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Novel ACLV1 Mutation Identified in Late Onset Hereditary Hemorrhagic Telangiectasia

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Abstract

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant disorder with variable expressivity. We present a 62-year-old patient with a rare, late-onset disease course featuring a novel mutation in ACVRL1, a signal transducer in the TGFβ/BMP pathway.

Keywords

Hereditary Hemorrhagic Telaniectasia, Osler-Weber-Rendu Syndrome, Anemia, Mutation

1. Introduction

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant disorder with variable expressivity frequently presenting with recurrent epistaxis at adolescence. Here, we present a patient (pt) with a rare, late-onset disease course featuring a novel mutation in ACVRL1, a signal transducer in the TGFβ/BMP pathway.

2. Case

62-year-old female who presented 08/26/15 with worsening episodic epistaxis, fatigue, dyspnea on exertion for 10 years. Physical exam revealed upper and lower distal extremity telangiectasias (**Figures 1-3**) along with numerous tongue lesions (**Figure 4**). Labs: HGB 9.4 g/dL (low), HCT 30.1% (low), MCV 78.7 fL (low), RDW 23%

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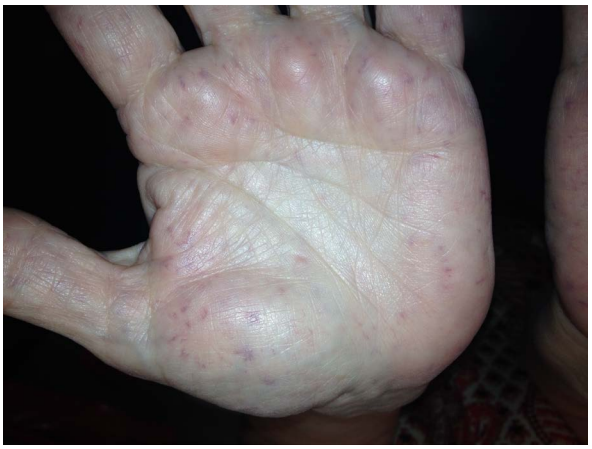

Figure 1. Telangiectasia of right palm.

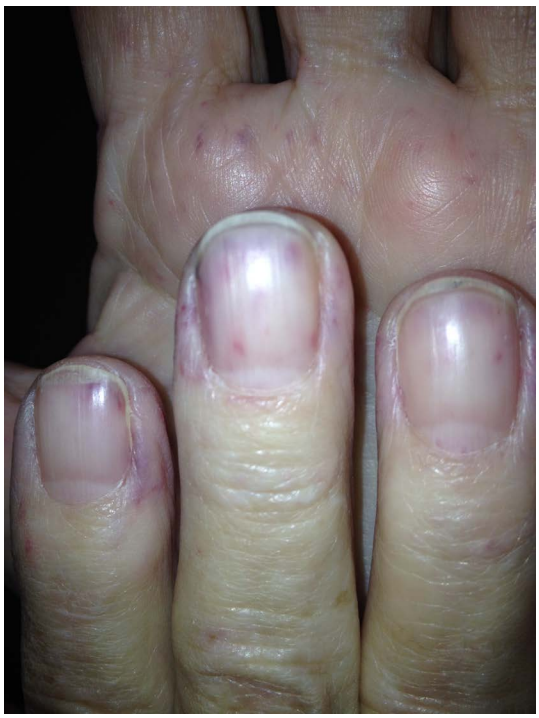

Figure 2. Telangiectasias left finger nails.

(high), Reticulocytes 112700 cells/uL (high), Ferritin 17 ng/mL (low). CMP, PT, PTT, & fibrinogen were normal. Esophagoduodenoscopy (EGD) revealed non-bleeding gastric antrum arteriovenous malformations (**Figure 5**). Colonoscopy was normal. Fiberoptic examination by otolaryngology revealed multiple telangiectasias in the nasal mucosa. CT chest abdomen and pelvis 10/1/14 lacked well-defined AV malformations. Targeted sequencing of the exons and exon-intron junctions of known HHT genes, ENG, ACVRL1, SMAD4, RASA1 and BMP9, returned a previously unreported missense mutation in ACVRL1, resulting in a c.998G > A nucleotide substitution and p. Ser333Asn amino acid alteration. The patient was a heterozygote for this alteration. Her final diagnosis is microcytic anemia due to chronic blood loss due to HHT related epistaxis. She was treated with oral iron and periodic ENT cauterizations with stabilization of symptoms and HGB (11.9 g/dL, 9/2/15).

