

# World Journal of *Clinical Cases*

*World J Clin Cases* 2023 October 6; 11(28): 6670-6973



## MINIREVIEWS

- 6670 Neurotransmitters regulate  $\beta$  cells insulin secretion: A neglected factor  
*Kong CC, Cheng JD, Wang W*

## ORIGINAL ARTICLE

## Case Control Study

- 6680 Factors influencing the surveillance of re-emerging intracranial infections in elective neurosurgical patients: A single-center retrospective study  
*Wang JL, Wu XW, Wang SN, Liu X, Xiao B, Wang Y, Yu J*

## Retrospective Study

- 6688 Clinical value of chemiluminescence method for detection of antinuclear antibody profiles  
*Xiang HY, Xiang XY, Ten TB, Ding X, Liu YW, Luo CH*
- 6698 Value of ultrasound guided biopsy combined with Xpert *Mycobacterium tuberculosis*/resistance to rifampin assay in the diagnosis of chest wall tuberculosis  
*Yan QH, Chi JY, Zhang L, Xue F, Cui J, Kong HL*
- 6707 Research on the intelligent internet nursing model based on the child respiratory and asthma control test scale for asthma management of preschool children  
*Pei CF, Zhang L, Xu XY, Qin Z, Liang HM*
- 6715 Effects of different doses of long-acting growth hormone in treating children with growth hormone deficiency  
*Xia W, Wang T, Pan JY*
- 6725 Efficacy and anti-inflammatory analysis of glucocorticoid, antihistamine and leukotriene receptor antagonist in the treatment of allergic rhinitis  
*Qiu C, Feng D*
- 6733 Subchondral fatigue fracture of the femoral head in young military recruits: Potential risk factors  
*Yang JZ, Chen P, Chen BH, Zhao B*
- 6744 Anemia status of infants and young children aged six to thirty-six months in Ma'anshan City: A retrospective study  
*Wang XM, Wang QY, Huang J*
- Observational Study
- 6754 Impact of coronary artery bypass grafting surgery on the chorioretinal biomicroscopic characteristics  
*Shahriari M, Nikkhah H, Mahjoob MP, Behnaz N, Barkhordari S, Cheraqpour K*

**Prospective Study**

- 6763** Effects of humanized nursing care on negative emotions and complications in patients undergoing hysteromyoma surgery  
*Liu L, Xiao YH, Zhou XH*

**Randomized Controlled Trial**

- 6774** Randomized controlled trial on the efficacy and safety of autologous serum eye drops in dry eye syndrome  
*Zheng N, Zhu SQ*

**SYSTEMATIC REVIEWS**

- 6782** Primary adrenal Ewing sarcoma: A systematic review of the literature  
*Manatakis DK, Tsouknidas I, Mylonakis E, Tasis NP, Antonopoulou MI, Acheimastos V, Mastoropoulou A, Korkolis DP*

**CASE REPORT**

- 6792** Pulmonary artery aneurysm protruding into the bronchus as an endobronchial mass: A case report  
*Li M, Zhu WY, Wu RR, Wang L, Mo MT, Liu SN, Zhu DY, Luo Z*
- 6797** Rare rectal gastrointestinal stromal tumor case: A case report and review of the literature  
*Dong RX, Wang C, Zhou H, Yin HQ, Liu Y, Liang HT, Pan YB, Wang JW, Cao YQ*
- 6806** Bilateral retinal nerve fiber layer thickness reduction in a 9-year-old myopic boy suffering from unilateral optic neuritis: A case report  
*Zhao FF, Yao SQ, Wang Y, Li TP, Yang JF, Pang CP, Cen LP*
- 6812** Application of negative pressure wound therapy after skin grafting in the treatment of skin cancer: A case report  
*Huang GS, Xu KC*
- 6817** Diagnosis and treatment of McCune-Albright syndrome: A case report  
*Lin X, Feng NY, Lei YJ*
- 6823** Paraneoplastic myopathy-related rhabdomyolysis and pancreatic cancer: A case report and review of the literature  
*Costantini A, Moletta L, Pierobon ES, Serafini S, Valmasoni M, Sperti C*
- 6831** Multi-organ hereditary hemorrhagic telangiectasia: A case report  
*Chen YL, Jiang HY, Li DP, Lin J, Chen Y, Xu LL, Gao H*
- 6841** Hyperprogression after anti-programmed death-1 therapy in a patient with urothelial bladder carcinoma: A case report  
*Yang HY, Du YX, Hou YJ, Lu DR, Xue P*
- 6850** Effectiveness of antidepressant repetitive transcranial magnetic stimulation in a patient with refractory psychogenic dysphagia: A case report and review of literature  
*Woo CG, Kim JH, Lee JH, Kim HJ*

- 6857** Entrapment neuropathy of common peroneal nerve by fabella: A case report  
*Lin JC, Tsai MH, Lin WP, Kuan TS, Lien WC*
- 6864** Importance of accurate diagnosis of congenital agenesis of the gallbladder from atypical gallbladder stone presentations: A case report  
*Sun HJ, Ge F, Si Y, Wang Z, Sun HB*
- 6871** Dorsal approach for isolated volar fracture-dislocation of the base of the second metacarpal: A case report  
*Kurozumi T, Saito M, Odachi K, Masui F*
- 6877** Rotationplasty type BIIIb as an effective alternative to limb salvage procedure in adults: Two case reports  
*Chen ZX, Guo XW, Hong HS, Zhang C, Xie W, Sha M, Ding ZQ*
- 6889** Primary cutaneous anaplastic large cell lymphoma with over-expressed Ki-67 transitioning into systemic anaplastic large cell lymphoma: A case report  
*Mu HX, Tang XQ*
- 6895** Confusing finding of quantitative fluorescent polymerase chain reaction analysis in invasive prenatal genetic diagnosis: A case report  
*Chen C, Tang T, Song QL, He YJ, Cai Y*
- 6902** Testicular mixed germ cell tumor: A case report  
*Xiao QF, Li J, Tang B, Zhu YQ*
- 6908** Leukemic transformation during anti-tuberculosis treatment in aplastic anemia-paroxysmal nocturnal hemoglobinuria syndrome: A case report and review of literature  
*Xiu NN, Yang XD, Xu J, Ju B, Sun XY, Zhao XC*
- 6920** Pancreatic arteriovenous malformation treated with transcatheter arterial embolization: Two case reports and review of literature  
*Shin SH, Cho CK, Yu SY*
- 6931** Cecal duplication cyst in an infant presenting as shock: A case report  
*Kim SM, Lee SH, Park GY, Kim SS, Lee CG, Jin SJ*
- 6938** Pulmonary reversed halo cycles and consolidations after immunotherapy: A case report  
*Suo H, Shi YJ, Huang ZD, Xu K, Huang H*
- 6943** Unusual case of emphysematous cystitis mimicking intestinal perforation: A case report  
*Kang HY, Lee DS, Lee D*
- 6949** Malignant proliferative ependymoma of the neck with lymph node metastasis: A case report  
*Wang K, Wen JZ, Zhou SX, Ye LF, Fang C, Chen Y, Wang HX, Luo X*
- 6955** Wandering spleen torsion with portal vein thrombosis: A case report  
*Zhu XY, Ji DX, Shi WZ, Fu YW, Zhang DK*

