Volume 3 | Number 1

# HHT FRONTLINES

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CLINICAL RESEARCH

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## PAZOPANIB MAY REDUCE BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Marie E. Faughnan, James R. Gossage, Murali M. Chakinala, S. Paul Oh, Raj Kasthuri, Christopher C. W. Hughes, Justin P. McWilliams, Joseph G. Parambil, Nicholas Vozoris, Jill Donaldson, Gitanjali Paul, Pamela Berry, Dennis L. Sprecher
*Angiogenesis. 2019 Feb; 22(1): 145-155*

The authors of this article describe the effect of pazopinib on bleeding in HHT.

*Pazopanib (Votrient) is an orally administered tyrosine kinase inhibitor that blocks VEGF receptors potentially serving as an anti-angiogenic treatment for Hereditary Hemorrhagic Telangiectasia (HHT). Findings from a prospective, multi-center, open-label, dose-escalating study [50 mg, 100 mg, 200 mg, and 400 mg], designed as a proof-of-concept study demonstrate efficacy of pazopanib on HHT-related bleeding, and to measure safety. Patients, recruited at 5 HHT Centers, required ≥ 2 Curacao criteria AND anemia OR severe epistaxis with iron deficiency. Co-primary outcomes, hemoglobin (Hgb) and epistaxis severity, were measured during and after treatment, and compared to baseline. Safety monitoring occurred every 1.5 weeks. Seven patients were treated with 50 mg pazopanib daily. Six/seven showed at least 50% decrease in epistaxis duration relative to baseline at some point during study; 3 showed at least 50% decrease in duration throughout Weeks 11 and 12. Six patients showed a decrease in ESS of > 0.71 (MID) relative to baseline at some point during study; 3/6 showed a sustained improvement. Four patients showed > 2 gm improvement in Hgb relative to baseline at one or more points during study. Health-related QOL scores improved on all SF-36 domains at Week 6 and/or Week 12, except general health (unchanged). There were 19 adverse events (AEs) including one severe AE (elevated LFTs, withdrawn from dosing at 43 days).*

Implications: Treatment with pazopanib may result in reduction of (severe) bleeding in HHT, with an improvement in Hb and/or epistaxis. The effect was achieved with a dose much lower than typically used for oncologic indications, with no serious adverse events. Further studies with pazopanib are warranted to evaluate efficacy.

## SAFETY OF THALIDOMIDE AND BEVACIZUMAB IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Elisabetta Buscarini , Luisa Maria Botella, Urban Geisthoff, Anette D. Kjeldsen, Hans-Jurgen Mager, Fabio Pagella, Patrizia Suppressa, Roberto Zarrabeitia, Sophie Dupuis-Girod, Claire L. Shovlin, on behalf of VASCERN-HHT
*Orphanet J Rare Dis 2019 Feb 4; 14(1):28. doi: 10.1186/s13023-018-0982-4*

The authors of this article describe the safety of treatment with thalidomide and bevacizumab in patients with HHT.

Hereditary Hemorrhagic Telangiectasia (HHT) is a multisystemic inherited vascular dysplasia that leads to nosebleeds and visceral arteriovenous malformations (AVMs). Anti-angiogenic drugs thalidomide and bevacizumab have been increasingly used off-label with variable results. The HHT working group within the European Reference Network (ERN) for Rare Multisystemic Vascular Diseases (VASCERN) developed a questionnaire-based retrospective capture of adverse events (AEs) classified using the Common Terminology Criteria for Adverse Events.