3. Discussion

Hereditary Hemorrhagic Telangiectasia (HHT), or Osler-Weber-Rendu syndrome, was first described in the 19th

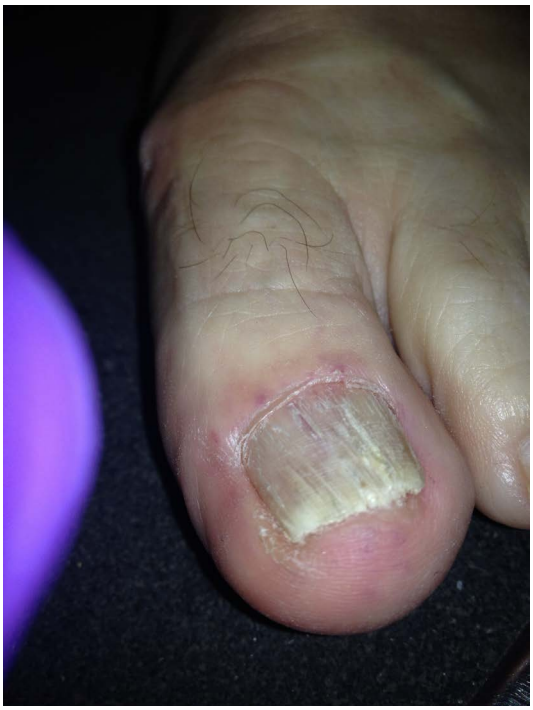

Figure 3. Telangiectasias of left great hallux.

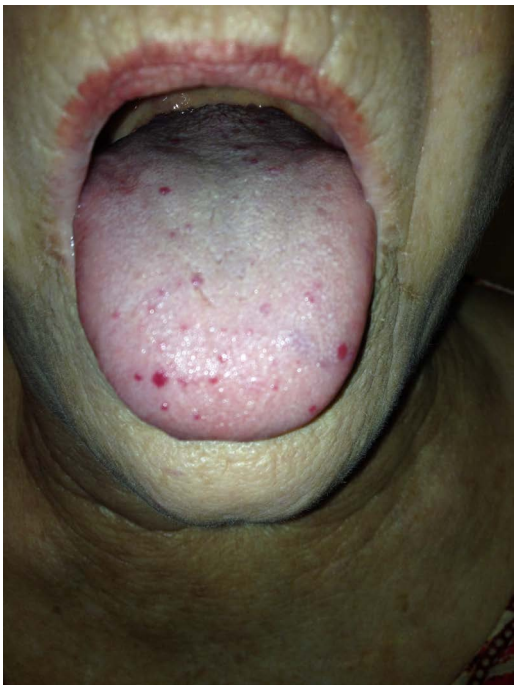

Figure 4. Telangiectasias of the tongue.

century as a hereditary disorder with abnormal vascular structures that caused recurrent bleeding from mucosa throughout the body [1]. Rendu first differentiated this disease from hemophilia when he studied a 52-year-old man with a clinical and family history of anemia, recurrent epistaxis, and telangiectasias. Osler and Weber produced more case reports on similar patients later on that made hereditary hemorrhagic telangiectasia well known within the medical community [2].

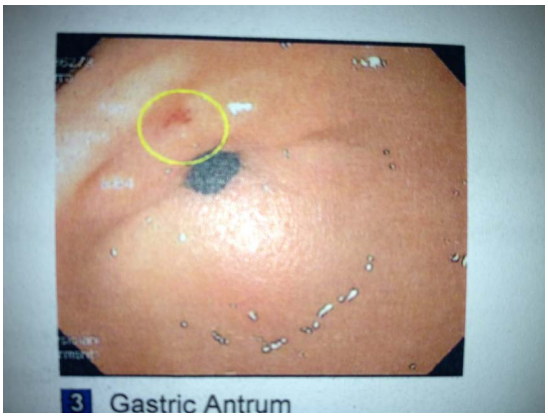

Figure 5. EGD showing gastric antrum AVM.

HHT affects various organs including the nose, skin, lung, brain, and gastrointestinal track. The most common and earliest clinical manifestation is epistaxis from telangiectasias in the nasal mucosa [3]. Over 90 percent of patients with HHT experience their first episode of epistaxis by the age of 21 [4]. Symptoms in the skin, lung, brain, and gastrointestinal track typically present later in the disease course. Common areas for telangiectasias to occur on the skin include the lips, tongue palate, fingers, face, or trunk [3]. Pulmonary arteriovenous malformations are the typical presentation of hereditary hemorrhagic telangiectasia in the respiratory tract. It is estimated that pulmonary arteriovenous malformations are seen in 5 to 15 percent of patients with hereditary hemorrhagic telangiectasia [5]. Neurological symptoms vary and include migraines, transient ischemic attacks, seizures, and hemorrhage [3]. Telangiectasias and hemorrhage are rare in the gastrointestinal track and typically are not symptomatic until the fifth or sixth decade if present. Liver involvement can also occur but is rarely seen [3]. Our patient presents with a late-onset variation of HHT. Epistaxis and other clinical manifestations did not appear until the sixth decade.

The incidence of HHT is approximated to be between 1:5000 and 1:8000. However, the disease is thought to be underreported due to the fact that most patients are unaware of their diagnosis [1].