- 6961** Intracranial infection and sepsis in infants caused by *Salmonella derby*: A case report  
*Yu JL, Jiang LL, Dong R, Liu SY*
- 6967** Large gastric hamartomatous inverted polyp accompanied by advanced gastric cancer: A case report  
*Park G, Kim J, Lee SH, Kim Y*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Hao Wang, MD, PhD, Associate Professor, Department of Emergency Medicine, John Peter Smith Health Network, Texas Christian University and University of North Texas Health Science Center, School of Medicine, Fort Worth, TX 76104, United States. [hwang@ies.healthcare](mailto:hwang@ies.healthcare)

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

*WJCC* mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

**INDEXING/ABSTRACTING**

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCC* as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Si Zhao*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jin-Lei Wang*.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

October 6, 2023

**COPYRIGHT**

© 2023 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Multi-organ hereditary hemorrhagic telangiectasia: A case report

Ying-Ling Chen, Hong-Yue Jiang, Dong-Ping Li, Jiang Lin, Yun Chen, Li-Li Xu, Hong Gao

**Specialty type:** Genetics and heredity

**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Baysal M, Turkey;  
Kumar S, India

**Received:** July 11, 2023

**Peer-review started:** July 11, 2023

**First decision:** August 4, 2023

**Revised:** August 21, 2023

**Accepted:** September 11, 2023

**Article in press:** September 11, 2023

**Published online:** October 6, 2023



**Ying-Ling Chen, Hong-Yue Jiang, Dong-Ping Li, Yun Chen, Li-Li Xu, Hong Gao,** Department of Gastroenterology and Hepatology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

**Jiang Lin,** Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

**Jiang Lin,** Shanghai Institute of Medical Imaging, Shanghai 200032, China

**Corresponding author:** Hong Gao, MD, Doctor, Department of Gastroenterology and Hepatology, Zhongshan Hospital, Fudan University, No. 180 Fenglin Road, Shanghai 200032, China. [gao.hong@zs-hospital.sh.cn](mailto:gao.hong@zs-hospital.sh.cn)

### Abstract

#### BACKGROUND

Type 2 hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant disease and is associated with *ALK1* gene mutations. Type 2 HHT patients primarily suffer from recurrent bleeding. There is currently no promising treatment.

#### CASE SUMMARY

A 5-year-old Chinese patient (III23) was admitted to Zhongshan Hospital for recurrent melena occurring over 2 mo. She had been experiencing epistaxis for years and had been diagnosed with idiopathic pulmonary hypertension 4 mo before presentation. Abdominal computed tomography examination showed hepatic arteriovenous malformation. Gene testing revealed a c.1121G>A mutation on the *ALK1* gene. According to the international diagnostic criteria, this patient was diagnosed with HHT. In addition, 8 more family members exhibited HHT symptoms to varying degrees. Gene testing in 5 family members (2 with HHT symptoms and 3 without HHT symptoms) revealed the *ALK1* c.1121G>A mutation in the 2 family members with HHT symptoms. This missense mutation results in the substitution of arginine for glutamine at amino acid position 374 (R374Q) in the conserved functional kinase domain of *ALK1*. Biological studies revealed that this mutation decreased the kinase activity of *ALK1* and impeded the phosphorylation of its substrate Smad1. Moreover, the R374Q mutant downregulated the protein level of collagen-1, a fibrogenic factor, indicating abnormal fiber generation during vascular formation.

#### CONCLUSION

The R374Q mutant of *ALK1* and its subsequent influence on fiber generation highly indicated its pathogenic role in this family with type 2 HHT. Detection of

this gene mutation will facilitate early diagnosis of suspected type 2 HHT patients, and mechanistic studies will provide insights for future therapy.

**Key Words:** Hereditary hemorrhagic telangiectasia; Pedigree; *ALK1*; Gene mutation; Case report

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant hereditary disease characterized by varying degrees of bleeding symptoms. The diagnosis of HHT is difficult when relying on bleeding symptoms, while gene testing is robust and reliable for identifying HHT patients. Here, we report a patient with type 2 HHT who was undiagnosed for HHT for years due to varied symptoms involving multiple organs. We found an *ALK1* gene mutation in the patient and her family members. We further verified the pathogenic role of this mutation in inducing vascular malformation by basic research studies.

**Citation:** Chen YL, Jiang HY, Li DP, Lin J, Chen Y, Xu LL, Gao H. Multi-organ hereditary hemorrhagic telangiectasia: A case report. *World J Clin Cases* 2023; 11(28): 6831-6840

**URL:** <https://www.wjgnet.com/2307-8960/full/v11/i28/6831.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v11.i28.6831>

## INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), a rare autosomal dominant hereditary disorder, is characterized by abnormal bleeding and telangiectasia occurring predominantly in the mucosa of the nose, oral cavity, and the skin of the face and hands[1]. The underlying pathology of HHT patients is due to the lack of normal capillaries that link the artery and vein. Therefore, blood from the arteries flows directly into the veins at high pressure and ruptures the fragile sites in the shallow mucosa or deep visceral organs[2]. The common epistaxis and telangiectasia are easily discovered and treated, while the atypically silent lesions in the lung, liver, stomach, and bowel are often neglected, leading to delayed diagnosis and severe damage[1]. Constant silent bleeding can contribute to severe anemia, and abrupt massive bleeding in major organs can lead to death.

In these circumstances, early diagnosis of HHT is of extreme importance to educate patients about precautions against aberrant bleeding and prevention of detrimental outcomes. Since HHT is a dominant hereditary disease that is primarily caused by aberrant mutation of the *ENG* gene (type 1 HHT)[3] or the *ALK1* gene (type 2 HHT)[4], gene sequencing of *ENG* and *ALK1* is a useful method for HHT diagnosis. However, hundreds of mutations on *ENG* and *ALK1* have been discovered[5], and mutations that are crucial for HHT occurrence have not been fully examined. Therefore, it is imperative to determine the pathogenic mutations that could be used for HHT diagnosis.

