prior generation had also developed several masses similar in appearance to others in the family as an adult. He had relatively sudden-onset of dementia and psychosis in his late 50’s that was rapidly progressive. He died of a traumatic injury.

This infant girl had severe multicentric myofibromatosis diagnosed prenatally based on the identification of multiple large masses on ultrasound. Clinical ES of DNA isolated from a preauricular myofibroma identified two GOF variants in PDGFRB: c.1691_1717del (p.I564_V572del), a 27-bp in-frame deletion in the juxtamembrane domain, and c.1997A>C (p.Asn666Thr), a previously reported GOF mutation. Her largest myofibroma had necrotic areas, and she remained hospitalized due to ongoing infection risk and surgical planning. During her hospitalization, imatinib monotherapy was initiated, and led to a swift and robust resolution of her myofibromas (Figure 1).

This 26-year old woman had unusual abnormalities of her skin, soft tissues and blood vessels from birth, then presented with progressive loss of vision in her left eye. She had normal height (54th centile). On exam, she looked older than her stated age, with sparse hair and coarse facial features. Her left leg and right arm were larger than the contralateral limbs. She also had several cutaneous patches of vascular malformations, and multiple fibromas including a nodular lesion of the tongue. Magnetic resonance angiogram showed a fusiform aneurysm of the internal carotid artery that was compressing the left optic nerve. Next-
Generation Sequencing based testing was performed on biopsied lesions. This identified a missense variant, p.Tyr562Cys, in *PDGFRB*. The variant was not detected in blood.

**LR05-118.** This girl was born with multicentric myofibromatosis and had progressive increase in head size that led to diagnosis of Dandy-Walker malformation and hydrocephalus that was managed with placement of a ventriculoperitoneal shunt soon after birth. She had an unusual growth pattern with tall height (>90th centile) documented by two years, which fell to less than the 10th centile by 8 years. Serial exams showed skin that became progressively fragile with easy bruising and scarring, and progressive scoliosis that required placement of rods. She also had multiple episodes of apnea requiring intubation, and died at age eight years. WES detected a de novo, pathogenic GOF variant of *PDGFRB*: c.1696T>C; p.Trp566Arg. Brain anatomy of this patient was recently reported (Aldinger et al., 2019).

**LR19-453.** This boy presented with congenital hydrocephalus and was found to have Dandy-Walker malformation, grey matter heterotopia, undescended testes, bilateral inguinal hernias and macrosomia (weight and length greater than the 95th centile). Echocardiogram at 6 months detected dilation of the right and left coronary arteries. By 13 years, he was no longer large, with weight at the 50th and length at the 75th centile. He had gradually developed soft and hyperextensible skin with preserved subcutaneous fat, progressive facial coarsening, moderate scoliosis and recurrent patellar dislocations. Exome sequencing identified a *de novo* pathogenic variant (c.1696T>C; p.Trp566Arg) in *PDGFRB*, the same change as in LR05-118.
LR17-436. This boy was described in a prior report of Penttinen syndrome (as patient 3) with a p.Val665Ala variant in PDGFRB (Johnston et al., 2015). As an infant and young child, he had normal hands and a largely normal facial appearance (Figure 3). At the time of the report, he had moderate developmental delay, borderline macrocephaly, and over time developed progressive midface retrusion, acroosteolysis, and thin, hyperextensible skin with loss of subcutaneous fat that was prone to scarring. Brain MRI showed asymmetric cerebellar hypoplasia more severe on the right and enlarged posterior fossa or mega-cisterna magna. Since the prior report, he has continued to progress, with increasing maxillary retrusion and malocclusion, progression of facial features, skin changes and near absence of subcutaneous fat. At 14 years, repeat brain MRI showed the same posterior fossa abnormalities as well as patchy white matter disease consistent with a new leukoencephalopathy. MRA of this chest and body demonstrated widespread vessel ectasia and a renal aneurysm. He was started on imatinib therapy, and after only 4 weeks had decreased visibility of blood vessels, improved skin turgor, decreased ocular discomfort and associated conjunctival injection, and reported decrease in skin sensitivity, eye irritation and hand pain (Figure 3). At 8 weeks of therapy, his scars had thinned and become less prominent, and his parents report they had to start trimming his fingernails again, which they had not done for some time.

DISCUSSION

To better understand the range of PDGFRB phenotypes, we performed detailed genotype-phenotype analysis on a cohort of 74 individuals with known or presumed mutations of
PDGFRB, including the 12 individuals reported here and another 62 for whom individual level data were provided in prior reports. The cohort included 46 individuals with confirmed PDGFRB pathogenic GOF variants, a PDGFRB+ group (Al Qawahmed et al., 2019; Arts et al., 2016; Brasseur et al., 2010; Bredrup et al., 2019; Cheung et al., 2013; Frezin et al., 2015; Gawliński et al., 2018; Guimier et al., 2019; Johnston et al., 2015; Karasozen et al., 2019; Lepelletier et al., 2017; Minatogawa et al., 2017; Mudry et al., 2017; Murray et al., 2017; Penttinen et al., 1997; Pond et al., 2018; Takenouchi et al., 2015; Zarate et al., 2019; Zhang et al., 2018; Zufferey et al., 2013), and another 28 with phenotype data only, mostly from older reports – a PDGFRB-S or suspected group (Guimier et al., 2019; Hausbrandt et al., 2010; Holzer-Fruehwald, Blaser, Rossi, Fruehwald-Pallamar, & Thurnher, 2012; Kaplan, Ojemann, Grange, Fuller, & Park, 2002; Kulkarni, Desai, Grundy, & Sergi, 2012; Pelluard-Nehmé et al., 2007; Spadola, Anooshiravani, Sayegh, Jequier, & Hanquinet, 2002). For the purposes of this analysis, we excluded the three individuals with unicentric Castleman disease with PDGFRB variants in affected lymph nodes, as 91% of individuals with unicentric Castleman disease were not found to harbor PDGFRB variants, and several other pathogenic variants were identified in affected tissue of other patients with the same phenotype (Li et al., 2019).

