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A 37-Year-Old Man with Familial Hereditary Hemorrhagic Telangiectasia and Pulmonary Arteriovenous Malformations Presenting with Seizures and a Diagnosis of Brain Abscesses

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 37-year-old
Final Diagnosis: Brain abscesses • hereditary haemorrhagic telangiectasia • pulmonary arteriovenous malformations
Symptoms: Tonic-clonic seizures
Clinical Procedure: Embolization
Specialty: General and Internal Medicine

Objective: Rare disease

Background: Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant genetic disease associated with arteriovenous malformations involving diverse organs. Neurological complications from brain abscesses (BA) secondary to pulmonary arteriovenous malformations (PAVMs) is a serious and recognized, albeit infrequent, medical problem. We report the case of a 37-year-old man with familial HHT and PAVMs who presented with seizures as a manifestation of BA.

Case Report: A 37-year-old man was admitted for first tonic-clonic seizures. He had a history of recurrent epistaxis and recurrent gastrointestinal bleeds treated with fulguration and oral iron therapy. A diagnosis of HHT was made because the patient met 3 of 4 Curaçao criteria. Physical examination revealed hypoxemia without dyspnea. A chest X-ray detected nodular pulmonary lesions in both lower lobes. Cranial computed tomography (CT) revealed 3 space-occupying lesions. Antiepileptics and dexamethasone were started. Cranial magnetic resonance and positron emission tomography suggested that lesions were BA. Thoracoabdominal CT with contrast revealed several bilateral PAVMs. Blood cultures were repeatedly negative. With the presumptive diagnosis of septic-embolic BA, empirical antibiotic therapy was started for 8 weeks. Neurological symptoms resolved and malformations >2 cm were selectively embolized. A genetic study revealed exon5 mutations in the ENG gene.

Conclusions: This report highlights the association between PAVMs in a patient with HHT and development of BA. Clinicians should be aware of this association so that diagnosis and treatment can be provided as fast as possible to ensure the best outcome for the patient. Embolization was performed as preventive treatment, and a genetic study was conducted as it is potentially useful for primary prevention in the patient's offspring.

Keywords: Arteriovenous Malformations • Embolization, Therapeutic • Telangiectasia, Hereditary Hemorrhagic • Brain Abscess • Seizures • ENG Protein, Human

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Background

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal genetic disease associated with multiple arteriovenous malformations [1]. There is a recognized association between pulmonary arteriovenous malformations (PAVMs) and the development of brain abscesses (BA) [2]. PAVMs are associated with HHT [3,4] and neurological complications from BA are a serious medical problem and can potentially recur if untreated. We report the case of a 37-year-old man with familial HHT and PAVMs who presented with seizures and diagnosis of BA.

Case Report

A 37-year-old non-smoking man was admitted in a post-critical state for tonic-clonic seizures preceded by peri-oral paraesthesia. He had a history of thalassaemia minor, recurrent epistaxis, and microcytic anaemia secondary to recurrent gastrointestinal bleeds due to angiectasias, treated with fulguration and oral iron therapy. Originally from Argentina, his mother also had a history of thalassaemia minor, as well as clinically diagnosed HHT with epistaxis and cutaneous and gastrointestinal telangiectasias. A diagnosis of HHT was made because the patient met 3 of 4 Curaçao criteria [5]. The patient explained that it was his first seizure episode. He reported no toxic syndrome, fever, dyspnea, or other clinical problems. On physical examination, the patient had finger and toe clubbing, did not have cyanosis, and did have central right facial palsy. An arterial blood gas test indicated partial pressure of oxygen (PaO2) 63.8 mmHg (oxygen saturation [SatO2] 93.4%).

A chest X-ray performed in the Emergency Department detected nodular pulmonary lesions in both lower lobes. Cranial computed tomography (CT) revealed 3 space-occupying lesions, 2 in the frontal lobes and 1 in the right parietal lobe. Treatment was started with levetiracetam and dexamethasone and the patient was admitted to Internal Medicine.

Differential diagnosis of the lesions included malignancies and infectious causes. Blood, urine, and cerebrospinal cultures and serology tests for HIV, syphilis, cysticercoids, and mycobacteria were all negative.