In this study, we analyzed a Chinese family with type 2 HHT and discovered a mutation, c.1121G>A (p.R374Q), in *ALK1*. Biological studies revealed that this mutation decreased the kinase activity of ALK1 and reduced expression of collagen-1, indicating its pathogenic role in dysregulating fiber generation during vascular formation. Hence, our study provided a potential genetic marker for type 2 HHT diagnosis, and the underlying mechanistic exploration provided the foundation of better treatments.

## CASE PRESENTATION

### Chief complaints

A 56-year-old Chinese female patient (III23) was admitted to Zhongshan Hospital for constant black stools occurring for 2 mo.

### History of present illness

The patient had recurrent epistaxis for years and noticed black stool for the prior 2 mo without abdominal pain or other gastrointestinal (GI) symptoms.

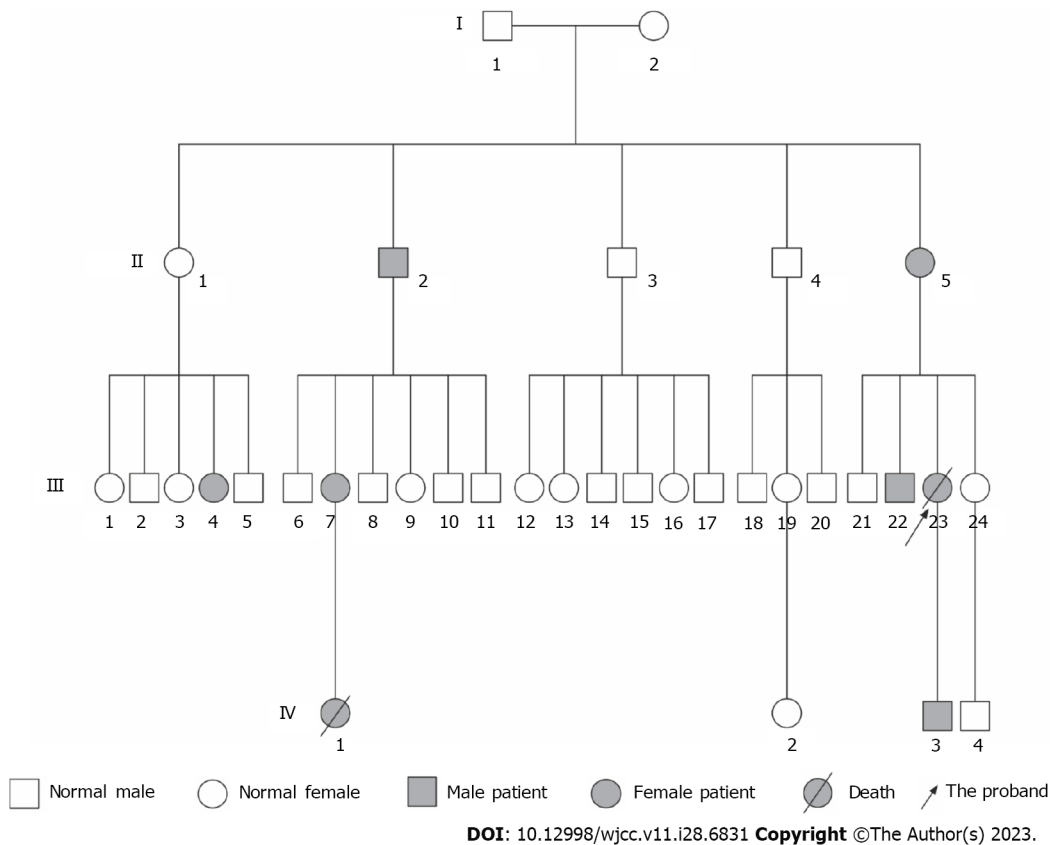
### History of past illness

The patient also suffered from fatigue and shortness of breath and was diagnosed with idiopathic pulmonary hypertension and right heart failure in a local hospital 4 mo prior to presentation.

### Personal and family history

Several individuals in the patient's family had symptoms of epistaxis and GI bleeding as shown in Figure 1. The patient's





**Figure 1** Distribution of hereditary hemorrhagic telangiectasia in this family. The information of I1 and I2 was unknown.

elder brother (III22) experienced GI bleeding. Her son (IV3) experienced only epistaxis. Another 5 members in this family experienced symptoms of epistaxis (II2, II5, III4, III7, and IV1). During the follow-up, a niece (IV1) was found to experience pulmonary hypertension in addition to epistaxis and died 2 years after being diagnosed with pulmonary hypertension.

### Physical examination

Physical examination upon admission revealed a body temperature of 37 °C, heart rate of 82 beats/min, respiratory rate of 20 breaths/min, and blood pressure of 100/70 mmHg. The skin examination showed a mild cyanosis. Cardiovascular examination revealed an expanded heart border to the right, and systolic murmur was detected at the tricuspid valve area. The abdomen was bilateral and soft. Percussion pain presented in the liver and spleen area.

### Laboratory examinations

A routine blood test identified hypochromic and microcytic erythrocytes with a low level of hemoglobin (58 g/L; normal range: 110-150 g/L). It also revealed abnormalities in total protein (53 g/L; normal range: 61-83 g/L), albumin (33 g/L; normal range: 35-50 g/L), and transglutaminase (63 U/L; normal range: < 47 U/L). Stool occult blood test was positive.

### Imaging examinations

Abdominal contrast-enhanced computed tomography (CT) scan showed dilated hepatic arteries (Figure 2A), diffuse parenchymal telangiectasia, and early filling of hepatic veins on the arterial phase (Figure 2B), which suggested a diagnosis of HHT. Barium X-ray examination for the upper GI tract indicated antral gastritis and duodenitis.