**Phenotype analysis by system across the entire cohort (N=74)**

Despite mounting evidence that all GOF mutations of PDGFRB are associated with a slowly but inexorably progressive course, descriptions of long-term follow-up are sparse, which implies that the features described in most published reports likely underestimate the ultimate phenotype in affected individuals. With this limitation in mind, we proceeded to analyze all clinical data at the
time of most the recent reports. We found consistent evidence of overlapping phenotypes in many individuals including almost all with long-term follow-up, an observation that seemed at odds with reports of 3 distinct syndromes with PDGFRB GOF mutations. This prompted us to first examine specific features by system across the entire cohort (N=74).

**Benign tumors and aneurysms**

**Myofibromas.** In the PDGFRB+ group, 6/46 subjects had solitary and 28/46 had multicentric myofibromas. These were often located in the skull, vertebrae and long bones, but could be found in any tissue including the brain. None of the individuals with solitary myofibromas had surveillance imaging performed to look for clinically silent lesions. In the PDGFRB-S group, 27 of 28 had clinical suspicion of myofibromas or myopericytomatas, and 24 described multicentric disease.

**Aneurysms and vascular dysplasia.** Multiple aneurysms were detected in all seven individuals who underwent vascular imaging (PDGFRB+ n=4; PDGFRB-S n=3), most often involving cerebral, coronary and renal arteries. Most were fusiform aneurysms, but a few were described as saccular. In a recent study of aneurysm specimens, 4/6 isolated fusiform aneurysms were found to have pathogenic GOF variants in PDGFRB, compared to 0/38 saccular aneurysm specimens, although no additional clinical data was provided for these individuals (Karasozen et al., 2019). The index subject had serial vascular imaging, which showed that the aneurysms developed over time in adolescence and adulthood (Karasozen et al., 2019).
Vascular abnormalities were common in the cohort. Vascular imaging in subjects LR19-455 and LR19-377a1 were normal in infancy, with no follow-up studies yet obtained. Individual LR19-453 had bilateral coronary artery aneurysms detected at six months that were still dilated to 3-5 mm at 13 years. LR17-436 had widespread vascular tortuosity and ectasia as well as a renal artery aneurysm detected at 14 years. Two unrelated children have been reported with multicentric myofibromas and progressive vascular dysplasia with aneurysms. The first developed multiple aneurysms of the thoracic and abdominal aorta, carotid, iliac, and leg vessels, and ultimately died (Wright et al., 2004). The second developed stenosis and aneurysms of renal and iliac arteries that were first detected at about 5 months of age and progressed over the following 10 months (Brasseur et al., 2010). Pathological examination in both children showed intimal thickening with fragmentation of medial elastic tissue consistent with fibromuscular dysplasia.

More troubling, sudden unexpected death at 19 years was reported in a PDGFRB mutation positive girl with a known aneurysm (Zarate et al., 2019), and in two individuals in our series (LR19-377a4, LR19-377a5) who were members of a family in which most affected individuals had myofibromas but no other clinical problems. Autopsies were not performed in any of the three, so we were unable to determine whether ruptured aneurysm was the cause of death.

**Overgrowth, atrophy and tissue degeneration**

**Overgrowth.** Birth length and weight were normal, varying from just below the 50th to the 95th centile in 13 individuals with data available. Growth data were inconsistently reported in the
literature, but four patients had height that accelerated over time with a final height above +3 SD (Minatogawa et al., 2017; Takenouchi et al., 2015; Zarate et al., 2019). No patients in our series had overgrowth when last seen, although LR05-118 had stature above the 90\textsuperscript{th} centile at two years, then had growth deceleration with height below the 10\textsuperscript{th} centile at eight years. Similarly, a previously-reported boy had accelerated growth with abrupt deceleration of weight gain after 4 years in parallel with an abrupt deceleration of height (Gawliński et al., 2018). This child had a height well above the 95\textsuperscript{th} centile at 4 years (xx SD), but by 10.5 years was below 50\textsuperscript{th} centile for age. Serial growth data were not available for other individuals. These data suggest an irregular pattern of growth, making it difficult to interpret the heights of other patients at a single point in time. Insufficient data regarding stature in patients with myofibromatosis are available to draw conclusions about growth patterns, and no studies have reported differences in height among family members. Perhaps the most compelling evidence that activating variants of $PDGFRB$ are associated with overgrowth comes from the index patient with multiple aneurysms, who had a high-level mosaic mutation in $PDGFRB$ (Karasozen et al., 2019). His left arm appeared normal, while his right arm was significantly enlarged, and he had striking skin changes over his entire right upper extremity and chest.

**Skeletal anomalies.** The most common skeletal anomaly was scoliosis, which was reported in 11 individuals, although in none with predominant myofibromatosis. As many prior reports did not comment on the lack of scoliosis, it is difficult to provide a denominator for the rate of scoliosis in this population. Scoliosis was described as severe in six, requiring surgery in at least three individuals. None had vertebral anomalies or myofibromas of the spine. Progressive hand
deformities, most likely related to progressive acro-osteolysis, were reported in 9 individuals although the reports do not mention appearance of the hands in early life. The hand differences were most severe in individuals who were described as having the “Penttinen” phenotype. Nine individuals had progressive loss of facial bones that led to midface retrusion. Another three had craniosynostosis, and one had microtia.

All of the individuals with severe skeletal findings also had osteopenia. Indeed, LR19-377a1 had multiple fractures at birth that were attributed to osteopenia, though other skeletal differences were not apparent at birth. While his myofibromas regressed on imatinib and no additional fractures were seen, his bone density did not appear to improve on x-rays. Other children with myofibromatosis have been reported to have osteopenia, though none have been reported with multiple fractures at birth. Patient LR17-436, who had clear acro-osteolysis and progressive midface retrusion, had a normal DEXA scan, suggesting that decreased bone density is not a consistent feature, and is unlikely to drive the mechanism for bone loss in the hands and maxillary arches of affected individuals.

