Dermatology Reports
https://www.pagepress.org/journals/index.php/dr/index

eISSN 2036-7406

Please cite this article as:

Ochiai S, Yamaguchi R, Takeda K, et al. A case of hereditary hemorrhagic telangiectasia with *ACVRL1* gene variant. *Dermatol Rep 2026 [Epub Ahead of Print] doi: 10.4081/dr.2026.10582*

Received: 13 October 2025; Accepted: 5 January 2026.

A case of hereditary hemorrhagic telangiectasia with *ACVRL1* gene variant

Sawako Ochiai,[1] Reimon Yamaguchi,[1] Kiminobu Takeda,[1] Naoto Oishi,[2] Sumihito Togi,[3] Hiroki Ura,[3] Yo Niida,[3] Akira Shimizu[1]

[1]Department of Dermatology, Kanazawa Medical University, Uchinada, Ishikawa; [2]Kurobe City Hospital, Kurobe, Toyama; [3]Center for Clinical Genomics, Kanazawa Medical University Hospital, Uchinada, Ishikawa, Japan

Correspondence: Akira Shimizu, Department of Dermatology, Kanazawa Medical University, 1-1, Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa, 920-0293, Japan. E-mail: ashimizu@kanazawa-med.ac.jp

Key words: hereditary hemorrhagic telangiectasia; *ACVRL1* gene; vascular disease.

Conflict of interest: the authors have no conflict of interest to declare.

Ethics approval and consent to participate: genetic analysis was carried out based on the research plan approved by the ethics committee of Kanazawa Medical University Hospital after obtaining patient consent.

Consent for publication: written informed consent was obtained from the patient for publication of this case report.

Availability of data and materials: the datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Dear Editor,

Hereditary hemorrhagic telangiectasia (HHT) is an inherited vascular disease characterized by multiple localized abnormal connections between an artery and a vein. The majority (>85%) of HHT patients are heterozygous for loss-of-function variants in the *ENG* (HHT1) or *ACVRL1* (HHT2) genes, while a minority (<5%) carry pathogenic variants in the *SMAD4* gene and show a combined juvenile polyposis and HHT phenotype (JP/HHT). In addition, a very rare group of patients with an HHT-like phenotype maps to variants in *GDF2* (also known as *BMP9*, HHT5).[1]

HHT2 (OMIM 600376) is caused by a heterozygous variant in the *ACVRL1* gene (OMIM 601284) on chromosome 12q13.13. In this report, we present a patient with HHT in whom a genetic analysis was carried out.

A 58-year-old female was referred to our hospital complaining of telangiectasias on the tongue, lips, and both hands. Her brother, father, and paternal grandmother had similar symptoms. The patient had recurrent epistaxis since her 20s and spots on her tongue since her 40s. About six months prior to her first visit, red spots on her lips and fingers had progressively increased, raising suspicion of HHT. She initially presented to a local hospital for a comprehensive evaluation and was subsequently referred to our department. Telangiectasias were scattered on the lower lip, tongue, and fingertips (Figure 1 a,b).

A head magnetic resonance imaging showed no cerebral arteriovenous malformations (AVMs). Chest and abdominal computed tomography showed minute AVMs in the liver, spleen, and pancreas. Genetic analysis was carried out based on the research plan approved by the ethics committee of Kanazawa Medical University Hospital after obtaining patient consent. The entire genomic region of the *ACVRL1*, *ENG*, *GDF2*, and *SMAD4* was screened using a long-range polymerase chain reaction (PCR)-based next-generation sequencing assay[2] and subsequent validation by Sanger sequencing was performed. The analysis revealed the known pathogenic missense variant NM_000020.3:c.1221G>T p.(Glu407Asp) in the *ACVRL1* gene (Figure 1c). The patient is followed up for AVMs of the liver, spleen, and pancreas.

Although two cases with the same missense variant of the *ACVRL1* gene as our patient are reported, the detailed description of the patients' clinical manifestations is unclear.[3] The two patients were reported to be associated with hepatic disease, and one had pulmonary hypertension.[3,4] In this report, we have shown the clinical manifestations of the patient with the mutation entirely.

HHT is a systemic vascular disorder inherited in an autosomal dominant pattern. Diagnosis has traditionally relied on the Curaçao criteria,[5] but more recent approaches also incorporate genetic testing to improve diagnostic accuracy and enable earlier detection (*ENG*, *ACVRL1*, *SMAD4*).[6] With

regard to cellular and molecular mechanisms, Arthur *et al.* stated that loss of the *ENG* (endoglin) or *ACVRL1* (hereafter the gene product indicated as ALK1 according to previous studies) in endothelial cells leads to AVMs in developing blood vessels.[1] A similar phenotype appears with combined deficiency of endothelial cell-specific *SMAD1* and *SMAD5*, or endothelial cell-specific *SMAD4*. The essential role of the BMP9/10-endoglin-ALK1-SMAD1/5-SMAD4 pathway was shown in protecting the vasculature from AVMs.