Cranial magnetic resonance (CMR) and positron emission tomography (PET) (**Figure 1**) suggested BA at a different area in both frontal lobes and in the right parietal lobe. A PET extension study ruled out extracranial acute inflammation. Thoracoabdominal CT with contrast revealed several bilateral pulmonary arteriovenous malformations (PAVMs) in the right upper lobe apical segment, right lower lobe, and left lower lobe (diameters 25 mm, 30 mm, and 26 mm, respectively). Transoesophageal echocardiography with physiological saline revealed delayed right-to-left passage of bubbles and no signs of endocarditis.

These results suggested a diagnosis of septic-embolic brain lesions due to PAVMs and HHT. Empirical antibiotic therapy was started with ceftriaxone and metronidazole for 8 weeks, in the absence of evidence of infection in the collected cultures. Neurological symptoms resolved and, in the control cerebral CT, the lesions had disappeared. After malformations >2 cm were selectively embolized (right upper lobe apical segment and left lower lobe AVMs) (**Figure 2**), the chronic hypoxemia (PaO2 87 mmHg) also normalized.

Three months after discharge, CT confirmed the absence of any brain radiological sequelae. A genetic study revealed exon5 mutations in the ENG gene that would explain the findings for this patient.

Discussion

HHT, also known as Rendu-Osler-Weber disease, is an inherited (autosomal dominant) vascular dysplasia with prevalence of 1 in 5000-8000 [6,7]. It is characterized by recurrent epistaxis, muco-cutaneous telangiectasia, gastrointestinal bleeding, and multiple arteriovenous circulatory malformations in the lung, brain, and liver [3,4]. Today, diagnosis of HHT is established on the basis of the Curaçao criteria [5].

PAVMs are abnormal communications between the pulmonary arteries and pulmonary veins, mostly congenital and associated with HHT in approximately 70% of cases [8]. PAVM frequency in HHT is reported to be 5-15% [3,4] and provide a right-to-left shunt between the pulmonary arterial and venous circulation. PAVMs may remain asymptomatic or manifest with hypoxaemia, hemoptysis, hemothorax, and/or neurologic symptoms. BA and ischemic strokes are serious PAVM complications [1,2], with incidence reported to be 5-6% in large series [8]. A careful review of a cohort in London with PAVMs, found that 79.5% of patients were diagnosed by chance or in the context of screening programs of PAVMs in families with HHT, and only 21.5% of individuals were diagnosed because of respiratory manifestations [9]. Our patient never had dyspnea even though he regularly participated in sports. His first symptoms appeared in the third decade of life, similar to what has been reported in diverse series [9,10]. He had recurrent epistaxis and gastrointestinal lesions but had not yet been diagnosed with HHT. Shovlin et al reported that only 39.3% of HHT cases are diagnosed prior to a first neurological event. The abscesses tend to occur in the third to fifth decade of life and are associated with high mortality [11]. The current treatment of choice is transcatheter embolization with coils or detachable balloons [9,12-15]. Embolization can be used to treat PAVMs if the condition is recognized, but no