**Skin.** Skin changes other than myofibromas were most often reported in individuals with severe and progressive disease, presenting as soft, hyperextensible and fragile skin with decreased subcutaneous fat and prominent vascular patterns in early childhood that became progressively thinner and more fragile over time. Other features included flesh colored papules, prominent scarring and poor wound healing that worsened with increasing age. Two individuals with
segmental mosaic mutations had skin abnormalities seen only over affected (often overgrown) areas (Karasozen et al., 2019; Zhong et al., 2018).

**Heart.** Echocardiogram or examination of the heart at autopsy demonstrated abnormalities in 11/13 individuals evaluated. The abnormalities including cardiac masses (n=6), hypertrophy (n=2), left ventricular dysfunction (n=1), and coronary aneurysm (n=4). Of note, patient LR19-453 had an echocardiogram at age 13 that showed a dysplastic mitral valve, particularly the posterior leaflet, which appeared to have thickened edges and a focal area of prolapse. This was not seen on prior echocardiogram at age 11, suggesting that cardiac abnormalities may develop over time.

**Diverse phenotypes in brain**

**Brain.** At least three individuals with severe phenotypes (including LR05-118) had rapid head growth in early infancy that led to diagnosis of hydrocephalus treated with ventriculo-peritoneal shunts and cerebellar hypoplasia with markedly enlarged posterior fossa size (CBLH-MCM), while others had recognition of CBLH-MCM with ventriculomegaly or hydrocephalus later in childhood (total N=10). The cerebellar malformations were sometimes described as Dandy-Walker malformation, but our review demonstrated consistent CBLH-MCM (Figures 3 and S2).

Across the entire cohort, brain imaging studies were abnormal in 31/33 individuals, and not done or at least not reported in the remaining 41 individuals. In addition to intracranial masses representing known or likely myofibromas (n=13) and aneurysms (n=4), abnormalities included
patchy or diffuse white matter signal changes consistent with a leukoencephalopathy (n=7), and atrophy (n=3).

Two previously reported patients with white matter disease had psychiatric symptoms including psychosis as a manifestation of neurologic disease. Individual LR19-377a7 had the abrupt onset of psychosis and dementia in his early 50’s. These are unlikely to occur in this age group in a previously healthy individual, making it likely that an organic process was the cause of his abrupt neurologic change. It is unknown whether this neurologic process was associated with his PDGFRB variant. Brain imaging in LR17-436 at 10.5 years showed cerebellar hypoplasia and mega-cisterna magna with normal white matter, while repeat imaging at 14 years showed new periventricular white matter signal changes similar to those described in other severely affected individuals. During the past several years, he has had problems with irritability, emotional lability and decrease in level of functioning. We suspect (but cannot prove) that his psychiatric changes are related to the progressive white matter abnormality.

**Phenotype-genotype analysis: PDGFRB-activating variant spectrum disorders**

While several features were observed across a wide spectrum of severity (i.e. myofibromas and vascular dysplasia with aneurysms), the cohort split relatively easily into two recognizable but still overlapping groups (Tables 2 and 3). Even our separation of the spectrum into less (PAVS1) and more (PAVS2) severe disorders is somewhat artificial, as all individuals with PDGFRB GOF mutations have increased risk for (1) vascular dysplasia with aneurysms, (2) myofibromas, and
(3) likely other features such as leukoencephalopathy. Although PAVS1 tends be less severe with myofibromas often resolving over time, morbidity and mortality are still increased.

PAVS1. The less severe group, which we designate PDGFRB activating spectrum disorder-1 or PAVS1 most often presents with multicentric myofibromas in infancy that often resolve, although most reports provide little or no long-term follow-up. These individuals were usually designated as having “infantile myofibromatosis” and had one of 5 different GOF variants (Tables 2 and 3) when molecular data was available. However, incomplete penetrance and highly variable expressivity within members of the same family have been seen in our multiplex family (LR19-377) and another reported family that include a few individuals with myofibromas recurring or at least first being noticed in adults (Murray et al., 2017). Although individuals with PAVS1 are largely spared the progressive skin and skeletal changes seen in those with more severe disease, they are at risk for serious and sometimes fatal complications beyond the myofibromas especially from vascular dysplasia and aneurysms (Brasseur et al., 2010; Wright et al. 2004). While reports of this are rare, two individuals in our multiplex family (LR19-377a4 and LR19-377a5) had sudden unexpected death in mid-adult life, while another (LR19-377a7) had sudden-onset and rapidly-progressive dementia and psychosis in his late 50’s that would be consistent with the leukoencephalopathy seen with more severe mutations. However, none of the three had an autopsy performed, so we cannot conclusively state that their deaths were related to PAVS1.
PAVS2. The second group, which we designate PDGFRB activating spectrum disorder or PAVS2 presented with complex and uniformly progressive multisystem disorders that consistently involved blood vessels, bone and connective tissue, skin and brain (Table 3). Several reports emphasized overgrowth or premature aging, but these individuals also had multisystem involvement with progression, similar to other individuals in this larger group. The first report described a “new progeroid disorder” that was later designated Penttinen syndrome (Penttinen 1997; Zufferey 2013). Based on reports of 5 individuals, the cardinal signs include progressive midface retrusion, acro-osteolysis, synechiae of the eyes (adhesions from iris to cornea or lens), and thin, fragile skin with loss of subcutaneous fat and prominent vessels. Whole exome sequencing in one family detected a p.Val665Ala variant that was subsequently found in another 4 individuals with a similar phenotype (Johnston 2015, Zhang 2018). Two other reports described a “novel overgrowth syndrome” later designated Kosaki overgrowth syndrome in three individuals with a recurrent p.Pro584Arg variant. The cardinal features consisted of overgrowth, flattened facial profile, irregularities of bone, progressive white matter disease or leukoencephalopathy, and cerebellar malformations with enlarged posterior fossa including Dandy-Walker malformation (Takenouchi 2015; Gawlinski 2018). Similar features were reported in three individuals with a p.Trp566Arg variant (Minatogawa 2017; Zarate 2019).