HHT is an autosomal dominant disorder displaying variable expressivity, locus heterogeneity, and allelic heterogeneity [6]. HHT is attributed to reduction or loss of function alleles in five genes, ENG, ACVRL1, MADH4, BMP9 and BMPR2, resulting in haploinsufficiency of the coded protein [1] [6]. These five genes are all involved in TGF-β signaling pathways responsible for the maintenance of cardiovascular homeostasis.

Other possible loci are currently under investigation [7] (**Table 1**).

Patients are separated into three major subtypes of HHT based on the affected gene, HHT1, HHT2, and juvenile polyposis-HHT overlap syndrome. HHT1 patients have a mutation in the ENG gene encoding the protein endoglin, a coreceptor for type I and II TGF-β pathways. HHT2 patients have a mutation in the ACLVR1 (activin receptor-like kinase 1) gene encoding ALK1, a type-1 receptor in the TGF-β superfamily. Mutations in these two genes account for ~99% of cases of HHT. The different HHT classification reflects differing natural histories, with HHT1 patients experiencing more severe GI bleeds and more frequent pulmonary arterial hypertension [8]. ~1% - 2% of HHT patients have a mutation in MADH4 that results in juvenile polyposis-HHT overlap syndrome [9]. MADH4 encodes Smad-4, a downstream transcription factor of ALK1. The remaining cases of HHT attributed to an identified gene account for <1% of total cases and are caused by mutations in GDF2/BMP9, a TFG-β ligand, and BMPR2, a type 2 TGF-β receptor [1] [6] [10].

An unreported missense mutation in the exon 7 of ACVRL1 resulting in a p. Ser333Asn amino acid alteration is the suspected cause of this patient's late-onset HHT (**Table 2**).

ALK1 acts in endothelial cells, where it functions as a regulator of the activation stage of angiogenesis, promoting endothelial cell proliferation and migration. TGF-β ligands, including BMP9, bind to a Type-2 TGF-β receptor, resulting in the phosphorylation of ALK1, or other Type-1 TGF-β receptor receptors. ALK1 subsequently phosphorylates Smad-1/5/8, causing dimerization with Smad-4 [11]. The Smad dimer then enters the nucleus where it acts as a transcription factor, regulating the transcription of angiogenesis genes such as VEGF. Reduced presence of endoglin, a coreceptor for ALK family of receptors, has been shown to decrease the activity of the ALK1 pathway, as well as the ALK5 pathway that counterbalances ALK1 activity by promoting cell

Table 1. Summary of genes causing HHT [6] [14].

Type	Gene/protein	Gene description	Mutation types	Mutation locations
HHT1	ENG/Endoglin	Member of TGFβ receptor complex	Point mutations; duplications; deletions; insertions	Exons 1 - 14;
HHT2	ACVRL1/ALK1	Type 1 cell surface receptor in TGFβ superfamily	Point mutations; duplications; deletions; insertions	Exons 2 - 10; Introns 3 - 9
HHT associated with Juvenile Polyposis	MADH4/Smad4	Transcription factor in TGFβ	Point mutations; duplications; deletions; insertions	Exons 4, 7, 10 - 13
HHT-5	BMP9 (GDF2)/BMP9	TGFβ ligand	Point mutations	Exons 1, 2

Table 2. Documented predicted pathogenic ACLVR-1 mutations according to the University of Utah HHT mutation database.

Nucleotide change	Mutation type	Protein change	Reference
c.?	Deletion	p.0	[15]
c.24A > T	Missense	p.Lys8Ans	[16]
c.31_50del20	Deletion	p.Leu11Glyfs*20	[17]
c.37delC	Deletion	p.Leu13Cysfs*2	[18]
c.50dupT	Duplication	p.Leu17Phefs*21	[19]
c.50_53delTGGT	Deletion	p.Leu*17	[20]
c.61 + 1G > A	Missense	p.?	[14]
c.61 + 10G > A	Splice Site	p.?	[21]
c.65delA	Deletion	p.Asp22Alafs*3	[14]
c.69delT	Deletion	p.Val24*	[14]
c.74_78delAGCCGins176bp	Delins	p.?	[19]
c.81dupT	Duplication	p.Arg28Serfs*10	[22]
c.86delG	Deletion	p.Gly29Alafs*4	[23]
c.88C > T	Missense	p.Pro30Ser	[24]
c.95T > G	Missense	p.Val32Gly	[25]
c.100dupT	Duplication	p.Cys34Leufs*4	[19]
c.100_115del16	Deletion	p.Cys34Hisfs*15	[26]
c.101G > A	Missense	p.Cys34Tyr	[24]
c.102C > A	Missense	p.Cys34*	[25]
c.106T > C	Missense	p.Cys36Arg	[14]
c.107G > A	Missense	p.Cys36Tyr	[27]
c.115_118dupCCAC	Duplication	p.His40Profs*130	[28]
c.121T > C	Missense	p.Cys41Arg	[28]
c.128_132delGGCCT	Deletion	p.Gly43Aspfs*124	[29]
c.129delG	Deletion	p.Pro44Leufs*10	[14]
c.136_137delTGinsCT	Delins	p.Cys46Leu	[29]
c.138C > A	Missense	p.Cys46*	[19]
c.139_140insCG	Insertion	p.Arg47Profs*8	[30]
c.139dupC	Duplication	p.Arg47Profs*122	[24]