*Results: Sixty-nine HHT patients received bevacizumab, 37 (50.6%) for high output cardiac failure/hepatic AVMs and 32 (49.4%) for bleeding. The 69 patients received bevacizumab for a mean of 11 months for a total of 63.8 person/years treatment. Sixty-seven received thalidomide, all for epistaxis and/or gastrointestinal bleeding; they received thalidomide for a mean of 13.4 months/patient for a total of 75 person/years treatment. AEs were reported in 58 patients, 33 with bevacizumab, 37 with thalidomide. Thirty-two grade 1–3 AEs related to bevacizumab were reported with an average incidence rate of 50 per 100 person-years. Thirty-four grade 1–3 AEs related to thalidomide were reported with an average incidence rate of 45.3 per 100 person-years. Bevacizumab AEs were more common in females (27 AEs in 46 women) than males (6 in 23, $p < 0.001$). Thalidomide AEs occurred at more similar rates in males (25 AEs in 41 men, 60.9%) and females (12 in 26 (46.2%), but were more common in ENG patients (17 in 17) than in ACVRL1 (14 in 34, $p < 0.0001$). For bevacizumab, the most common reports were of joint pains (7/69, 10%), headache (3/69, 4.4%) and proteinuria (2/69, 3%). For thalidomide, peripheral neuropathy (12/67, 18%); drowsiness (8/67, 12%); and dizziness (6/67, 9%). Fatal adverse events were more common in males ($p = 0.009$), and in patients with ENG pathogenic variants ($p = 0.012$). One fatal AE was possibly related to bevacizumab (average incidence rate: 1.5 per 100 person-years); 3 fatal AEs were possibly related to thalidomide (average incidence rate: 4 per 100 person-years).*

Implications: With the increase in use of bevacizumab and thalidomide in HHT patients, more adverse events are reported. The available data supports appropriate weighing of the toxicities which can arise from these drugs in HHT settings.

## PULMONARY ARTERIAL HYPERTENSION AND HEREDITARY HEMORRHAGIC TELANGIECTASIA

Veronique M. M. Vorselaars, Anna E. Hosman, Cornelis J. J. Westermann, Repke J. Snijder, Johannes J. Mager, Marie-Jose Goumans, Marco C. Post
*Int. J. Mol. Sci. 2018, 19, 3203; doi: 10.3390/ijms19103203*

This article is a review on pulmonary hypertension in HHT.

*Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant inherited diseasecharacterised by multisystemic vascular dysplasia. Heritable Pulmonary Arterial Hypertension (HPAH) is a rare (0,5-1% in all HHT patients, 1-2% in HHT2) but severe complication of HHT. Both diseases can be the result of genetic mutations in ACVLR1 and ENG encoding for proteins involved in the transforming growth factor-beta (TGF-superfamily), a signalling pathway that is essential for angiogenesis. Changes within this pathway can lead to both the proliferative vasculopathy of HPAH and arteriovenous malformations seen in HHT. Clinical signs of the disease combination may not be specific but early diagnosis is important for appropriate treatment. This review describes the molecular mechanism and management of HPAHand HHT. This review discusses the combination of PAH and HHT particularly, but it is important to note that other types of PH, associated with HHT can occur by several different mechanisms. This often involves PH due to left sided heart disease or high output PH due to a left-to-right shunt in the presence of AVMs in the liver resulting in a hyperkinetic state. Increase in cardiac output leads to an elevation in mean PAP (estimated increase in mean PAP up to 0.5 to 3.0 mmHg per litre/min increase in cardiac output). Especially in HHT, anemia due to epistaxis and gastro-intestinal bleeding may trigger this cascade as a result of increased cardiac output. Precapillary PH may be the result of Chronic Thromboembolic Pulmonary Hypertension (CTEPH) since HHT patients may encounter an increased thrombotic risk. Furthermore, all other forms of PH, not related to HHT, could exist in HHT patients as well. The overall occurrence of echocardiographic-based suspected PH in unselected HHT patients is found between 4% and 20%. Right heart catheterization is indispensable in symptomatic cases since subclassification of PH is based on invasive measurement of hemodynamics. Any of the types of PH in combination with HHT can lead to a worse prognosis.*

Implications: The combination of HPAH and HHT is rare (0,5-1% in all HHT patients, 1-2% in HHT2) but may have severe consequences. Both diseases can be the result of mutations affecting the TGF-signalling pathway essential for angiogenesis. Clinical signs may not be specific but early diagnosis is important for appropriate treatment and prognosis. Therefore, awareness of this disease combination is important for all clinicians working with HHT or PAH patients.