The common features in PAVS2 include progressive multi-system abnormalities that include overgrowth (often early overgrowth with subsequent growth deceleration), progressive vascular dysplasia that begins as tortuosity and evolves to fusiform (and less often saccular) aneurysms, progressive leukoencephalopathy, and unusual abnormalities of bone, skin and subcutaneous
tissues, brain and other tissues. Myofibromas have been described in 3 patients with PAVS2 in the literature and our present patient LR05-188, though it is not possible to determine whether additional patients developed myofibromas at a later age or in a location that was not detected without imaging. While we found a few features that may be specific to one or a few specific GOF variants, all reported individuals with severe GOF variants (Table 3) had obvious and progressive multi-system involvement that was similar across variants. The best supported single genotype-specific features include progressive midface retrusion and acro-osteolysis of the hands with p.Val665Ala, and persistent (rather than early childhood only) overgrowth with p.Pro584Arg. However, too few individuals have been described to define any mutation-specific features, particularly given the typically brief follow-up reported. In sum, our analysis does not support the continued use of different eponyms for putatively different points along the same phenotypic spectrum, which will only prove confusing to future generations of geneticists, much less other specialists. We favor abandoning these terms in favor of PAVS1 and PAVS2.

**Phentypic features in newborns**

Infants with PAVS1 will often have myofibromas at the time of birth, though some affected individuals will have no clinically evident myofibromas in infancy. Most infants with PAVS2 are relatively normal in appearance at birth, though cerebellar hypoplasia with mega cisterna magna can be visualized on imaging in some individuals. Imaging is typically triggered by abnormal neurologic features such as hypotonia. The remainder of the phenotypic features in PAVS1 and PAVS2 develop over time and are not evident in the neonatal period.
In vitro functional studies

In vitro studies suggest that the germline variants found in patients with PAVS1 are probably less activating than those associated with PAVS2. One study monitored activation of several downstream targets of the stimulated wild-type receptor that require PDGR as a co-activator, and found that Arg561Cys and Asn666Lys were activated even in the absence of PDGR. Further, they found that the germline Pro584Arg variant (PAVS2) elicited a stronger response than Arg561Cys (PAVS1). The same study found that all of the activated mutants (Arg561Cys, Asn666Lys and Pro584Arg) in their study were sensitive to tyrosine kinase inhibitors.

Comparison to activating variants in other receptor tyrosine kinases and effectors

The broad phenotypic spectrum combined with key features in common that we see with PDGFRB GOF mutations is not unique among receptor tyrosine kinases and other key components of major intracellular signaling pathways. In PIK3CA-related overgrowth spectrum (PROS), some patients have recognizable less (e.g. megalencephaly-capillary malformation syndrome, capillary malformation with overgrowth) or more (e.g. CLOVES, congenital infiltrating lipomatosis of the face, macrodactyly) severe phenotypes with shared underlying molecular pathophysiology and overlapping morbidities, and show promise using precision medicine for targeted therapy regardless of phenotypic category.

Similarly, almost all individuals with pathogenic variants in FGFR2 have major features that are shared, including high risk for multisuture craniosynostosis, multilevel airway obstruction and
midface retrusion. Some variants in \textit{FGFR2} have additional features that are found with only 1-2 genotypes that led to use of specific eponyms. For example, children with the p.Ser252Trp or p.Pro253Arg variants have polysyndactyly and synonychia, and are referred to historically as having “Apert syndrome”. Similarly individuals with p.Tyr375Cys or p.Ser372Cys variants have the additional clinical feature of cutis gyrata, and are described as having “Beare-Stevenson syndrome”. Other specific variants have been found in children who have received designations of Crouzon or Pfeiffer syndromes, with significant variability between family members often described. Though specific clinical features can help to narrow down the specific variant that will be detected, the \textit{FGFR2}-associated craniosynostosis syndrome share far more similarities than differences. Indeed, the most critical clinical features requiring management of children with \textit{FGFR2}-associated craniosynostosis syndromes are shared across all genotypes. Hence, we view the practice of describing these as separate diagnostic entities as a false distinction that serves to make classification systems more confusing than needed. Many affected children are extremely difficult to diagnose as infants if not born with craniosynostosis, even though most will develop multisuture craniosynostosis over time. The feature most often used to distinguish between Pfeiffer and Crouzon syndromes is whether thumb anomalies are present, a feature that has almost no clinical bearing on the overall clinical status of the child.

Thus, we have found analogous similarities and challenges in classification of the syndromes associated with the receptor tyrosine kinases \textit{FGFR2} and \textit{PDGFRB} and the immediately downstream effector \textit{PIK3CA}. Each of these genes is associated with a wide range of clinical phenotypes, which were first described as recognizable and distinct patterns of malformation...
before the molecular basis was discovered. Although some recurrent genotypes have unique features that can be recognized at diagnosis, all or almost all genotypes have shared risks for specific and often progressive medical conditions that are broadly shared. For each these paradigm-defining genes, the principles of monitoring and medical management (and recently targeted therapy for PIK3CA and PDGFRB) are shared across the described genotypes, showing us that the differences in phenotype are dwarfed by the commonalities.