Continued

c.140G > C	Missense	p.Arg47Pro	[27]
c.142G > A	Missense	p.Gly48Arg	[31]
c.143G > A	Missense	p.Gly48Glu	[32]
c.143_147delGGGCCinsAGCCT	Delins	p.Gly48_Ala49delinsGluPro	[33]
c.145dupG	Duplication	p.Ala49Glyfs*120	[34]
c.145delG	Deletion	p.Ala49Profs*5	[35]
c.147delC	Deletion	p.Trp50Glyfs*4	[36]
c.148T > G	Missense	p.Trp50Gly	[37]
c.149G > A	Missense	p.Trp50*	[29]
c.150G > T	Missense	p.Trp50Cys	[38]
c.150G > A	Missense	p.Trp50*	[39]
c.152G > A	Missense	p.Cys51Tyr	[34]
c.154A > G	Missense	p.Thr52Ala	[24]
c.155delC	Deletion	p.Thr52Lysfs*2	[30]
c.164_169delTGGTGC	Deletion	p.Leu55_Val56del	[40]
c.172G > T	Missense	p.Glu58*	[35]
c.183delG	Deletion	p.Arg61Serfs*61	[19]
c.190delC	Deletion	p.Gln64Argfs*58	[39]
c.191delA	Deletion	p.Gln64Argfs*58	[24]
c.193G > T	Missense	p.Glu65*	[14]
c.197A > C	Missense	p.His66Pro	[37]
c.199C > T	Missense	p.Arg67Trp	[35]
c.200G > A	Missense	p.Arg67Gln	[38]
c.202G > T	Missense	p.Gly68Cys	[27]
c.203dupG	Duplication	p.Cys69Leufs*100	[40]
c.203delG	Deletion	p.Gly68Alafs*54	[39]
c.205_209dupTGCGG	Duplication	p.Asn71Alafs*53	[20]
c.205T > C	Missense	p.Cys69Arg	[37]
c.206G > T	Missense	p.Cys69Phe	[19]
c.206G > A	Missense	p.Cys69Tyr	[25]
c.208G > A	Missense	p.Gly70Arg	[19]
c.214_219delTTGCAC	Deletion	p.Leu72_His73del	[19]
c.215delT	Deletion	p.Leu72Cysfs*50	[29]
c.218_219insAA	Insertion	p.His73Glnfs*50	[28]
c.229_240del12	Deletion	p.Cys77_Arg80del	[29]
c.230G > A	Missense	p.Cys77Tyr	[20]
c.231C > G	Missense	p.Cys77Trp	[34]
c.235G > A	Missense	p.Gly79Arg	[40]
c.237dupG	Duplication	p.Arg80Alafs*89	[23]
c.243dupC	Duplication	p.Thr82Hisfs*87	[21]
c.244_246delACC	Deletion	p.Thr82del	[27]
c.246delC	Deletion	p.Glu83Serfs*39	[41]
c.252dupC	Duplication	p.Val85Argfs*84	[42]

Continued

c.259C > G	Missense	p.His87Asp	[19]
c.263A > G	Missense	p.Tyr88Cys	[17]
c.265T > C	Missense	p.Cys89Arg	[14]
c.266G > A	Missense	p.Cys89Tyr	[20]
c.269G > A	Missense	p.Cys90Tyr	[25]
c.270C > G	Missense	p.Cys90Trp	[43]
c.270C > A	Missense	p.Cys90*	[44]
c.283T > C	Missense	p.Cys95Arg	[28]
c.286A > G	Missense	p.Asn96Asp	[34]
c.287A > G	Missense	p.Asn96Ser	[45]
c.289_295delCACAACG	Deletion	p.His97Cysfs*23	[14]
c.289_294delCACAAC	Deletion	p.His97_Ans98del	[35]
c.293A > G	Missense	p.Asn98Ser	[46]
c.301_307delCTGGTGC	Deletion	p.Leu101Trpfs*19	[31]
c.313 + 1G > A	Missense	p.?	[14]
c.314 − 3C > G	Splice Site	p.?	[46]
c.319delC	Deletion	p.Gln107Asnfs*15	[37]
c.321delA	Deletion	p.Gln107Hisfs*15	[40]
c.329C > A	Missense	p.Ser110*	[14]
c.334C > T	Missense	p.Gln112*	[14]
c.352C > T	Missense	p.Gln118*	[39]
c.353_360dupAGCTGGCC	Duplication	p.Leu121Serfs*4	[47]
c.374_375dupCC	Duplication	p.Val126Profs*40	[39]
c.383C > A	Missense	p.Ala128Asp	[48]
c.400delG	Deletion	p.Ala134Profs*31	[34]
c.406_409delGGTG	Deletion	p.Gly136Serfs*28	[34]
c.423G > A	Missense	p.Trp141*	[38]
c.430C > T	Missense	p.Arg144*	[23]
c.435dupG	Duplication	p.Arg146Glufs*23	[24]
c.435delG	Deletion	p.Arg146Glyfs*19	[49]
c.439C > T	Missense	p.Gln147*	[39]
c.448C > T	Missense	p.Gln150*	[28]
c.474A > T	Missense	p.Gly158Gly	[24]
c.475G > T	Missense	p.Glu159*	[38]
c.476_477delAG	Deletion	p.Glu159Valfs*9	[20]
c.480_486dupCAGTCTC	Duplication	p.Ile163Glnfs*8	[43]
c.480_481delCA	Deletion	p.Leu162Hisfs*6	[26]
c.481A > G	Missense	p.Ser161Gly	[19]
c.505C > T	Missense	p.Gln169*	[43]
c.510delC	Deletion	p.Asp171Thrfs*87	[31]
c.525_525 + 1delGG	Deletion	p.Asp176Thrfs*82	[25]
c.525 + 1G > C	Splice Site	p.?	[43]
c.525 + 1G > A	Splice Site	p.?	[17]