## UPTAKE AND RADIOLOGICAL FINDINGS OF SCREENING CEREBRAL MAGNETIC RESONANCE SCANS IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Gavin Fatania, Clare Gilson, Alan Glover, Ali Alsafi, James E Jackson, Maneesh C Patel, Claire L. Shovlin
*Intractable & Rare Diseases Research 2018; 7(4): 236-244*

The authors of this article investigated how often abnormal findings occur when patients with HHT undergo an MRI of the brain to screen for cerebral arteriovenous malformations

*Hereditary Hemorrhagic Telangiectasia (HHT) results in arteriovenous malformations (AVMs), most commonly in the lungs, liver and brain. Discussion of cerebral vascular malformations is an important element of patient management. The study's objectives were to examine uptake and results of screening cerebral Magnetic Resonance (MR) scans, excluding symptomatic patients requiring neurological investigations. The remaining non-symptomatic individuals received formal pre-test counselling that differed according to family history. For the 603 patients with no neurological symptoms of concern, screening scan uptake was higher after publication of the ARUBA trial. Patients with a family history of cerebral hemorrhage were 4 to 14-fold more likely to have a screening scan than patients with no such family history. For patients without neurological symptoms suggesting cerebral AVMs, none of the 59 screening scans performed at our institution demonstrated a cerebral AVM. Four scans (6.8%) demonstrated small aneurysms. The most common abnormality was cerebral infarction (20/59, 33.9%), predominantly identified in patients with pulmonary AVMs. Of 29 pulmonary AVM patients with no previous history of clinical stroke, 16 (55.2%) had between 1 and 5 silent infarcts. For HHT patients with pulmonary AVMs, the most frequently affected sites were the cerebellum (40%) and thalamus (14.3%), and the age-adjusted odds ratio for an infarct was 21.6 (95% confidence intervals 3.7, 126), p = 0.001.*

Implications: The authors conclude that for cerebral screening programs in HHT, the findings support informed patient choice, incorporating understanding that cerebral AVMs are rare in non-symptomatic HHT patients, but that screening scans commonly detect silent cerebral infarction due to pulmonary AVMs.

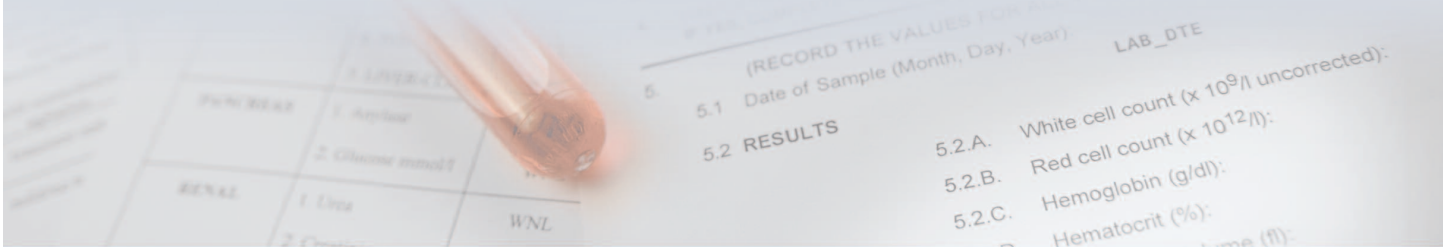
## RECURRENCE OF HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT) AFTER LIVER TRANSPLANTATION: CLINICAL IMPLICATIONS AND PHYSIOPATHOLOGICAL INSIGHTS

Jérôme Dumortier, Sophie Dupuis-Girod, Pierre-Jean Valette, Alexander Valent, Olivier Guillaud, Jean-Christophe Saurin, Valérie Hervieu, Philip Robinson, Henri Plauchu, Pierre Paliard, Olivier Boillot, Jean-Yves Scoazec
*Hepatology. 2018 Dec 14; doi: 10.1002/hep.30424*

The authors of this article describe the results of liver transplantation in HHT patients.