**Targeted therapy with tyrosine kinase inhibitors**

*In vitro* assays of PDGFRB protein activity have demonstrated significant increased kinase activity with several pathogenic variants (i.e. p.Arg561Cys, p.Asn666Lys) compared to wild type. The overactivity can be partly corrected by tyrosine kinase inhibitors such as imatinib and sumatinib (Arts et al., 2016; Sramek et al., 2018), providing strong rationale for treatment trials. In one report, an infant with numerous myofibromas and a germline PDGFRB p.Arg561Cys mutation had a rapid and durable response to combined therapy with sumitinib and vinblastine, as did his affected older sister (Mudry et al., 2017). Another boy with overgrowth, atrophy and degeneration of multiple tissues associated with a germline PDGFRB p.Asn666His variant was treated with imatinib monotherapy, which improved his joint contractures, course facial features and midfoot circumference, and most importantly significant improvement in quality of life (Pond et al, 2018).
We report two unrelated infants (LR19-455 and LR19-377a1) with multicentric myofibromas who had robust clinical responses to imatinib monotherapy. Individual LR19-377a1 was taken off therapy after 3 months, and developed regrowth of his myofibromas, though much improved from the time he was started on therapy as his tongue base lesion did not regrow. Both children tolerated imatinib therapy well at a dose of 6 mg/kg/day, though LR19-455 had slowing of weight gain prompting fortification of formula. In both LR19-455 and LR19-377a1 the clinical response to medical therapy avoided major surgical intervention. LR19-377a1 would likely have required a tracheotomy and tongue base surgery to treat severe airway obstruction. LR19-455 would have required a major resection of the preauricular mass with significant morbidity and risk for disfigurement and cranial nerve VII injury. LR17-436 was recently started on imatinib monotherapy, and two months after initiation of therapy now has visible improvements in skin turgor, color, decreased visibility of veins, decreased prominence of hypertrophied areas of scarring, improved appearance of sclerae, and decreased contractures in hands with improved range of motion and functional improvement. Figures 1-2 demonstrates treatment responses to imatinib monotherapy after 3-4 weeks of treatment for these three individuals.

Our analysis provides strong support for a PDGFRB-activating variant spectrum of disease with differences in severity between different pathogenic variants and argues against continued use of different syndromic terms for different recurrent pathogenic variants. We acknowledge that some clinical features cluster with specific pathogenic variants, and that mosaicism can have a major impact on the phenotype. But all pathogenic GOF variants carry similar risks for morbidity.
(e.g. aneurysms, white matter disease) and precision medicine using imatinib may be beneficial regardless of the specific mutation.

**Surveillance and therapy**

Based on our experience and analysis of prior reports, we propose several recommendations for health management in individuals with GOF variants in PDGFRB. MR angiography should be performed at diagnosis and repeated intermittently. Given the very wide age range when vascular dysplasia is first identified (from 5 months to teen years so far), insufficient evidence exists to recommend a specific interval for repeat vascular imaging to screen for vascular dysplasia and aneurysms. Similarly, echocardiograms should be performed at diagnosis and repeated intermittently to detect myofibromas, aneurysms, structural and valvular disease. Brain MRI should be obtained at diagnosis to evaluate for structural abnormalities of the posterior fossa, intracranial myofibromas, and hydrocephalus, and should be repeated in adolescence and intermittently in adults to detect leukencephalopathy, particularly with any history of mood or behavior changes.

Our experience in 3 individuals and several prior reports of dramatic response to treatment with tyrosine kinase inhibitors (i.e. imatinib, sunitinib) in individuals with different pathogenic GOF variants also support a single spectrum of disease. One prior report showed that addition of a tyrosine kinase to a standard treatment regimen with vinblastine led to a more robust response
with multicentric myofibromas. Our experience suggests that imatinib monotherapy may be sufficient for treatment of multicentric myofibromas with minimal side effects.

Another report described a boy with an intermediate phenotype associated with a p.Asn666His variant who had significant improvement in skin quality and joint contractures after initiation of imatinib therapy (Pond et al., 2018). Our patients LR19-455 and LR19-377a1 are the first patients to our knowledge to be given first line treatment with imatinib monotherapy, and had a robust and rapid response. LR17-436 was also started on imatinib therapy and had dramatic improvements in skin color, turgor and scarring, improved contractures in both hands, and decreased eye pain within 8 weeks of initiating treatment. He has also had an improvement in mood, though it is difficult to determine whether this is a primary effect of treatment, secondary to the positive effect of the medication on other organ systems, or due to his newfound hope about the possibility of continued improvements with therapy.

Conclusions

Individuals with PDGFRB GOF variants in our present patients and those in the literature support a single spectrum of disease, with variation in phenotype resulting from (1) the GOF severity of the specific mutation, (2) constitutional vs. mosaic disease; and (3) occurrence of mosaic second hits affecting the risk of tumor development. The risk of aneurysms appears to be age-dependent and associated with more severe disease, but may also be a significant risk in families with less severe disease. Individuals with germline activating variants of PDGFRB
should receive ongoing medical screening, including baseline echocardiogram, brain MRI to evaluate for myofibromas, structural anomalies and white matter disease, and MRA of the brain, neck, chest, abdomen and pelvis to look for aneurysms and vascular ectasia. Single drug therapy with tyrosine kinase inhibitors should be considered for infants with multicentric myofibromas and for individuals with progressive disease. Future studies are needed to determine whether long-term treatment with tyrosine kinase inhibitors will affect the occurrence and progression of vessel ectasia, aneurysms and white matter disease associated with activating variants of PDGFRB.