Continued

c.525 + 1delG	Deletion	p.?	[19]
c.525 + 3A > G	Splice Site	p.?	[17]
c.525 + 3A > T	Splice Site	p.?	[50]
c.526-7C > G	Splice Site	p.?	[37]
c.526-3C > G	Splice Site	p.?	[30]
c.526-1G > A	Missense	p.?	[14]
c.526G > T	Missense	p.Asp176Tyr	[37]
c.526delG	Deletion	p.Asp176Thrfs*82	[19]
c.536A > C	Missense	p.Asp179Ala	[51]
c.540_541insA	Insertion	p.Asp181Argfs*44	[29]
c.563delC	Deletion	p.Ser188*	[19]
c.567delG	Deletion	p.Leu190Serfs*68	[47]
c.573delC	Deletion	p.Phe192Serfs*66	[26]
c.590C > T	Missense	p.Thr197Ile	[24]
c.593T > A	Missense	p.Val198Glu	[52]
c.598C > G	Missense	p.Arg200Gly	[43]
c.601C > T	Missense	p.Gln201*	[45]
c.601C > A	Missense	p.Gln201Lys	[30]
c.602A > G	Missense	p.Gln201Arg	[53]
c.602A > C	Missense	p.Gln201Pro	[19]
c.611T > G	Missense	p.Leu204Trp	[19]
c.614T > G	Missense	p.Val205Gly	[43]
c.617A > G	Missense	p.Glu206Gly	[20]
c.617_625delAGTGTGTGG	Deletion	p.Glu206_Val208del	[54]
c.620delG	Deletion	p.Cys207Leufs*51	[14]
c.623_624dupTG	Duplication	p.Gly209Trpfs*50	[39]
c.626-9_629del13	Deletion	p.?	[37]
c.626-5_634del14	Deletion	p.?	[39]
c.626-3C > G	Splice Site	p.?	[55]
c.632G > A	Missense	p.Gly211Asp	[51]
c.639T > G	Missense	p.Tyr213*	[14]
c.641delG	Deletion	p.Gly214Alafs*44	[45]
c.643G > A	Missense	p.Glu215Lys	[31]
c.647T > G	Missense	p.Val216Gly	[19]
c.649T > G	Missense	p.Trp217Gly	[45]
c.650G > A	Missense	p.Trp217*	[20]
c.651G > A	Missense	p.Trp217*	[24]
c.653_654delGGinsCC	Delins	p.Arg218Pro	[52]
c.656G > A	Missense	p.Gly219Asp	[24]
c.661T > G	Missense	p.Trp221Gly	[14]
c.662G > A	Missense	p.Trp221*	[19]
c.663G > A	Missense	p.Trp221*	[47]
c.664_668delCACGG	Deletion	p.His222*	[31]