*Liver Transplantation (LT) has been proposed as a curative treatment in Hereditary Hemorrhagic Telangiectasia (HHT) with severe hepatic involvement. We provide a long-term evaluation of graft status after LT for HHT, with a focus on the risk of recurrence. The present study included all patients prospectively followed-up after LT for HHT in the Lyon liver transplant unit from 1993 to 2010 with a survival of more than 1 year. Protocol clinical, radiological, and histological examinations were performed at regular intervals. Fourteen patients were included (13 women and 1 man). Median age at LT was 52.5 years (range [33.1-66.7]). In 8 patients (7 female), disease recurrence was diagnosed by abnormal radiological features, suggestive of microcirculatory disturbances. Typical vascular lesions, including telangiectasia, were demonstrated by liver biopsy in 5 of these patients. The median interval between LT and diagnosis of recurrence was 127 months (range [74-184]). The risk of recurrence increased over time; estimated cumulative risk was 47.9% at 15 years. Liver tissue analysis found the coexistence of an angiogenic process combined with endothelial microchimerism, as shown by the presence of vascular lining cells of recipient origin.*

Implications: The data shows that HHT recurrence occurs usually after a long delay in a significant number of patients treated by LT for liver complications of HHT. This strongly supports the necessity of life-long follow-up and suggests that therapeutic strategy needs discussion and evaluation, especially regarding the role of potential adjuvant treatments to LT (such as anti-angiogenic medications) when recurrent disease appears.



## LIVER TRANSPLANTATION TRENDS AND OUTCOMES FOR HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT) IN THE UNITED STATES

Vivek N. Iyer, Behnam Saberi, Julie K. Heimbach, Joseph J. Larson, Suresh Raghavaiah, Ivo Ditah, Karen Swanson, Patrick S. Kamath, KD Watt, Timucin Taner, Michael J. Krowka, Michael D. Leise
*Transplantation 2018 Oct 16; doi: 10.1097*

The authors of this article describe the outcomes of liver transplantation for HHT patients in the USA.

*Liver arteriovenous malformations (AVM) in Hereditary Hemorrhagic Telangiectasia (HHT) can necessitate liver transplantation. Currently, there is limited data on HHT patients undergoing LT in the United States. Two sources of available data were utilized: (1) Scientific Registry of Transplant Recipients (SRTR) database (1998-2016) and (2) the Single Center Liver transplant Database (Mayo Clinic Rochester, MN). The aims of this study were (1) to determine trends in LT for HHT related liver involvement in the US using the SRTR database and (2) To identify clinical characteristics, indications, and outcomes for LT in HHT.*

*Thirty-nine HHT patients were listed for LTs in the SRTR database from 1998-2016 – 1998-2001 (n=1); 2002-2005 (n=4); 2006-2010 (n=10) and 2011-2016 (n=24). Twenty-four underwent LT at a median age of 47.5 (IQR 37.0, 58.5). Median calculated MELD score at time of LT was 8.0 (IQR 7.0, 9.5) and 75% received an exception MELD score. Two status 1 patients died during transplant surgery. Nineteen (86%) patients were alive after a median post-LT follow-up of 48 months while 2 patients were lost to follow-up. Five of the aforementioned HHT patients underwent LT at Mayo Clinic, 4 with HOCF and 1 with biliary ischemia. All 5 were alive at the time of last follow-up with good graft function and resolution of heart failure.*

Implications: Outcomes following liver transplantation for HHT patients are excellent with 86% survival after a median follow-up of 48 months and resolution of heart failure. Liver transplantation listing for HHT has increased substantially in more recent times.

## CEREBRAL CAVERNOUS MALFORMATIONS DEVELOP THROUGH CLONAL EXPANSIONS OF MUTANT ENDOTHELIAL CELLS

Matthew R. Detter, Daniel A. Snellings, and Douglas A. Marchuk
*Circulation Research 2018 Oct 26, 123 (10): 1143-1151, doi:10.1161/CIRCRESAHA.118313970*