ACKNOWLEDGMENTS

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Table 1. Phenotypic features of patients from present study with confirmed *PDGFRB* activating variants. Unless otherwise indicated, variants were detected in blood. Abbreviations: CBLH-MCM, cerebellar hypoplasia with megacisterna magna; PAVS1, *PDGFRB* Activating Variant Spectrum disorder 1; PAVS2, *PDGFRB* Activating Variant Spectrum 2

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at last evaluation</strong></td>
<td>10 months</td>
<td>35 years</td>
<td>6 months</td>
<td>26 years</td>
<td>8 years</td>
<td>13 years</td>
<td>14 years</td>
</tr>
<tr>
<td>Myofibromas - infancy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myofibromas - later childhood/adult</td>
<td>n/a</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aneurysms</td>
<td>-</td>
<td>n/a</td>
<td>+</td>
<td>n/a</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Vascular ectasia</td>
<td>-</td>
<td>n/a</td>
<td>-</td>
<td>+</td>
<td>n/a</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tall statures</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Skin thin and fragile</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Skin prominent vessels</td>
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<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Irregular skull contour</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Midface retrusion early</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acro-osteolysis hands</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CBLH-MCM</td>
<td>-</td>
<td>n/a</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* >90th %ile early in childhood, then slowed growth with ultimate height <10th %ile

**LR19-377a1 had two variants, p.Arg561Cys in germline, and p.Asn666Lys in tumor only.

***LR19-455 has 2 variants - p.I564_V572del and p.N666T. Though neither was found in the blood, it is hypothesized that p.I564_V572del is segmental mosaic and that p.N666T was predicted to be somatic in the myofibroma itself.
Table 2. Proposed nomenclature for PDGFRB-activating variant spectrum disorders

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Protein change</th>
<th>LOM</th>
<th>Prior syndrome</th>
<th>Genotype-specific features</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAVS1</td>
<td>p.Pro560Leu</td>
<td>con</td>
<td>Infantile myofibromatosis</td>
<td>Multiple myofibromas</td>
</tr>
<tr>
<td></td>
<td>p.Arg561Cys</td>
<td>con</td>
<td>”</td>
<td>”</td>
</tr>
<tr>
<td></td>
<td>p.Ile564_Val572del</td>
<td>con</td>
<td>”</td>
<td>”</td>
</tr>
<tr>
<td></td>
<td>p.Lys567Glu</td>
<td>con</td>
<td>”</td>
<td>”</td>
</tr>
<tr>
<td></td>
<td>p.Pro660Thr</td>
<td>con</td>
<td>”</td>
<td>”</td>
</tr>
<tr>
<td>PAVS2</td>
<td>p.Arg561_Tyr562delinsHis</td>
<td>none</td>
<td>none</td>
<td>Multiple fusiform aneurysms</td>
</tr>
<tr>
<td></td>
<td>p.Tyr562Cys</td>
<td>mos</td>
<td>none</td>
<td>Overgrowth especially height</td>
</tr>
<tr>
<td></td>
<td>p.Trp566Arg</td>
<td>con</td>
<td>Kosaki overgrowth synd</td>
<td>Overgrowth especially height</td>
</tr>
<tr>
<td></td>
<td>p.Val665Ala</td>
<td>con</td>
<td>Pentinen syndrome</td>
<td>Acro-osteolysis midface, hand</td>
</tr>
<tr>
<td></td>
<td>p.Asn666His</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>p.Asn666Ser</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

Abbreviations: con, constitutional; LOM, level (and location) of mutation – constitutional vs. segmental mosaic; mos, segmental mosaic; PAVS1/2, PDGFRB-activating variant spectrum disorder 1 or 2; synd, syndrome. Complete mutation p.Arg561_Tyr562delinsHis.
### Table 3. Phenotypic features in this series and previously reported patients with each PDGFRB activating variant spectrum group or subgroup by genotype

<table>
<thead>
<tr>
<th>Prior name</th>
<th>Amino acids</th>
<th>Amino acid substitutions</th>
<th>Myofibromas</th>
<th>New features after infancy</th>
<th>Vascular abnormalities</th>
<th>Vascular ectasia</th>
<th>Brain abnormalities</th>
<th>CBLH-MCM</th>
<th>Skin abnormalities</th>
<th>Skeletal abnormalities</th>
<th>Acro-osteolysis of hands</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAVS1</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAVS2 (other)</td>
<td>666</td>
<td>p.Asn666Ser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PAVS2 with</td>
<td>665, 666</td>
<td>p.Asn666Ser</td>
<td></td>
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<td></td>
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<tr>
<td>progressive</td>
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<tr>
<td>osteolysis</td>
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</table>

**Notes:** Dark grey shading indicates feature has been reported in the phenotypic category. Light grey with “suspected” designation indicates that the feature has been suspected but not confirmed based on individual LR19-377a7. The relative frequency of each feature could not be determined because all evolved over time, and the absence of a feature in published reports could be explained by: (1) the subject did not have that feature; (2) the subject had not developed the feature at the time of the report; or (3) surveillance imaging had not been performed to assess for the feature. Individuals with severe, progressive midface retrusion also had malocclusion. Abbreviations: IM, infantile myofibromatosis; PAVS1/2, PDGFRB-activating variant spectrum disorder 1 or 2.
Table S1. Phenotypic categories reported in patients with PDGFRB-associated disorders with constitutional, segmental and focal (lesion only) distribution of variant.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Constitutional</th>
<th>Mosaic</th>
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<tbody>
<tr>
<td></td>
<td>Constitution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Segmental</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesion only</td>
<td></td>
</tr>
<tr>
<td>Loss-of-function</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Idiopathic basal ganglia calcification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain-of-function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penttinen syndrome</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Intermediate phenotypes</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Kosaki overgrowth syndrome</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Infantile myofibromatosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Myopericytomatosis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Multifocal aneurysms with overgrowth, skin atrophy</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Isolated myofibromas</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Isolated myopericytomas</td>
<td></td>
<td>+</td>
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<tr>
<td>Isolated fusiform aneurysms</td>
<td></td>
<td>+</td>
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</tbody>
</table>

Notes: 1Constitutional defined as variant allele fraction of 40-50%, mosaic as variant allele fraction <40%; segmental implies that multiple tissues or regions were involved but not the entire body; 2Mosaicism predicted but often not confirmed.
FIGURE LEGENDS

Figure 1. Response to imatinib monotherapy in two patients with infantile myofibromatosis, Patient LR19-377a1 (a-h) and Patient LR19-455 (i-r). Photographs of the patient at birth (a-c) demonstrate numerous subcutaneous nodules on chest and back (a-b) as well as a large necrotic lesion at occiput (c). MRI showed large circular mass at base of tongue, at red arrow (d). After two months of imatinib therapy, the masses were barely visible on the trunk and back (e-f). After 30 days of therapy, the tongue mass was no longer palpable (h). Repeat imaging shows near-complete resolution of the tongue base mass (red arrow). Patient LR19-455. Had a large preauricular myofibroma at birth (i). At one month of age she had undergone surgical debridement but continued to have a large mass (j, k). After three weeks of pharmacologic therapy, the mass was no longer visible, though healing skin from the previous surgical debridement can be seen (l, m). Imaging of large facial myofibroma included fetal MRI (n), MRI at one month of age (o, p), and MRI three weeks after treatment with imatinib (q, r).