Continued

c.667G > C	Missense	p.Gly223Arg	[31]
c.670G > A	Missense	p.Glu224Lys	[25]
c.673A > T	Missense	p.Ser225Cys	[16]
c.673_674delAG	Deletion	p.Ser225Cysfs*11	[47]
c.676G > C	Missense	p.Val226Leu	[30]
c.677T > A	Missense	p.Val226Glu	[45]
c.682delG	Deletion	p.Val228Serfs*30	[31]
c.683T > A	Missense	p.Val228Asp	[19]
c.686A > T	Missense	p.Lys229Met	[55]
c.686A > G	Missense	p.Lys229Arg	[31]
c.696_698delCTC	Deletion	p.Ser233del	[56]
c.698C > T	Missense	p.Ser233Leu	[37]
c.698C > A	Missense	p.Ser233*	[57]
c.704delA	Deletion	p.Asp235Valfs*23	[31]
c.709C > T	Missense	p.Gln237*	[25]
c.716G > A	Missense	p.Trp239*	[46]
c.743_744delCA	Deletion	p.Thr248Serfs*143	[29]
c.760_762delGAC	Deletion	p.Asp254del	[18]
c.759_761delCGA	Deletion	p.Asp254del	[31]
c.772 + 3_772 + 4dupAA	Duplication	p.?	[43]
c.772 + 5G > A	Missense	p.?	[14]
c.772 + 21T > A	Splice Site	p.?	[25]
c.773-2A > G	Splice Site	p.?	[31]
c.773-2A > C	Splice Site	p.?	[19]
c.778A > C	Missense	p.Ile260Leu	[24]
c.793A > C	Missense	p.Thr265Pro	[37]
c.811_823del13bp	Deletion	p.Thr271Serfs*26	[35]
c.818T > C	Missense	p.Leu273Pro	[48]
c.821_824dupGGCT	Duplication	p.Ile276Alafs*117	[40]
c.822G > A	Missense	p.Trp274*	[45]
c.827T > C	Missense	p.Ile276Thr	[48]
c.835_837dupTAC	Duplication	p.Tyr279dup	[14]
c.838C > G	Missense	p.His280Asp	[25]
c.839A > G	Missense	p.His280Arg	[45]
c.842delA	Deletion	p.Glu281Glyfs*20	[26]
c.851C > T	Missense	p.Ser284Phe	[48]
c.853dupC	Duplication	p.Leu285Profs*107	[20]
c.853C > T	Missense	p.Leu285Phe	[31]
c.854T > C	Missense	p.Leu285Pro	[58]
c.858C > G	Missense	p.Tyr286*	[25]
c.858C > A	Missense	p.Tyr286*	[35]
c.863_909del47	Deletion	p.Phe288Cysfs*88	[14]
c.864dupT	Duplication	p.Leu289Serfs*103	[38]

Continued

c.866T > C	Missense	p.Leu289Pro	[24]
c.870delG	Deletion	p.Arg219Aspfs*10	[14]
c.874delC	Deletion	p.Gln292Argfs*9	[30]
c.874C > T	Missense	p.Gln292*	[19]
c.875A > C	Missense	p.Gln292Pro	[26]
c.881T > G	Missense	p.Leu294Arg	[45]
c.905T > G	Missense	p.Leu302Arg	[26]
c.913T > C	Missense	p.Ser305Pro	[48]
c.913delT	Deletion	p.Ser305Profs*49	[59]
c.914C > T	Missense	p.Ser305Phe	[17]
c.916G > C	Missense	p.Ala306Pro	[31]
c.917C > A	Missense	p.Ala306Glu	[30]
c.921_927dupATGCGGC	Duplication	p.Leu310Metfs*84	[47]
c.924C > A	Missense	p.Cys308*	[38]
c.925G > T	Missense	p.Gly309Cys	[25]
c.925G > A	Missense	p.Gly309Ser	[39]
c.936C > G	Missense	p.His312Gln	[60]
c.940C > T	Missense	p.His314Tyr	[31]
c.941_951del11	Deletion	p.His314Leufs*74	[30]
c.950T > C	Missense	p.Ile317Thr	[14]
c.956G > A	Missense	p.Gly319Asp	[25]
c.961C > T	Missense	p.Gln321*	[39]
c.969dupA	Duplication	p.Pro324Thrfs*68	[43]
c.972delA	Deletion	p.Ala325Profs*29	[31]
c.976A > G	Missense	p.Ile326Val	[59]
c.982C > T	Missense	p.His328Tyr	[17]
c.983A > C	Missense	p.His328Pro	[27]
c.985C > T	Missense	p.Arg329Cys	[14]
c.986G > A	Missense	p.Arg329His	[23]
c.988G > T	Missense	p.Asp330Tyr	[35]
c.988G > C	Missense	p.Asp330His	[30]
c.988G > A	Missense	p.Asp330Asn	[39]
C.991_1044del54bp	Missense	p.Phe331_Asp348del54bp	[30]
c.992T > C	Missense	p.Phe331Ser	[24]
c.994_995insGACTTA	Insertion	p.Phe331_Lys332insArgLeu	[14]
c.997A > G	Missense	p.Ser333Gly	[26]
c.998G > T	Missense	p.Ser333Ile	[38]
c.998G > A	Missense	p.Ser333Asn	[14]
c.1000delC	Deletion	p.Arg334Alafs*20	[54]
c.1000_1005delCGCAATinsG	Delins	p.Arg334Glyfs*56	[31]
c.1003A > C	Missense	p.Asn335His	[45]
c.1010dupT	Duplication	p.Val338Glyfs*54	[14]
c.1010T > C	Missense	p.Leu337Pro	[31]