HHT's onset and clinical manifestations vary due to the second-hit mechanism.[7] Various triggers may act synergistically with the heterozygous pathogenic variant in HHT-associated genes, contributing to the development of vascular lesions.

Among the postulated mechanisms are mechanical trauma, light, inflammation, vascular injury, angiogenic stimuli, shear stress, modifier genes, and somatic second-hit variants in the wild-type HHT gene allele.

In this report, we presented the missense variant in the *ACVRL1* gene coding ALK1. ALK-1 consists of an N-terminal extracellular domain, a transmembrane region, and an intracellular region consisting almost entirely of serine/threonine kinase domains.[8] ALK1 consists of 13 exons, and the coding regions are exons 2-10.[9] The current variant, NM_000020.3:c.1221G>T p.(Glu407Asp), is located in exon 8, which is in the intracellular kinase domain of ALK1. Abdalla et al. mapped the 11 variable amino acids onto this molecular model, revealing that they are predominantly clustered within the core of the kinase C-lobe. The Glu407 missense variant was found in α-helical structures, and they also suggested that potential alterations in the hydrogen bonding scheme and/or the presence of induced steric clashes were considered. Although the functional analysis of our patient's variant has not been performed yet, loss of kinase domain function may be involved.

Loss-of-function variants in *ENG* and *ACVRL1* cause anomalous angiogenesis, leading to the development of vascular malformations.[6] One of the primary mechanisms underlying aberrant vascular endothelial growth factor-related angiogenesis in HHT patients appears to be the overactivation of phosphatidylinositol 3-kinase signaling in endothelial cells.[10]

Clinical presentations include vascular lesions of all types, with HHT1 showing pulmonary and cerebral AVMs and HHT2 exhibiting hepatic malformations and pulmonary hypertension. Severe symptoms include cerebral hemorrhage, gastrointestinal bleeding, and hemoptysis, with an increased risk of colorectal cancer in JP/HHT syndrome. Thus, identifying genetic variants may predict complications.

References

1. Arthur HM, Roman BL. An update on preclinical models of hereditary haemorrhagic telangiectasia: Insights into disease mechanisms. Front Med (Lausanne) 2022;9:973964.
2. Nomura F, Shimizu A, Togi S, et al. SNP Array Screening and Long Range PCR-Based Targeted Next Generation Sequencing for Autosomal Recessive Disease with Consanguinity: Insight from a Case of Xeroderma Pigmentosum Group C. Genes (Basel) 2023;14:2079.
3. Abdalla SA, Pece-Barbara N, Vera S, et al. Analysis of ALK-1 and endoglin in newborns from families with hereditary hemorrhagic telangiectasia type 2. Hum Mol Genet 2000;9:1227-37.
4. Kuehl HK, Caselitz M, Hasenkamp S, et al. Hepatic manifestation is associated with ALK1 in hereditary hemorrhagic telangiectasia: identification of five novel ALK1 and one novel ENG mutations. Hum Mutat 2005;25:320.
5. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-7.
6. McDonald J, Wooderchak-Donahue W, VanSant Webb C, et al. Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era. Front Genet 2015;6:1.
7. Bernabeu C, Bayrak-Toydemir P, McDonald J, Letarte M. Potential Second-Hits in Hereditary Hemorrhagic Telangiectasia. J Clin Med 2020;9.
8. Hanks SK, Quinn AM, Hunter T. The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. Science 1988;241:42-52.
9. Abdalla SA, Cymerman U, Johnson RM, et al. Disease-associated mutations in conserved residues of ALK-1 kinase domain. Eur J Hum Genet 2003;11:279-87.
10. Iriarte A, Figueras A, Cerda P, et al. PI3K (Phosphatidylinositol 3-Kinase) Activation and Endothelial Cell Proliferation in Patients with Hemorrhagic Hereditary Telangiectasia Type 1. Cells 2019;8.

Figure 1. Clinical manifestation at initial examination. Multiple telangiectasias were seen on the lips, tongue (**a**), and fingertips (**b**). Genetic analysis was carried out using the next-generation sequencing (long-PCR-based method) and subsequent Sanger sequencing. Analysis revealed a known missense mutation, NM_000020.3:c.1221G>T p.(Glu407Asp), in the *ACVRL1* gene in the patient (**c**).