Figure 2. Patient LR17-436 pre-and post-treatment. a. Photographs at baseline (column 1), after four weeks of therapy with imatinib (face, back) and after eight weeks of therapy (hands, elbows, knees) in column 2. Column 3 contains photographs after 4 months of therapy. Note decreased visibility of veins in face, neck and back after only four weeks of therapy. Lesions on the palms resolved, and thickness and pigmentation of scars had improved. b. Photographs of LR17-436 as an infant and child. Note normal appearance of hands and face as an infant, with gradual progression of facial phenotype and acroosteolysis.
Figure 3. Brain imaging in four individuals with PDGFRB GOF spectrum disorder. Sequences shown include midline T1 sagittal images (first column), and T2 (or Flair in P) axial images at the level of the mid-cerebellum (second column), basal ganglia (third column) or mid-lateral ventricles (4th column). The horizontal white lines to the right of the lower brainstem (left column) mark the typical inferior limit of the vermis. A-D: Images at 3 months in a boy (LR19-377) with the recurrent p.Arg561Cys pathogenic variant demonstrate a mildly thin corpus callosum that is normal for age and a small arachnoid cyst in the left middle fossa. E-H: MRI at 6 months in a girl (LR05-118) with the recurrent p.Trp566Arg pathogenic variant show a large head with prominent occiput, thin and stretched corpus callosum, severe brainstem kink at the medulla-cervical cord junction, massively enlarged cisterna magna (**) and severe cerebellar vermis (v) and hemisphere (h) hypoplasia. I-L: MRI in infancy in a boy (LR19-453) with the same recurrent p.Trp566Arg pathogenic variant show less severe but otherwise the same abnormalities including thin and stretched corpus callosum, severely enlarged third and lateral ventricles with a shunt on the left, smaller kink at the medulla-cervical cord junction, moderately enlarged cisterna magna (**), moderate cerebellar vermis (v) hypoplasia, and moderate right more severe than left cerebellar hemisphere (h) hypoplasia. M-P: MRI at 14 years in a boy (LR17-436) with the recurrent p.Val665Ala pathogenic variant shows a striking mid-facial recursion, otherwise normal head contour and corpus callosum, moderately enlarged cisterna magna (**), moderate cerebellar vermis (v) hypoplasia, and left more severe than right cerebellar hemisphere (h) hypoplasia. Several hyperintense (bright) lesions are seen in the posterior periventricular white matter (arrows in P) as well. This boy was previously reported as patient 3 in Johnston et al 2015 (PMID 26279204). In the last three individuals (E-P), the vermis...
is seen in the normal position or rotated only slightly upward, so all three are classified as mega-cisterns magna with cerebellar hypoplasia rather than Dandy-Walker malformation.

Figure S1. Pedigree of family of LR19-377a1.

Figure S2. Brain imaging in four previously reported individuals with PDGFRB GOF spectrum disorder using the same sequences as in Figure M. A-D: MRI at 6 years in a boy (LR19-366) with a p.Arg561_Tyr562delins. He had hydrocephalus involving the third and lateral ventricles, thin brainstem, severe cerebellar vermis (v) and moderate cerebellar hemisphere (h) hypoplasia, and massively enlarged cisterna magna (**) associated with compression and severe volume loss of the posterior cerebral hemispheres and corpus callosum (Guimier 2019). E-H: MRI at 19 years in a girl (LR19-325) with the recurrent p.Trp566Arg pathogenic variant shows slit ventricles following a shunt for hydrocephalus, subtle periventricular white matter hyperintensity (white arrows in G, H), mild kink at the medulla-cervical spine junction, severe cerebellar vermis (v) and moderate right more severe than left hemisphere (h) hypoplasia, and massively enlarged cisterna magna (**) associated with severe volume loss of the posterior cerebral hemispheres and corpus callosum (Zarate 2019). In both of the prior individuals, the vermis is only slightly rotated upward, and thus classified as mega-cisterns magna with cerebellar hypoplasia rather than Dandy-Walker malformation. I-L: MRI at 17 years in a girl with the p.Pro584Arg pathogenic variant shows a very prominent brow, flattened corpus callosum, small frontal horns and enlarged posterior lateral ventricles, periventricular white matter hyperintensities that become nearly confluent in posterior regions (white arrow in L), and mild cerebellar vermis (v) and hemisphere hypoplasia (Minatogawa 2017). M-P: MRI at 29 years in a man with the recurrent p.Val665Ala pathogenic variant shows high and prominent forehead,
mildly enlarged lateral ventricles, bilateral cysts in the middle cranial fossa, mild cerebellar
vermis (v) and left hemisphere (h) hypoplasia, and mildly enlarged cisterna magna (**). These
images come from the original proband reported by Penttinen et al. (Penttinen 1997; Johnston
2015).
REFERENCES


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<th>Circle one: other adult relative</th>
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<td>Time</td>
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<td>Time</td>
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If your child is too young or intellectually impaired to comprehend an explanation of this study, please sign as his/her parents or legal guardian. By signing, you permit his/her participation in this study. The participant should also assent (sign) if he/she has a developmental age of 13-17 years. If anyone taking part in this research study is a foster child or a ward of the state, please tell the researcher.