*Methods and Results: A Ccm3 mouse model with the confetti fluorescent reporter simultaneously deleted Ccm3 and labeled the mutant EC with 1 of 4 possible colors. Z-series confocal images were acquired from serial brain sections and created 3-dimensional reconstructions of entire CCMs to visualize mutant ECs during CCM development. Observations showed a pronounced pattern of CCMs lined with mutant ECs labelled with a single confetti color (n=42). The close 3-dimensional distribution, as determined by the nearest neighbor analysis, of the clonally dominant ECs within the CCM was statistically different than the background confetti labelling of ECs in non-CCM control brain slices as well as computer simulation (P<0.001). Many of the small (<100μm diameter) CCMs consisted, almost exclusively, of the clonally dominant mutant ECs labelled with the same confetti color, whereas the large (>100 μm diameter) CCM contained both of the clonally dominant mutant cells and wild-types ECs. The model of CCM develop in which an EC acquires a second somatic mutation, undergoes clonal expansion to initiate CCM formation, and then incorporates neighboring wild-types ECs to increase the size of the malformation.*

*Conclusions: This is the first study to visualize, with single-cell resolution, the clonal expansion of mutant ECs within CCMs. The incorporation of wild-type ECs into the growing malformation presents another series of cellular events whose elucidation would enhance our understanding of CCMs and may provide novel therapeutic opportunities.*

*Implications: This is the first study that demonstrated clonal expansion of mutant ECs that acquired second mutation in CCM lesions. Although, acquisition of second mutations and clonal expansion of mutant ECs have not been experimentally demonstrated in AVM lesions in HHT patients it would be of interest to examine this in the future.*

## SYSTEMATIC PHARMACOLOGICAL SCREENS UNCOVER NOVEL PATHWAYS INVOLVED IN CEREBRAL CAVERNOUS MALFORMATIONS

Cécile Otten, Jessica Knox, Gwénola Boulday, Mathias Eymery, Marta Haniszewski, Martin Neuenschwander, Silke Radetzki, Ingo Vogt, Kristina Hähn, Coralie De Luca, Cécile Cardoso, Sabri Hamad, Carla Igual Gil, Peter Roy, Corinne Albiges-Rizo, Eva Faurroberrt, Jens P von Kries, Mónica Campillos, Elisabeth Tournier-Lasserve, W Brent Derry, and Salim Abdelilah-Seyfried.
*EMBO Molecular Medicine, 2018 Oct; 10 (10): e9155, doi: 10.15252/emmm.201809155.*

*Cerebral cavernous malformations (CCMs) are vascular lesions in the central nervous system causing strokes and seizures which currently can only be treated through neurosurgery. The disease arises through changes in the regulatory networks of endothelial cells that must be comprehensively understood to develop alternative, non-invasive pharmacological therapies. The results of small-molecule suppression screens of 5,268 unique substances applied to CCM mutant worm, zebrafish, mouse, or human endothelial cells are presented in this study. A systems biology-based target prediction tool integrated the results with the whole-transcriptome profile of zebrafish CCM2 mutants, revealing signaling pathways relevant to the disease and potential targets for small-molecule-based therapies. Indirubin-3-monoxime alleviated the lesion burden in murine preclinical models of CCM2 and CCM3 and suppressed the loss-of-CCM phenotypes in human endothelial cells. A multi-organism-based approach revealed new components of the CCM regulatory network and for future novel small-molecule-based therapeutic applications.*

Implications: The authors carried out a screen for repurposing drugs that assayed 5,268 small-molecules from several compound collections and combined these with systems biology approaches for target prediction and overlapping signaling pathways. Similar approaches might be useful for the identification of novel drug targeting strategies in HHT.

## SOLUBLE ENDOGLIN REGULATES EXPRESSION OF ANGIOGENESIS-RELATED PROTEINS AND INDUCTION OF ARTERIOVENOUS MALFORMATIONS IN A MOUSE MODEL OF HEREDITARY HEMORRHAGIC TELANGIECTASIA.