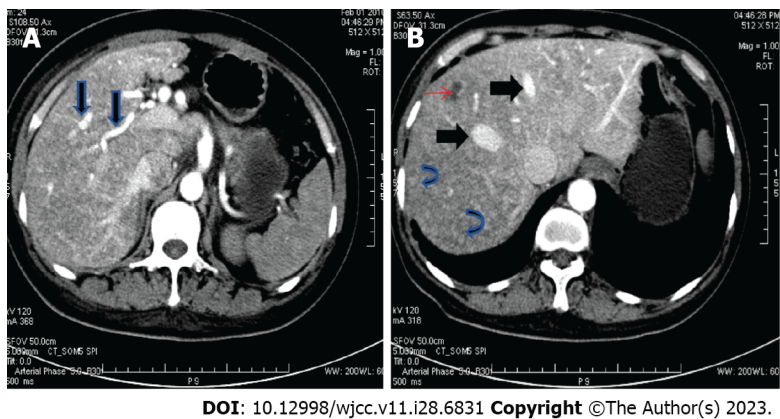
### Further diagnostic work-up

Since the patient experienced epistaxis and hepatic arteriovenous malformations (AVMs) were revealed on the abdominal CT scan, HHT was highly suspected. HHT is a dominant hereditary disease and is primarily caused by mutations in *ENG* (type 1 HHT)[3], *ALK1* (type 2 HHT)[4], and *SMAD4*[6]. Therefore, we subsequently performed gene testing in several individuals in this family, including the patient (III23), her elder brother (III22), a sister (III24), her son (IV3), a nephew (IV4), and a niece (IV2).

We amplified the *ALK1* gene using the primers as shown in Table 1 and sent the PCR DNA products for Sanger sequencing. The DNA sequencing showed that a missense mutation, c.1121G>A, in exon 8 of *ALK1* occurred in the patient (III23), her son (IV3), and elder brother (III22). They all experienced symptoms of HHT, indicating type 2 HHT in this family (Figure 3A and B). This mutation did not occur in the other 3 family members (III24, IV2, and IV4) who did not experience HHT symptoms (Figure 3B). The c.1121G>A mutation contributed to a translational change from arginine

Table 1 Primers of exon 3, exon 7, and exon 8 of the <i>ALK1</i> gene for polymerase chain reaction	
Gene	Primer, 5'-3'
<i>ALK1-exon3-F</i>	AGCTGGGACCACAGTGGCTGA
<i>ALK1-exon3-R</i>	GAGGGCAGGGGCCAAGAAGAT
<i>ALK1-exon7-F</i>	GACGACTCCAGCCTCCCTTAG
<i>ALK1-exon7-R</i>	CAAGCTCCGCCACCTGTGAA
<i>ALK1-exon8-F</i>	AGGTTTGGGAGAGGGGCAGGA
<i>ALK1-exon8-R</i>	GGCTCCACAGGCTGATCCCCCTT

F: Forward; R: Reverse.



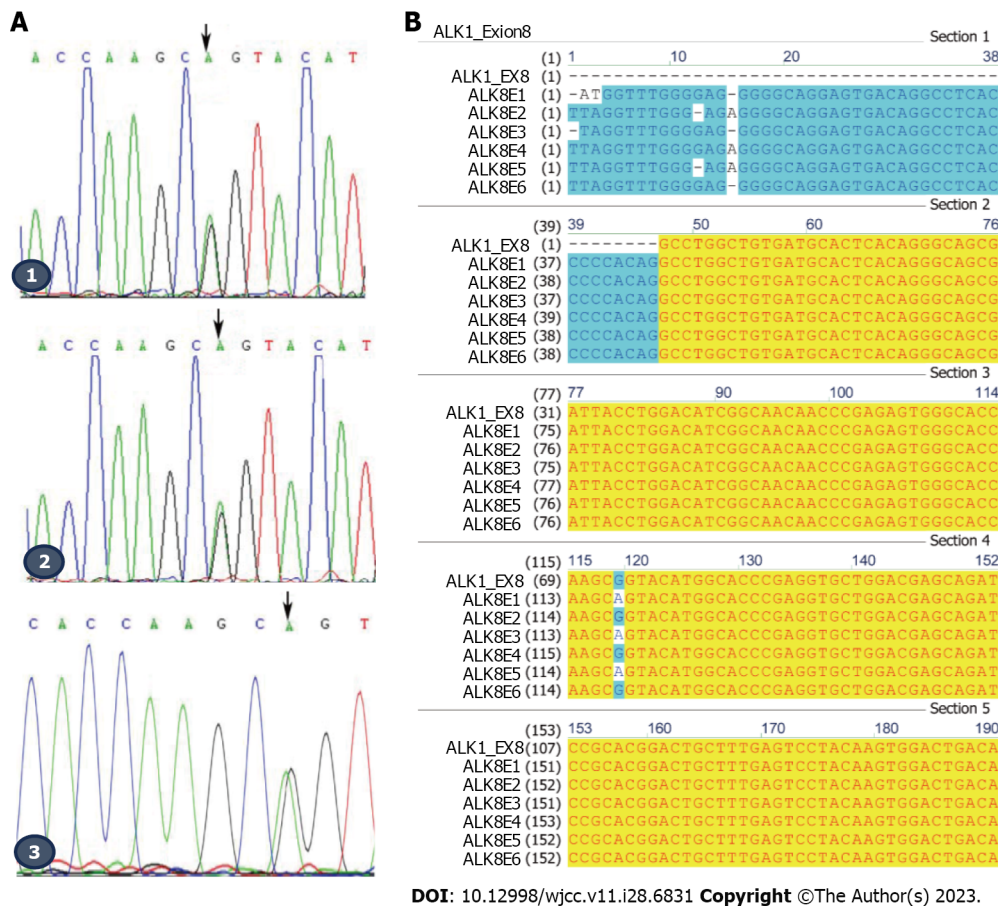
**Figure 2** Computed tomography scan of the abdomen in the patient with hereditary hemorrhagic telangiectasia. A: Dilated and tortuous hepatic arteries (arrow); B: Early enhancement of enlarged hepatic veins (thick arrows), diffuse parenchymal telangiectasia (curved arrows), and an incidentally found liver cyst (thin arrow).

to glutamine at amino acid position 374 (R374Q) of the *ALK1* protein. These results indicated that the c.1121G>A mutation might contribute to the pathogenesis of type 2 HHT in this family.

To address this question, we performed biochemical studies to investigate the effect of the c.1121G>A mutation on the biological function of *ALK1*. First, we detected the mutant protein expression in cultured cells. The western blot showed no significant difference in *ALK1* protein levels between the wildtype (WT) and R374Q groups (Figure 4A). The immunofluorescence assay also showed that the mutant *ALK1* protein could be detected in cells, and it was mainly located at cell membranes similar to the WT *ALK1* protein (Figure 4B). These results indicated that the c.1121G>A mutation exerted no influence on protein expression or subcellular distribution.