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Use of Photographs Statement
I understand that facial photographs can identify my child. I will initial the lines below to indicate my wishes for how the photographs are used and how long they are stored.

☐ Researchers may use my child’s photos for research, publication, and presentation. I understand that this means that people outside of this research study will be able to see my child’s face and may be able to recognize him or her. A copy of the publication if my photograph is used will be made available to me.

OR

☐ Researchers can use my child’s photos for research only, but NOT in any publication or presentation.

11. Family’s contact information

Email: 
Phone: 
Address: 

12. Seattle Children’s researcher’s statement/signature

I have fully explained the research study described by this form. I have answered the family’s questions and will answer any future questions to the best of my ability. I will tell the family of any changes in the procedures or in the possible harms/possible benefits of the study that may affect their health or their willingness to stay in the study.

Jordan Zeiger
Printed Name of Researcher Obtaining Parental Permission

Signature of Researcher Obtaining Parental Permission

5/24/2019
Date

11:15
Time

13. Interpreter information (if applicable)

SANNA WANG
Printed Name of Interpreter

5/24/2019
Date
Use of Photographs Permissions

_____ Researchers may use my photos for publication and presentation without notifying me. This means that people outside the study will be able to see my photos, possibly including my face.

OR

_____ Researchers may use my photos for publication and presentation, however I would like to see the photos before they are shown to anyone else.

OR

_____ Researchers may not use my photos for any publication or presentation.

Publications Resulting from Research

_____ I want to receive the publications from research using the study bank.

OR

_____ I do not want to receive the resulting publications.

Genetic Information

_____ I want to know if something related to my health is found. (Important: We can only release some information, and only if it may affect decisions about your health care. This does not replace tests ordered by your own doctor.)

OR

_____ I do not want to know.

Participant Contact Information

Name:

Address:

Phone:

Email:
Use of Photographs Permissions

☑️ Researchers may use my photos for publication and presentation without notifying me. This means that people outside the study will be able to see my photos, possibly including my face.

OR

☐ I would like to see the photos before they are shown to anyone else.

OR

☐ Researchers may not use my photos for any publication or presentation.

Publications Resulting from Research

☑️ I want to receive the publications from research using the study bank.

OR

☐ I do not want to receive the resulting publications.

Genetic Information

☐ I want to know if something related to my health is found.

(Important: We can only release some information, and only if it may affect decisions about your health care. This does not replace tests ordered by your own doctor.)

OR

☐ I do not want to know.

Participant Contact Information

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Table 1. Phenotypic features of patients from present study with confirmed PDGFRB activating variants. Unless otherwise indicated, variants were detected in blood. Abbreviations: CBLH-MCM, cerebellar hypoplasia with megacisterna magna; PAVS1, PDGFRB Activating Variant Spectrum disorder 1; PAVS2, PDGFRB Activating Variant Spectrum 2

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* >90th %ile early in childhood, then slowed growth with ultimate height <10th %ile

**LR19-377a1 had two variants, p.Arg561Cys in germline, and p.Asn666Lys in tumor only.

***LR19-455 has 2 variants - p.I564_V572del and p.N666T. Though neither was found in the blood, it is hypothesized that p.I564_V572del is segmental mosaic and that p.N666T was predicted to be somatic in the myofibroma itself.
<table>
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<td>p.Lys567Glu</td>
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<td>p.Pro660Thr</td>
<td>con</td>
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Abbreviations: con, constitutional; LOM, level (and location) of mutation – constitutional vs. segmental mosaic; mos, segmental mosaic; PAVS1/2, PDGFB-activating variant spectrum disorder 1 or 2; synd, syndrome. 1Complete mutation p.Arg561_Tyr562delinsHis.
Table 3. Phenotypic features in this series and previously reported patients with each PDGFRB activating variant spectrum group or subgroup by genotype

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<th>Prior name</th>
<th>PAVS1</th>
<th>PAVS2 with consistent overgrowth</th>
<th>PAVS2 (other)</th>
<th>PAVS2 with progressive osteolysis</th>
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<td>584</td>
<td>562, 566, 567, 666</td>
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- **Myofibromas**
- **New features after infancy**
- **Vascular abnormalities**
  - **Aneurysms**
  - **Vascular ectasia**
- **Brain abnormalities**
  - **Leukoencephalopathy** suspected
  - **CBLH-MCM**
- **Skin abnormalities**
  - Thin, fragile
  - Prominent vessels
- **Skeletal abnormalities**
  - Tall stature >3SD
  - Scoliosis
  - Irregular skull contour
  - Midface retrusion early
  - Midface retrusion progressive*
  - Acro-osteolysis of hands

**Notes:** Dark grey shading indicates feature has been reported in the phenotypic category. Light grey with “suspected” designation indicates that the feature has been suspected but not confirmed based on individual LR19-377a7. The relative frequency of each feature could not be determined because all evolved over time, and the absence of a feature in published reports could be explained by: (1) the subject did not have that feature; (2) the subject had not developed the feature at the time of the report; or (3) surveillance imaging had not been performed to assess for the feature. Individuals with severe, progressive midface retrusion also had malocclusion. Abbreviations: IM, infantile myofibromatosis; PAVS1/2, PDGFRB-activating variant spectrum disorder 1 or 2.
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Author/s:
Wenger, TL; Bly, RA; Wu, N; Albert, CM; Park, J; Shieh, J; Chenbhanich, J; Heike, CL; Adam, MP; Chang, I; Sun, A; Miller, DE; Beck, AE; Gupta, D; Boos, MD; Zackai, EH; Everman, D; Ganapathi, S; Wilson, M; Christodoulou, J; Zarate, YA; Curry, C; Li, D; Guimier, A; Amiel, J; Hakonarson, H; Webster, R; Bhoj, EJ; Perkins, JA; Dahl, JP; Dobyns, WB

Title:
Activating variants in PDGFRB result in a spectrum of disorders responsive to imatinib monotherapy

Date:
2020-07

Citation:

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