Eunate Gallardo-Vara, Simon Tual-Chalot, Luisa M. Botella, Helen M. Arthur, and Carmelo Bernabeu.
*Disease Models & Mechanisms, 2018 Sept 1; 11 (9), doi: 10.1242/dmm.034397*

*Using a neonatal retinal mouse model of HHT1 with depleted endoglin in the vascular endothelium, sEng treatment shown to decrease the number of AVMs and have a normalizing effect on the vascular phenotype with respect to vessel branching, density and migration of the vascular plexus towards the retinal periphery. Data shows that circulating sEng can influence vascular development and AVMs by modulating angiogenesis, and that its effect on endothelial cells depends on the expression of endogenous endoglin. Using human and mouse endothelial cells, sEng downregulated several pro-angiogenic and pro-migratory proteins involved in angiogenesis. However, this effect is much reduced in endothelial cells that lack endogenous transmembrane endoglin, suggesting that the antiangiogenic activity of sEng is dependent on the presence of endogenous transmembrane endoglin protein. In fact, sEng partially restores the phenotype of endoglin-silenced endothelial cells to that of normal endothelial cells.*

Implications: The authors, for the first time, demonstrated context-dependent role of sEng in regulating angiogenesis and vascular pathogenesis. In contrast to previous studies with normal membrane bound Eng expression, in the absence of membrane bound Eng, sEng can rescue angiogenic defects in HHT1 and reduce the number of AVMs. Additional studies would be required to examine whether sEng could be used in the future as a therapeutic drug for the resolution of AVMs in HHT1 patients.

## SMAD4 PREVENTS FLOW INDUCED ARTERIOVENOUS MALFORMATIONS BY INHIBITING CASEIN KINASE

Roxana Ola, Sandrine H. Künzel, Feng Zhang, Gael Genet, Raja Chakraborty, Laurence Pubouin-Fragner, Kathleen Martin, William Sessa, Alexandre Dubrac, and Anne Eichmann.
*Circulation 2018 Nov 20, 138 (21): 2379-2394, doi: 10.1161/CIRCULATIONAHA.118.033842*

*Objectives: This study addressed whether SMAD4 was required for AVM formation and regulation of PI3K activity.*

*Methods: A tamoxifen-inducible, postnatal, endothelial-specific Smad4 mutant mice model was generated.*

*Results : Findings show a loss of endothelial Smad4 resulted in AVM formation and lethality. AVMs formed in regions with high blood flow in developing retinas and other tissues. Mechanistically, BMP9 signaling antagonized flow-induced AKT activation in an ALK1- and SMAD4-dependent manner. Smad4iΔEC endothelial cells in AVMs displayed increased PI3K/AKT signaling, and pharmacological PI3K inhibitors or endothelial Akt1 deletion both rescued AVM formation in Smad4iΔEC mice. BMP9-induced SMAD4 inhibited casein kinase 2 (CK2) transcription, in turn limiting PTEN phosphorylation and AKT activation. Consequently, CK2 inhibition prevented AVM formation in Smad4iΔEC mice.*

*Conclusions: Study revealed SMAD4 as an essential effector of BMP9-10/ALK1 signaling that affects AVM pathogenesis via regulation of CK2 expression and PI3K/AKT1 activation in a mouse (retinal) model.*

Implications: The authors showed that SMAD4 acts as a repressor of CK2, and therapeutic targeting of CK2 using available inhibitors might potentially be a new approach to prevent AVM formation in JP-HHT patients.

## DECREASED EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 1 CONTRIBUTES THE PATHOGENESIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA TYPE 2

Takako Saito, Marcel Bokhove, Romina Croci, Sara Zamora-Caballero, Ling Han, Michelle Letarte, Daniele de Sanctis, and Luca Jovine
*Circulation 2018 Dec 4, 138 (23): 2698-2712, doi: 10.1161/CIRCULATIONAHA.117.033062.*

Study examined HHT2 vascular lesions in the neonatal mouse retina and the airway system after Mycoplasma pulmonis infection

*Methods: Acvrl1+/- mouse embryonic stem cells lines were created in vitro and underwent sprouting angiogenesis and genetic complementation experiments were performed.*

*Results: Acvrl1+/- retinas at postnatal day 7 showed excessive angiogenesis and numerous endothelial "tip cells" at the vascular front that displayed migratory defects. Vascular endothelial growth factor receptor 1 (VEGFR1; Flt-1) levels were reduced in Acvrl1+/- mice and HHT2 patients.*

*Conclusions: Findings demonstrate a key role of VEGFR1 in HHT2 pathogenesis and provide mechanisms explaining why HHT2 blood vessels respond abnormally to angiogenic signals. This supports the case for using anti-VEGF therapy in HHT2.*

Implications: In this study the authors identified association between ALK1 signaling and VEGFR1. Strikingly, HHT2 patients showed decreased VEGFR1 levels in plasma and arterial skin vessels, that promotes elevated VEGF-VEGFR2 signaling. The authors further suggest that HHT2 patients with elevated VEGFR1 expression might be less sensitive anti-VEGF therapies, although this requires additional testing of this hypothesis.