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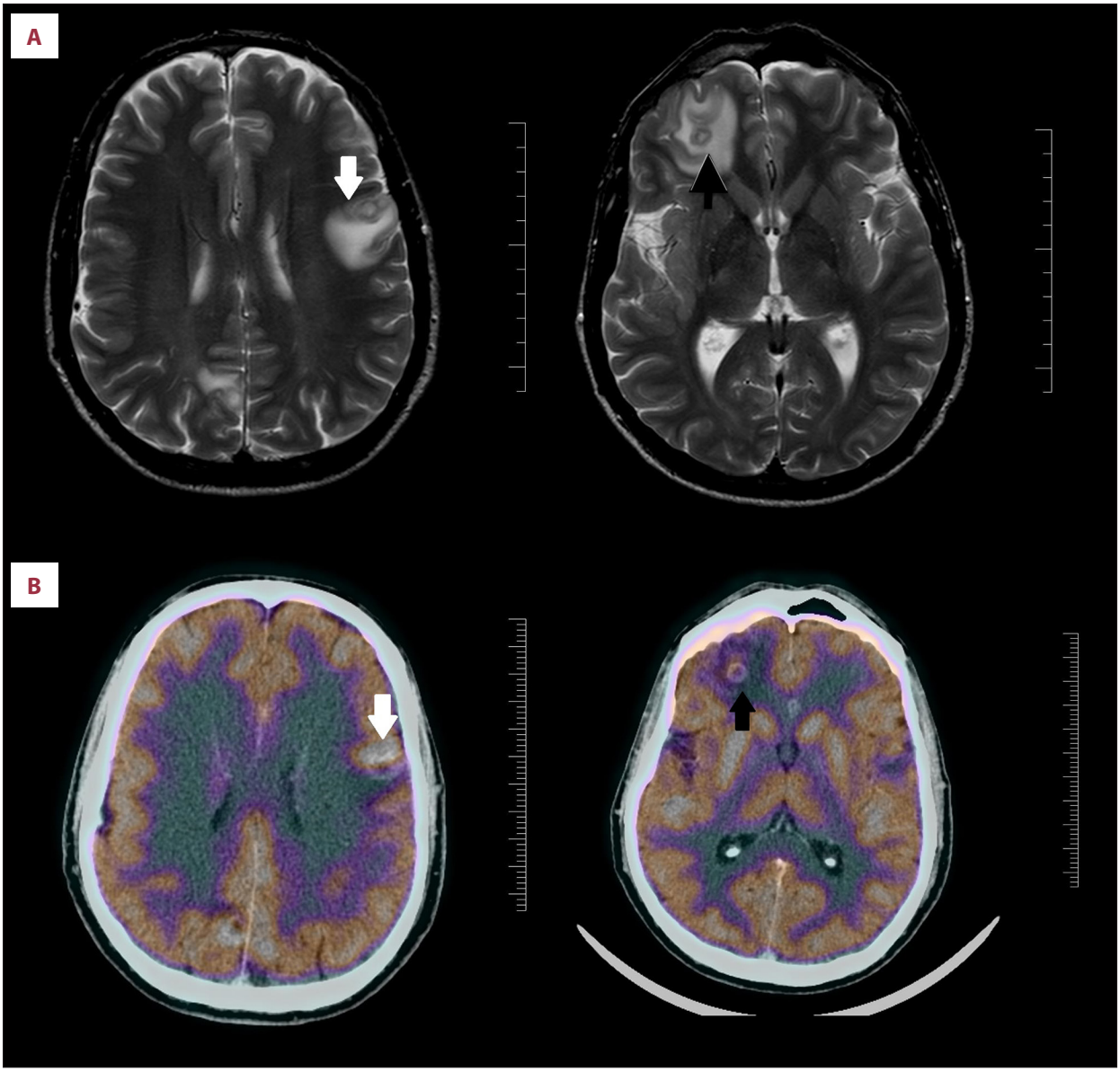

Figure 1. Cranial images showing space-occupying lesions suggestive of brain abscesses. (**A**) Cranial magnetic resonance imaging of the brain showing increased signal in T2-weighted of the right parietal lobe (white arrow) and left frontal lobe (black arrow). (**B**) Positron emission tomography imaging showed increased signal at the same locations: in right parietal lobe (white arrow) and left frontal lobe (black arrow).

direct evidence for reduction of BA or stroke incidence has been reported [9]. As ischemic stroke and brain abscesses are attributed to paradoxical embolic events through PAVM right-to-left shunts, this offers the opportunity to explore potentially relevant mechanisms related to other more common conditions, such as patent foramen ovale [16]. Therefore, it is advisable to perform appropriate examinations to rule out these options.

Diverse microbiological cultures were negative in our case, similar to the 2 HHT patients with PAVMs and BA described by Larsen et al [17]. The literature shows that about 30% of all cultures are negative when a diagnosis of BA is made [2,18] and that HHT patients often have >1 bacterial isolate compared to non-HHT patients [19].

This report documents a rare case of possible embolic BA in the presence of PAVMs in a patient with HHT. BA secondary to PAVMs is a serious medical problem and can recur if untreated. Early detection and prevention of secondary neurological episodes could help increase life expectancy and quality of life in patients with HHT. We selectively embolized the largest malformations to reduce the possible recurrence of neurological