Continued

c.1010delT	Deletion	p.Leu337Argfs*17	[25]
c.1013T > A	Missense	p.Val338Asp	[30]
c.1022A > T	Missense	p.Asn341Ile	[30]
c.1023C > G	Missense	p.Asn341Lys	[31]
c.1027C > T	Missense	p.Gln343*	[14]
c.1030T > C	Missense	p.Cys344Arg	[61]
c.1031G > T	Missense	p.Cys344Phe	[31]
c.1031G > A	Missense	p.Cys344Tyr	[33]
c.1039G > C	Missense	p.Ala347Pro	[31]
c.1040C > A	Missense	p.Ala347Asp	[45]
c.1040_1042delCCG	Deletion	p.Ala347del	[62]
c.1042delG	Deletion	p.Asp348Thrsf*6	[39]
c.1043_1048 + 1dupACCTGGG	Insertion	p.?	[14]
c.1046T > C	Missense	p.Leu349Pro	[45]
c.1048G > C	Missense	p.Gly350Arg	[39]
c.1048G > A	Missense	p.Gly350Ser	[26]
c.1048 + 1G > C	Missense	p.?	[14]
c.1048 + 1G > A	Splice Site	p.?	[25]
c.1048 + 5G > T	Splice Site	p.?	[47]
c.1048 + 5G > A	Missense	p.?	[14]
c.1049-4_1049-2delACAinsCC	Delins	p.?	[28]
c.1054G > C	Missense	p.Ala352Pro	[35]
c.1055C > A	Missense	p.Ala352Asp	[46]
c.1061T > A	Missense	p.Met354Lys	[29]
c.1061_1068delTGCACTCA	Deletion	p.Met354Thrfs*35	[39]
c.1062_1080dup19	Duplication	p.Try361Alafs*37	[40]
c.1069C > T	Missense	p.Gln357*	[48]
c.1073delG	Deletion	p.Gly358Alafs*57	[39]
c.1083C > A	Missense	p.Tyr361*	[14]
c.1102_1105delCCGA	Deletion	p.Pro368Glufs*46	[14]
c.1107_1108delAG	Deletion	p.Arg369Serfs*22	[39]
c.1111G > A	Missense	p.Gly371Ser	[19]
c.1112dupG	Duplication	p.Thr372Hisfs*20	[23]
c.1115C > T	Missense	p.Thr372Ile	[28]
c.1118delA	Deletion	p.Lys373Serfs*42	[19]
c.1120C > T	Missense	p.Arg374Trp	[38]
c.1120_1137del18	Deletion	p.Arg374_Glu379del	[39]
c.1121G > A	Missense	p.Arg374Gln	[23]
c.1122_1125dupGTAC	Duplication	p.Met376Valfs*17	[31]
c.1123T > C	Missense	p.Tyr375His	[23]
c.1124A > G	Missense	p.Tyr375Cys	[52]
c.1126A > G	Missense	p.Met376Val	[31]
c.1127T > G	Missense	p.Met376Arg	[56]

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c.1127T > A	Missense	p.Met376Lys	[40]
c.1127T > C	Missense	p.Met376Thr	[27]
c.1129G > A	Missense	p.Ala377Thr	[27]
c.1132C > T	Missense	p.Pro378Ser	[45]
c.1133C > A	Missense	p.Pro378His	[48]
c.1135G > A	Missense	p.Glu379Lys	[31]
c.1139T > G	Missense	p.Val380Gly	[39]
c.1142T > C	Missense	p.Leu381Pro	[60]
c.1144G > C	Missense	p.Asp382His	[19]
c.1153_1157dupATCCG	Duplication	p.Thr387Serfs*30	[45]
c.1157G > A	Missense	p.Arg386His	[48]
c.1171G > T	Missense	p.Glu391*	[23]
c.1187C > A	Missense	p.Thr396Asn	[19]
c.1189G > A	Missense	p.Asp397Asn	[39]
c.1190A > G	Missense	p.Asp397Gly	[21]
c.1193T > A	Missense	p.Ile398Asn	[8]
c.1195T > C	Missense	p.Trp399Arg	[52]
c.1195T > G	Missense	p.Trp399Gly	[14]
c.1196G > C	Missense	p.Trp399Ser	[51]
c.1199C > A	Missense	p.Ala400Asp	[35]
c.1204G > A	Missense	p.Gly402Ser	[31]
c.1205G > A	Missense	p.Gly402Asp	[47]
c.1208T > C	Missense	p.Leu403Pro	[37]
c.1214T > A	Missense	p.Leu405Gln	[14]
c.1215delG	Deletion	p.Trp406Glyfs*9	[19]
c.1218G > C	Missense	p.Trp406Cys	[39]
c.1219G > A	Missense	p.Glu407Lys	[14]
c.1220A > G	Missense	p.Glu407Gly	[17]
c.1221G > T	Missense	p.Glu407Asp	[33]
c.1231C > T	Missense	p.Arg411Trp	[18]
c.1232G > C	Missense	p.Arg411Pro	[31]
c.1232G > A	Missense	p.Arg411Gln	[56]
c.1246G > A	Splice Site	p.Gly416Ser	[37]
c.1246 + 1G > A	Splice Site	p.?	[24]
c.1249A > T	Missense	p.Ile417Phe	[19]
c.1261T > G	Missense	p.Tyr421Asp	[47]
c.1269delA	Deletion	p.Phe425Serfs*14	[29]
c.1270C > A	Missense	p.Pro424Thr	[38]
c.1270C > T	Missense	p.Pro424Ser	[48]
c.1271C > G	Missense	p.Pro424Arg	[45]
c.1271C > T	Missense	p.Pro424Leu	[39]
c.1273T > C	Missense	p.Phe425Leu	[14]
c.1273T > G	Missense	p.Phe425Val	[41]
c.1274_1276delTCT	Deletion	p.Phe425del	[41]
c.1275C > G	Missense	p.Phe425Leu	[31]
c.1277A > G	Missense	p.Tyr426Cys	[24]
c.1280A > T	Missense	p.Asp427Val	[28]
c.1297C > T	Missense	p.Pro433Ser	[39]