## HIGH PREVALENCE OF KRAS/BRAF SOMATIC MUTATIONS IN BRAIN AND SPINAL CORD ARTERIOVENOUS MALFORMATIONS

Tao Hong, Yupeng Yan, Jingwei Lin, Ivan Radovanovic, Xiangyuan Ma, Yang W. Shao, Jiaxying Yu, Yongjie Ma, Peng Zhang, Feng Ling, Schuchen Huang, Hongqi Zhang, and Yibo Wang
*Brain 2019 Jan, 142 (1): 23-34, doi: 10.1093/brain/awy307*

*Methods: In a cohort of 31 patients (21 with brain and 10 with spinal arteriovenous malformations), tissues and paired blood samples were analyzed with ultradeep next generation sequencing of a panel of 422 common tumor genes to identify somatic mutations. Droplet digital polymerase chain reactions confirmed panel sequenced mutations and identified the additional low variant frequency mutations.*

*Results: High prevalence (87.1%) of KRAS/BRAF somatic mutations were found in brain and spinal arteriovenous malformations with no other replicated tumor-related mutations. The prevalence of KRAS/BRAF mutations was 81.0% (17 of 21) in brain and 100% (10 of 10) in spinal arteriovenous malformations. Detection indicated BRAF mutations and two novel mutations in KRAS (p.G12A and p.S65_A66insDS) in CNS arteriovenous malformations for the first time. The mutation variant frequencies were negatively correlated with nidus volumes of brain (P= 0.038) and spinal (P=0.028) arteriovenous malformations but not ages.*

*Conclusions: Findings support a causative role of somatic tumor-related mutations of KRAS/BRAF in the overwhelming majority of brain and spinal arteriovenous malformations. This pathway homogeneity and high prevalence implies the development of targeted therapies with RAS/RAF pathway inhibitors without the necessity of tissue genetic diagnosis.*

Implications: In this study the authors identified high prevalence of somatic KRAS/BRAF in sporadic brain and spinal cord AVMs. Although, this has not been demonstrated in HHT patients, it would be interesting to investigate whether KRAS/BRAF mutation can be potentially occur as a second hit in AVM lesions in HHT patients.

## ALK1 SIGNALING IN DEVELOPMENT AND DISEASE: NEW PARADIGMS

Beth L. Roman and Andrew P. Hinck
*Cellular and Molecular Life Sciences, 2017 Dec, 74(24), 4539-4560, doi: 10.1007/s00018-017-2636-4*

*Activin A receptor like type 1 (ALK1) is a transmembrane serine/threonine receptor kinase in the transforming growth factor-beta receptor family that is expressed on endothelial cells. Defects in ALK1 signaling cause the autosomal dominant vascular disorder, hereditary hemorrhagic telangiectasia (HHT), which is characterized by development of direct connections between arteries and veins, or arteriovenous malformations (AVMs). Although previous studies have implicated ALK1 in various aspects of sprouting angiogenesis, including tip/stalk cell selection, migration, and proliferation, recent work suggests an intriguing role for ALK1 in transducing a flow-based signal that governs directed endothelial cell migration within patent, perfused vessels. This review presents an updated view of the mechanism of ALK1 signaling, put forth a unified hypothesis to explain the cellular missteps that lead to arteriovenous malformations (AVMs) associated with ALK1 deficiency, and discusses emerging roles for ALK1 signaling in disease beyond hereditary hemorrhagic telangiectasia (HHT).*

Implications: In this review the authors focus on ALK1 function, and outline that ALK1 and ENG might have independent functions outside of their interaction in vascular development and AVM prevention. As such, new approaches to HHT therapeutics should be stratified based on underlying genetics and must consider functions of ALK1 and endoglin beyond HHT.