Previous computer modeling studies demonstrated that the substitution of arginine to glutamine at amino acid position 374 (p.R374Q) could disturb H-bonding schemes of the intracellular kinase domain of *ALK1*[7]. Therefore, we assumed that the R374Q mutation could affect the kinase activity of *ALK1*. *ALK1* is one of the components of TGF- $\beta$  receptor that can phosphorylate Smad1 once activated and mediate signal reactions associated with vascular angiogenesis [8]. We detected the phosphorylation level of Smad1 in 293T, HepG2, and Hela cell lines. The results showed that the phosphorylation of Smad1 was significantly reduced in the mutant group compared to the WT group (Figure 5A). To further verify the inhibitory effect of the R374Q mutation on the kinase activity of *ALK1*, we introduced a Smad1-responsive transcriptional reporter, BRE4-luciferase reporter plasmid, to 293T, HepG2, and Hela cell lines. When transfecting WT *ALK1* into those cells, we observed robust gene expression of the BRE4-luciferase. When the R374Q mutant was overexpressed, the expression of the BRE4-luciferase was significantly reduced compared to the WT group (Figure 5B). Hence, the R374Q mutation impeded the kinase activity of *ALK1*.

Telangiectasis is a pathologic change in HHT that is characterized by abnormal vascular dilation. It may occur when fiber generation in vessel walls is decreased. Previous studies suggested that *ALK1*/Smad1 played an important role in organ fibrosis such as in the liver and kidney[8]. Hence, we investigated whether the R374Q mutation affected profibrotic activity. The result showed that the R374Q mutant significantly abrogated the protein expression of a fibrogenic factor, collagen-1 (Figure 5C), indicating that the R374Q mutant could inhibit fiber generation during vascular formation.



**Figure 3 Identification of *ALK1* mutations.** A: Mutation of *ALK1* in this hereditary hemorrhagic telangiectasia family. 1: Proband (III23); 2: Proband's son (IV3); 3: Proband's elder brother (III22). Arrows indicate the mutated nucleotide at position 1121 in exon 8 of *ALK1*; B: Sequence of exon 8 of *ALK1* and the mutation exhibited in this hereditary hemorrhagic telangiectasia family. ALK8E1: Proband (III23); ALK8E2: Proband's sister (III24); ALK8E3: Proband's elder brother (III22); ALK8E4: Proband's nephew (IV4); ALK8E5: Proband's son (IV3); ALK8E6: Proband's niece (IV2).

## FINAL DIAGNOSIS

The patient was diagnosed with type 2 HHT according to the Curaçao criteria[9]. In addition, the patient was also diagnosed with pulmonary arterial hypertension, right heart failure, and severe iron anemia.

## TREATMENT

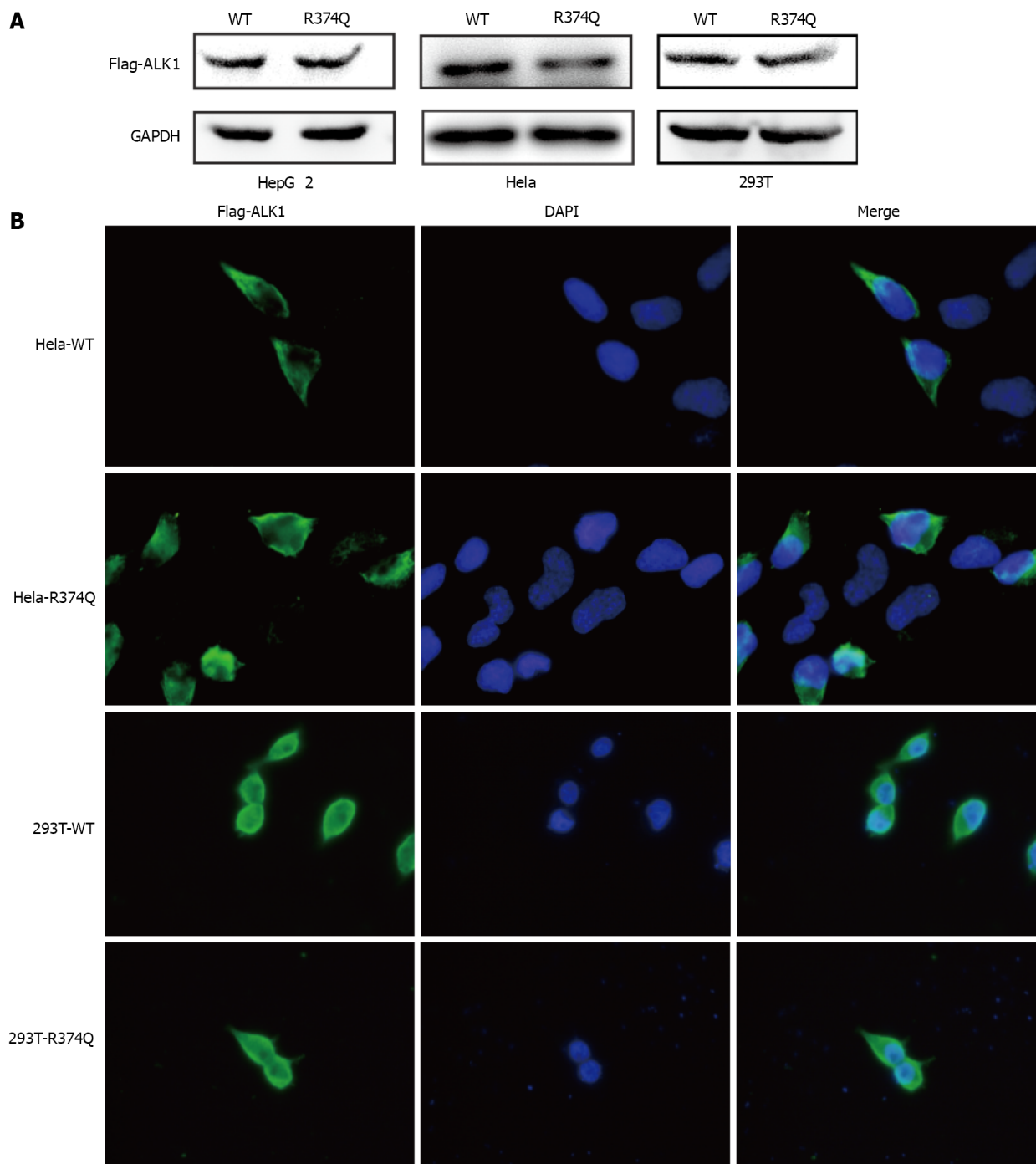
Omeprazole and hydrotalcite were administrated to prevent upper GI bleeding. The patient did not experience new active bleeding and was discharged.

## OUTCOME AND FOLLOW-UP

The patient constantly experienced melena after discharge. One month later, she went to a local pulmonary hospital because of pulmonary arterial hypertension-associated shortness of breath. She experienced acute vomiting of blood as well as melena while receiving treatment at the pulmonary hospital. Scattered erythematous mucosa was identified in the stomach without typical ulcers (Figure 6). After hemostatic therapy, she was discharged. However, the patient consistently had symptoms of GI bleeding and died of heart failure 1 year later.