Continued

c.1298C > G	Missense	p.Pro433Arg	[24]
c.1299delC	Deletion	p.Ser434Alafs*5	[23]
c.1302_1303delCTinsA	Delins	p.Ser434Argfs*5	[37]
c.1309delG	Deletion	p.Asp437Thrfs*2	[19]
c.1310A > G	Missense	p.Asp437Gly	[19]
c.1313T > C	Missense	p.Met438Thr	[39]
c.1313T > G	Missense	p.Met438Arg	[19]
c.1315A > T	Missense	p.Lys439*	[14]
c.1318_1320delAAG	Deletion	p.Lys440del	[24]
c.1321G > A	Missense	p.Val441Met	[48]
c.1324_1326delGTG	Deletion	p.Val442del	[19]
c.1324G > A	Missense	p.Val442Met	[53]
c.1325T > C	Missense	p.Val442Ala	[57]
c.1331_1332dupTG	Duplication	p.Asp445Trpfs*21	[14]
c.1336C > T	Missense	p.Gln446*	[19]
c.1345C > A	Missense	p.Pro449Thr	[47]
c.1345C > T	Missense	p.Pro449Ser	[45]
c.1346C > T	Missense	p.Pro449Leu	[29]
c.1347dupC	Duplication	p.Thr450Hisfs*4	[14]
c.1354_1355delCC	Deletion	p.Pro452*	[14]
c.1355C > T	Missense	p.Pro452Leu	[48]
c.1377 + 1G > A	Splice Site	p.?	[41]
c.1378-2A > G	Splice Site	p.?	[29]
c.1378-1G > T	Splice Site	p.?	[47]
c.1385C > G	Missense	p.Ser462*	[63]
c.1388delG	Deletion	p.Gly463Alafs*2	[53]
c.1390delC	Deletion	p.Leu464*	[64]
c.1396C > T	Missense	p.Gln466*	[19]
c.1408G > T	Missense	p.Glu470*	[39]
c.1413C > A	Missense	p.Cys471*	[24]
c.1428dupC	Duplication	p.Ser477Leufs*17	[31]
c.1433C > A	Missense	p.Ala478Asp	[58]
c.1435C > T	Missense	p.Arg479*	[63]
c.1436G > A	Missense	p.Arg479Gln	[61]
c.1436G > C	Missense	p.Arg479Pro	[45]
c.1436G > T	Missense	p.Arg479Leu	[31]
c.1438C > T	Missense	p.Leu480Phe	[20]
c.1450C > G	Missense	p.Arg484Gly	[65]
c.1450C > T	Missense	p.Arg484Trp	[18]
c.1450delCinsTG	Delins	p.Arg484Trpfs*10	[63]
c.1451G > A	Missense	p.Arg484Gln	[20]
c.1451G > T	Missense	p.Arg484Leu	[57]
c.1460A > C	Missense	p.Lys487Thr	[51]
c.1468C > T	Missense	p.Gln490*	[18]
c.1475T > A	Missense	p.Ile492Asn	[8]

Quiescence [12]. In healthy individuals, increases in endoglin levels can be seen after episodes of vascular damage. Circulating endothelial cells of HHT patients display a decreased level of endoglin and dysfunctional ALK1 and ALK5 signaling pathways. Recent data suggests ALK1 may also play a role in regulating the resolution phase of angiogenesis, further expanding the mechanism behind HHT dysgenesis [13].

4. Conclusion

Here we have a late-onset variation of HHT in the presence of a novel, suspected pathogenic mutation in ACVRL1. HHT patients typically present with recurrent nosebleeds by the age of 30 (90%), superficial telangiectasias by the age of 40 (67%) and GI bleeding starting in their 50s. This patient reported recurrent epistaxis onset in her late middle age and at the age of 62 did not complain of GI bleeds. Abdomen, pelvis and chest CT revealed an absence of visceral AVMs. A mutation occurring at the same nucleotide position, c.998, but resulting in a different amino acid change, has been found in multiple other HHT patients. The clinical presentation of these patients is unknown; however the presentation of our patient suggests that a c.998G > A missense mutation causes a late-onset HHT clinical presentation manageable with supportive care.

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