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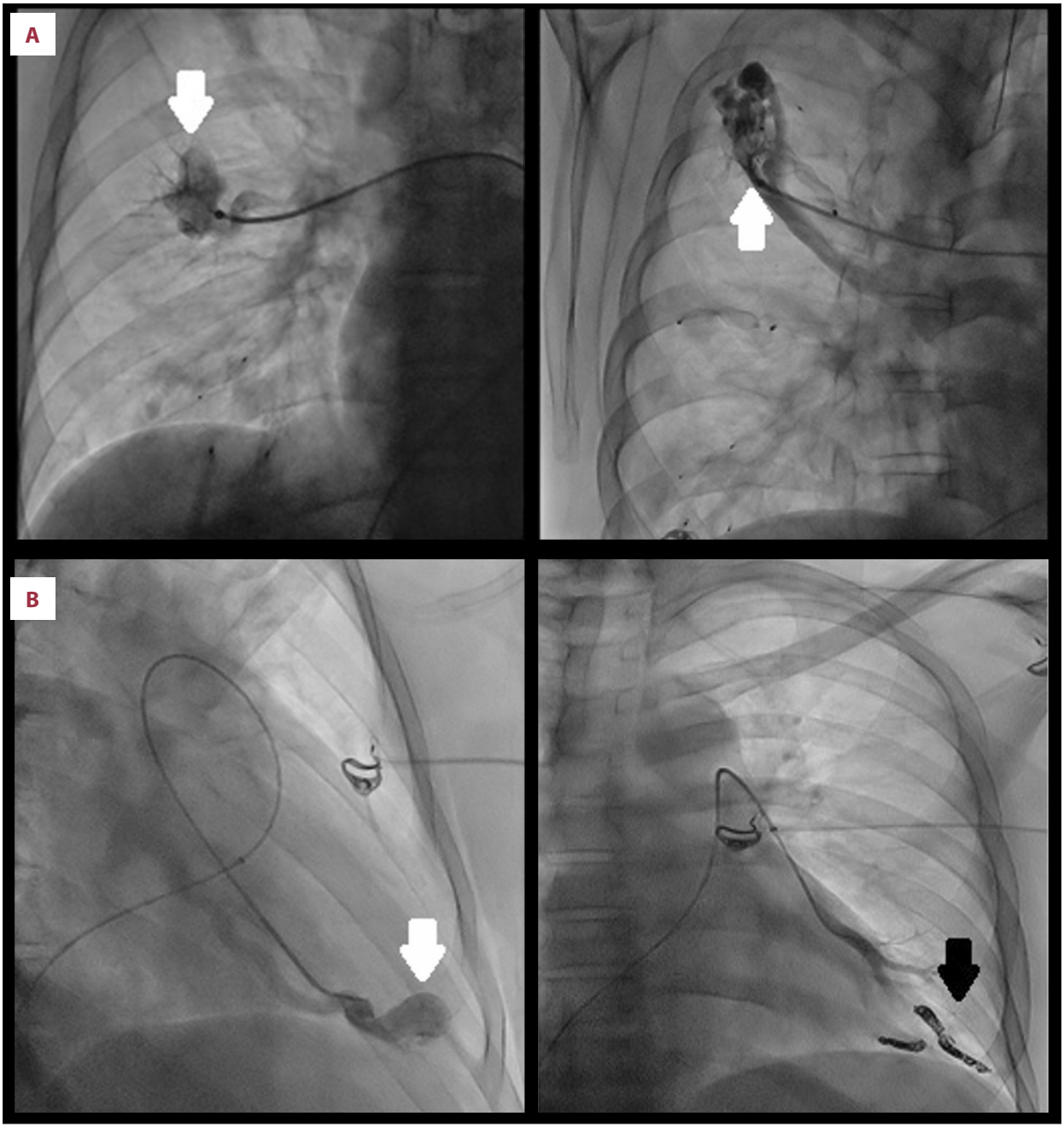

Figure 2. (**A, B**) Pulmonary images demonstrations the presence of multiple arteriovenous malformations. Chest X-ray showing some pre-embolectomy fluoroscopy images larger than 2 centimeters. Two were localized at the right upper lobe apical segment and 1 at the left lower lobe (white arrows). Post-embolectomy fluoroscopy image at left lower lobe (black arrow).

events and to improve the patient's chronic hypoxia. This recommended prevention and treatment is described in the literature [1,9]. A genetic study revealed exon5 mutations in the ENG gene in HHT type 1 [1]. The ENG gene codes for endoglin on chromosome 9 [20], which is essential for maintaining vascular integrity [21]. This genetic study allowed us to make a preventive diagnosis to his offspring and thus facilitate a personalized follow-up the Pediatric Unit.