## DISCUSSION

HHT is an autosomal dominant hereditary disease that occurs in 1 out of 5000 people[10]. However, the real incidence might be higher because many potential HHT patients are not diagnosed due to their varied presentation of symptoms. The HHT-related vascular malformation can occur in any organ, thereby contributing to the diversity of symptoms that



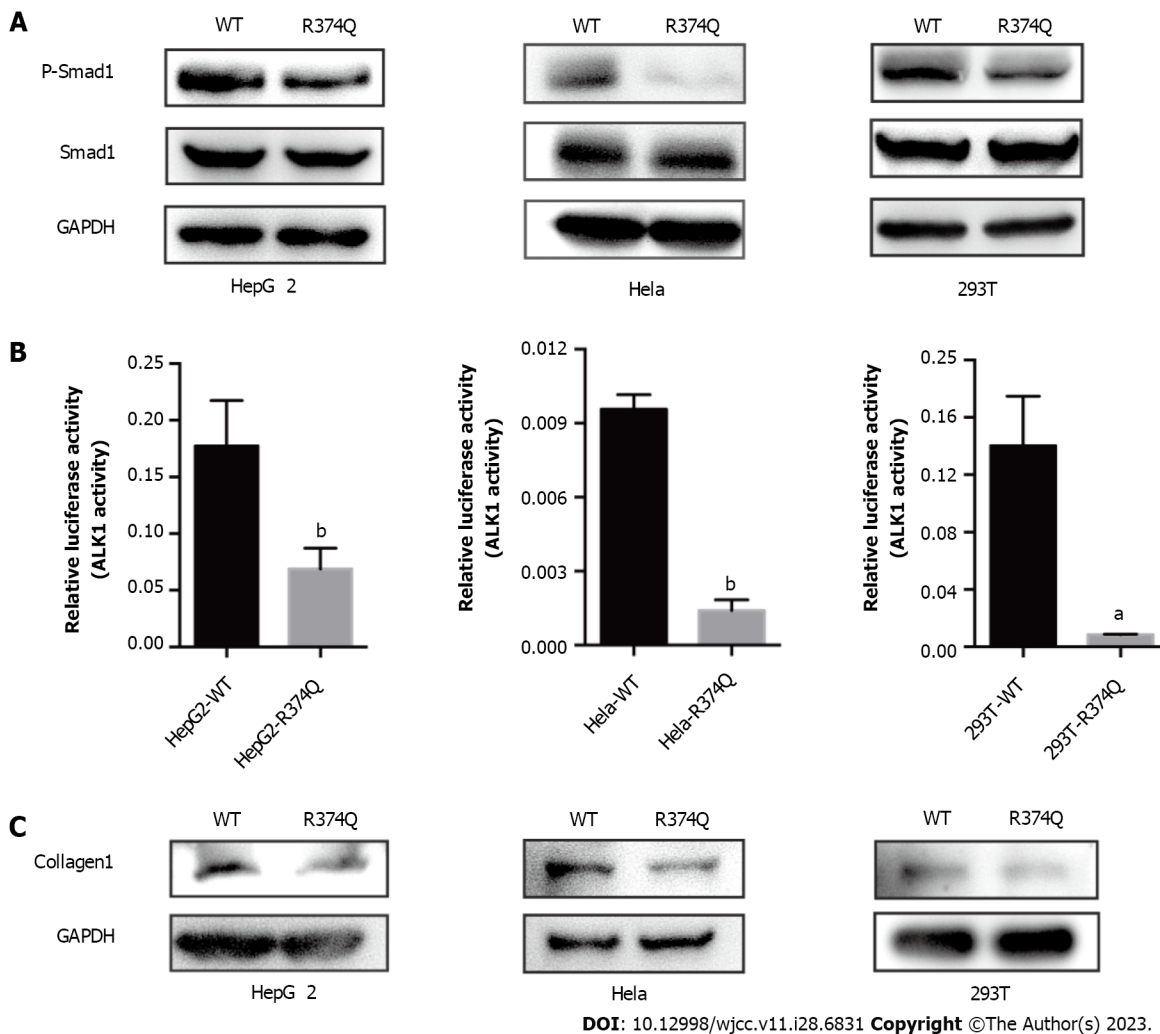
DOI: 10.12998/wjcc.v11.i28.6831 Copyright ©The Author(s) 2023.

**Figure 4 The c.1121G>A mutation does not affect *ALK1* gene expression.** A: ALK1 protein of the wildtype and the arginine to glutamate substitution at amino acid position 374 (R374Q) groups were detected by immunoblot in HepG2, HeLa, and 293T cell lines; B: Immunofluorescence assay was performed to visualize the expression and distribution of ALK1 in HeLa and 293T cell lines. WT: Wildtype.

vary from superficial skin telangiectasia to epistaxis to deeper organ issues, like pulmonary hypertension, GI bleeding, cerebral bleeding, *etc.* In addition, patients can have symptoms involving one organ or multiple organs concurrently. Patients with common epistaxis and telangiectasia are easily recognized, while those with atypically silent lesions in the lung, liver, and stomach are often neglected. In this case, the patient who was diagnosed with pulmonary hypertension was not screened for HHT until she presented with more indicative symptoms like GI bleeding.

The delayed diagnosis can be avoided by utilizing gene testing. HHT is an autosomal dominant hereditary disease[1] that is caused by gene mutations in *ENG* (type 1 HHT)[3], *ALK1* (type 2 HHT)[4], *SMAD4* (juvenile polyposis JP-HHT) [11], and *BMP9* (HHT5)[12]. Over a thousand mutations have been reported within the *ENG* and *ALK1* genes (<http://arup.utah.edu/database/HHT/index.php>). However, whether all the reported mutations are involved in causing HHT symptoms is unknown. Therefore, it is crucial to determine the pathogenic mutations of HHT. Identifying the diagnostic HHT pathogenic gene pool is of great value to enable patients with limited symptoms to be diagnosed in a timely