Conclusions

This report highlights the neurological complications from BA secondary to PAVMs, a condition very commonly associated with HHT, which is a serious medical problem. Clinicians should be aware of this association so that diagnosis and treatment can be initiated as fast as possible to ensure the best outcome for the patient. Embolization as preventive treatment to

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avoid future complications should be considered for BA due to PAVMs. Genetic studies may be useful, allowing primary prevention for the patient's offspring.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Locke T, Gollamudi J, Chen P. Hereditary hemorrhagic telangiectasia (HHT). Treasure Island: StatPearls Publishing; 2022
2. Kjeldsen AD, Vase P, Green A. Hereditary haemorrhagic telangiectasia: A population-based study of prevalence and mortality in Danish patients. J Intern Med. 1999;245:31-39
3. Dakeishi M, Shioya T, Wada Y, et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. Hum Mutat. 2002;19:140-48
4. Plauchu H, de Chadare´vian J-P, Bideau A, et al. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet. 1989;32:291-97
5. McDonald J, Bayrak-Toydemmir P, DeMille D, et al. Curaçao diagnostic criteria for hereditary hemorrhagic telangiectasia is highly predictive of a pathogenic variant in ENG or ACVRL1 (HHT 1 and HHT2). Genet Med. 2020;22(7):1201-5
6. Guttmacher AE, Marchuk DA, White RI. Hereditary hemorrhagic telangiectasia. N Engl J Med. 1995;333:918-24
7. Haarmann S, Budihardja AS, Ho¨lzle F, Wolff KD. Subcutaneous temporal abscess as a clinical manifestation of pulmonary arteriovenous malformations in a patient with hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease). Int J Oral Maxillofac Surg. 2007;36:1211-14
8. Tabakow P, Jarmundowicz W, Czapiga B, Czapiga E. Brain abscess as the first clinical manifestation of multiple pulmonary arteriovenous malformations in a patient with hereditary hemorrhagic telangiectasia (RenduOsler-Weber disease). Folia Neuropathol. 2005;43:41-44
9. Shovlin CL, Jackson JE, Bamford KB, et al. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax. 2008;63:259-66
10. Giordano P, Sangerardi M, Suppressa P, et al. Pulmonary arteriovenous malformations and cerebral abscess recurrence in a child hereditary hemorrhagic telangiectasia. J Pediatr Hematol Oncol. 2015;37:e200-3
11. Geisthoff UW, Koester M, Fischinger J, Schneider G. [Rendu-Osler-Weber syndrome – a complex systemic disease.] MMW Fortschr Med. 2004;146:33-35 [in German]
12. White R Jr., Lynch-Nylan A, Terry P, et al. Pulmonary arteriovenous malformations: Techniques and long-term outcomes of embolotherapy. Radiology. 1988;169:663-69
13. Haitjema TJ, Overtoom TT, Westermann CJ, et al. Embolisation of pulmonary arteriovenous malformations: results and follow-up in 32 patients. Thorax. 1995;50:719-23
14. Gupta P, Mordin C, Curtis J, et al. Pulmonary arteriovenous malformations: Effect of embolization on right-to-left shunt, hypoxaemia and exercise tolerance in 66 patients. Am J Roentgenol. 2002;179:347-55
15. Cottin V, Chinet T, Lavole' A, et al. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia patients: A series of 126 patients. Medicine. 2007;86:1-17
16. Hodgson CH, Burchell HB, Good CA, et al. Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula. Study of a large family. N Engl J Med. 1959;261:625-36
17. Larsen L, Marker CR, Kjeldsen AD, Poulsen FR. Prevalence of hereditary hemorrhagic telangiectasia in patients operated for cerebral abscess: a retrospective cohort analysis. Eur J Clin Microbiol Infect Dis. 2017;36:1975-80
18. Dupuis-Girod S, Giraud S, Decullier E, et al. Hemorrhagic hereditary telangiectasia (Rendu-Osler disease) and infectious diseases: An underestimated association. Clin Infect Dis 2007;44:841-45
19. Mathis S, Dupuis-Girod S, Plauchu H, et al. Cerebral abscesses in hereditary haemorrhagic telangiectasia: A clinical and microbiological evaluation. Clin Neurol Neurosurg. 2012;114:235-40
20. McAllister KA, Grogg KM, Johnson DW et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet. 1994;8:345-51
21. Mc Donald J, Wooderchak-Donahue W, VanSant Weeb C, et al. Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era. Front Genet. 2015;6:1

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