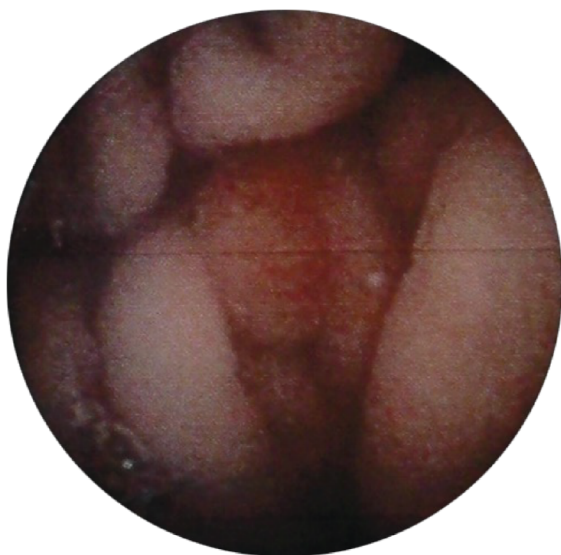


**Figure 5 The arginine to glutamate substitution at amino acid position 374 mutation affects ALK1 kinase activity.** A: Influence of ALK1 on Smad1 phosphorylation was investigated by immunoblotting. Protein levels of Smad1 and phosphorylated Smad1 (P-Smad1) were detected in HepG2, Hela, and 293T cell lines; B: Kinase activity of ALK1 was detected in the wildtype (WT) group and the mutant group through the BRE4 reporter luciferase assay (<sup>a</sup> $P < 0.05$  and <sup>b</sup> $P < 0.01$  vs the wildtype group); C: Protein level of collagen-1 was detected by immunoblotting in HepG2, Hela, and 293T cell lines. R374Q: Arginine to glutamate substitution at amino acid position 374. WT: Wildtype.

manner.

Herein, we identified the mutation c.1121G>A in exon 8 of *ALK1* in 3 patients in this family, which supported a diagnosis of type 2 HHT. The mutation, c.1121G>A, contributes to a substitution at amino acid position 374 (R374Q) that is located in the conserved functional kinase domain of ALK1. Typically the active loop (between amino acids 371 and 374) has a conformational change when activated and then facilitates its binding with substrates or ATP[13]. We investigated the influence of the R374Q mutation on ALK1 activity. According to our studies, the R374Q mutation did not affect protein expression or cellular localization, but it decreased the kinase activity of ALK1. It induced a lower gene product in the BRE4 luciferase reporter assay and impeded the phosphorylation of Smad1. Since the Smad1/Smad5 pathway is involved in TGF- $\beta$ -mediated angiogenesis[8], the decreased level of phosphorylated Smad1 indicates that the R374Q mutant inhibited the kinase activity of ALK1 as well as downstream reactions, leading to abnormal angiogenesis. Moreover, telangiectasia is a pathological manifestation in type 2 HHT. The lack of protective fibers in vessel walls causes the abnormal dilatation. Exploration of the effect of the R374Q mutant on fibrogenesis revealed that the R374Q mutant reduced the protein level of collagen-1, a fibrogenic factor that can enhance fiber generation[14]. Hence, the R374Q mutant played a role in downregulating fibrogenesis and eventually causing vascular malformation.

According to these biomolecular studies, the R374Q mutant of ALK1 played a pathological role in HHT development in this family. The R374Q mutation was also reported in other HHT families[2,7,15-18], further demonstrating its prevalent occurrence and pathological effect in HHT. Intriguingly, most of the HHT patients with the R374Q mutation were reported experiencing hepatic AVMs and GI bleeding, suggesting a possible correlation between genotype to phenotype[2,7,15]. Besides, independent studies in different populations found that hepatic AVMs and GI bleeding were more common in patients with *ALK1* mutations[19,20]. In this family, the proband suffered from GI bleeding and hepatic AVMs. Her elder brother experienced GI bleeding, while her son only experienced epistaxis. The diversity of phenotype in the son might be attributed to incomplete penetrance. Given the poor prognosis of the HHT patients carrying the



DOI: 10.12998/wjcc.v11.i28.6831 Copyright ©The Author(s) 2023.

**Figure 6** Capsule endoscopy examination showed mucosal erosion in the stomach.

R374Q mutation, this son is most likely to develop hepatic AVMs and GI bleeding when he gets older.

Unfortunately, there is no effective treatment to stop the progression of HHT. The son of the proband can only be educated on precautions against aberrant bleeding and to stop bleeding quickly to prevent detrimental outcomes. To develop novel therapeutic strategies, a transgenic mouse model is recommended to introduce specific mutations to HHT-associated genes, like c.1121G>A on the *ALK1* gene, and monitor the phenotype of the HHT-mimic mice. Effective drug treatments that impede HHT progression and improve survival could be developed in this type of animal model.

---

## CONCLUSION

Overall, we discovered a gene mutation c.1121G>A (p.R374Q) in *ALK1* in a Chinese family with type 2 HHT. Detection of this mutation may facilitate early diagnosis of HHT, which would enable medical care to be implemented in a timely manner to prevent fatal damage. In addition, the study of the pathogenic mechanism of the R374Q mutant might provide insights for impeding HHT pathogenic progress and developing treatments.

---

## ACKNOWLEDGEMENTS

We thank Ronggui Hu, Xingxing Xu, and Yonghui Tao (Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences) for providing technical support. We thank the Yueguang Chen laboratory (Department of Biological Sciences and Bio-technology, Tsinghua University, Beijing, China) for providing the BRE4 reporter plasmid as a gift.

---

## FOOTNOTES

**Author contributions:** Chen YL contributed to manuscript writing and experiment performance; Jiang HY performed the majority of the experiments; Li DP, Chen Y, and Xu LL contributed to revision of the manuscript; Lin J interpreted the computed tomography scan results; Gao H recruited the patient and contributed to the supervision of the entire study; and all authors read and approved the final manuscript.

**Informed consent statement:** Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016) and revised the manuscript according to the requirements of CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to

distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

**Country/Territory of origin:** China

**ORCID number:** Hong Gao 0000-0002-2263-9214.

**S-Editor:** Chen YL

**L-Editor:** A

**P-Editor:** Chen YL

## REFERENCES

- 1 Ragsdale JA. Hereditary hemorrhagic telangiectasia: from epistaxis to life-threatening GI bleeding. *Gastroenterol Nurs* 2007; **30**: 293-9; quiz 300 [PMID: 17724405 DOI: 10.1097/01.SGA.0000287202.36602.fb]
- 2 Abdalla SA, Geisthoff UW, Bonneau D, Plauchu H, McDonald J, Kennedy S, Faughnan ME, Letarte M. Visceral manifestations in hereditary haemorrhagic telangiectasia type 2. *J Med Genet* 2003; **40**: 494-502 [PMID: 12843319]
- 3 McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrell J. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet* 1994; **8**: 345-351 [PMID: 7894484 DOI: 10.1038/ng1294-345]
- 4 Johnson DW, Berg JN, Baldwin MA, Gallione CJ, Marondel I, Yoon SJ, Stenzel TT, Speer M, Pericak-Vance MA, Diamond A, Guttmacher AE, Jackson CE, Attisano L, Kucherlapati R, Porteous ME, Marchuk DA. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet* 1996; **13**: 189-195 [PMID: 8640225 DOI: 10.1038/ng0696-189]
- 5 Albiñana V, Zafra MP, Colau J, Zarrabeitia R, Recio-Poveda L, Olavarrieta L, Pérez-Pérez J, Botella LM. Mutation affecting the proximal promoter of Endoglin as the origin of hereditary hemorrhagic telangiectasia type 1. *BMC Med Genet* 2017; **18**: 20 [PMID: 28231770 DOI: 10.1186/s12881-017-0380-0]
- 6 Gallione CJ, Richards JA, Letteboer TG, Rushlow D, Prigoda NL, Leedom TP, Ganguly A, Castells A, Ploos van Amstel JK, Westermann CJ, Pyeritz RE, Marchuk DA. SMAD4 mutations found in unselected HHT patients. *J Med Genet* 2006; **43**: 793-797 [PMID: 16613914 DOI: 10.1136/jmg.2006.041517]
- 7 Abdalla SA, Cymerman U, Johnson RM, Deber CM, Letarte M. Disease-associated mutations in conserved residues of ALK-1 kinase domain. *Eur J Hum Genet* 2003; **11**: 279-287 [PMID: 12700602 DOI: 10.1038/sj.ejhg.5200919]
- 8 Lafyatis R. Transforming growth factor  $\beta$ -at the centre of systemic sclerosis. *Nat Rev Rheumatol* 2014; **10**: 706-719 [PMID: 25136781 DOI: 10.1038/nrrheum.2014.137]
- 9 Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000; **91**: 66-67 [PMID: 10751092]
- 10 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 [PMID: 10095814 DOI: 10.1046/j.1365-2796.1999.00398.x]
- 11 Gallione C, Aylsworth AS, Beis J, Berk T, Bernhardt B, Clark RD, Clericuzio C, Danesino C, Drautz J, Fahl J, Fan Z, Faughnan ME, Ganguly A, Garvie J, Henderson K, Kini U, Leedom T, Ludman M, Lux A, Maisenbacher M, Mazzucco S, Olivieri C, Ploos van Amstel JK, Prigoda-Lee N, Pyeritz RE, Reardon W, Vandezande K, Waldman JD, White RI Jr, Williams CA, Marchuk DA. Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP-HHT syndrome. *Am J Med Genet A* 2010; **152A**: 333-339 [PMID: 20101697 DOI: 10.1002/ajmg.a.33206]
- 12 Woodechak-Donahue WL, McDonald J, O'Fallon B, Upton PD, Li W, Roman BL, Young S, Plant P, Fülöp GT, Langa C, Morrell NW, Botella LM, Bernabeu C, Stevenson DA, Runo JR, Bayrak-Toydemir P. BMP9 mutations cause a vascular-anomaly syndrome with phenotypic overlap with hereditary hemorrhagic telangiectasia. *Am J Hum Genet* 2013; **93**: 530-537 [PMID: 23972370 DOI: 10.1016/j.ajhg.2013.07.004]
- 13 Gu Y, Jin P, Zhang L, Zhao X, Gao X, Ning Y, Meng A, Chen YG. Functional analysis of mutations in the kinase domain of the TGF-beta receptor ALK1 reveals different mechanisms for induction of hereditary hemorrhagic telangiectasia. *Blood* 2006; **107**: 1951-1954 [PMID: 16282348 DOI: 10.1182/blood-2005-05-1834]
- 14 Twardowski T, Fertala A, Orgel JP, San Antonio JD. Type I collagen and collagen mimetics as angiogenesis promoting superpolymers. *Curr Pharm Des* 2007; **13**: 3608-3621 [PMID: 18220798 DOI: 10.2174/138161207782794176]
- 15 Chen YJ, Yang QH, Liu D, Liu QQ, Eyries M, Wen L, Wu WH, Jiang X, Yuan P, Zhang R, Soubrier F, Jing ZC. Clinical and genetic characteristics of Chinese patients with hereditary haemorrhagic telangiectasia-associated pulmonary hypertension. *Eur J Clin Invest* 2013; **43**: 1016-1024 [PMID: 23919827 DOI: 10.1111/eci.12138]
- 16 Fontalba A, Fernandez-L A, Garcia-Alegria E, Albiñana V, Garrido-Martin EM, Blanco FJ, Zarrabeitia R, Perez-Molino A, Bernabeu-Herrero ME, Ojeda ML, Fernandez-Luna JL, Bernabeu C, Botella LM. Mutation study of Spanish patients with hereditary hemorrhagic telangiectasia. *BMC Med Genet* 2008; **9**: 75 [PMID: 18673552 DOI: 10.1186/1471-2350-9-75]
- 17 Heimdal K, Dalhus B, Rødningen OK, Kroken M, Eiklid K, Dheyauldeen S, Røysland T, Andersen R, Kulseth MA. Mutation analysis in Norwegian families with hereditary hemorrhagic telangiectasia: founder mutations in ACVRL1. *Clin Genet* 2016; **89**: 182-186 [PMID: 25970827 DOI: 10.1111/cge.12612]
- 18 Letteboer TG, Zewald RA, Kamping EJ, de Haas G, Mager JJ, Snijder RJ, Lindhout D, Hennekam FA, Westermann CJ, Ploos van Amstel JK. Hereditary hemorrhagic telangiectasia: ENG and ALK-1 mutations in Dutch patients. *Hum Genet* 2005; **116**: 8-16 [PMID: 15517393 DOI: 10.1007/s00439-004-1196-5]
- 19 Karlsson T, Cherif H. Mutations in the ENG, ACVRL1, and SMAD4 genes and clinical manifestations of hereditary haemorrhagic telangiectasia: experience from the Center for Osler's Disease, Uppsala University Hospital. *Ups J Med Sci* 2018; **123**: 153-157 [PMID: 30251589 DOI: 10.1080/03009734.2018.1483452]
- 20 Lux A, Salway F, Dressman HK, Kröner-Lux G, Hafner M, Day PJ, Marchuk DA, Garland J. ALK1 signalling analysis identifies angiogenesis

related genes and reveals disparity between TGF-beta and constitutively active receptor induced gene expression. *BMC Cardiovasc Disord* 2006; 6: 13 [PMID: 16594992 DOI: 10.1186/1471-2261-6-13]





Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

